Veterinary Applied Pharmacology and Therapeutics

Formerly Hoare's Veterinary Materia Medica and Therapeutics

by

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PREFACE

Wallis Hoare's *Veterinary Materia Medica and Therapeutics* served the veterinary profession well for over 50 years, but changing ideas and requirements, combined with increases in both the number and types of therapeutic agents, made it progressively more difficult to compile each succeeding edition within the framework of the original book. Whole new classes of drugs have been discovered and many of the older drugs have been re-assessed since the publication of the last edition; in consequence, abandonment of the old book and an entirely new approach to the whole subject became imperative.

With the increase in importance attached to the teaching of Experimental Pharmacology and related subjects there has been a considerable decline in the teaching of drug characteristics and their clinical applications; the need for a modern text book of Applied Pharmacology and Therapeutics has thereby been made more urgent. In these circumstances, and making use of personal experience as a practitioner, teacher, examiner and technical adviser, an attempt has been made in this new book to provide the student with the maximum possible help. It is also hoped that teachers and practitioners may find the book of value.

To cover twenty years of new material and yet to retain what among the older therapeutics is still of use has been a task of considerable magnitude, and it has been necessary to modify the original form of several chapters after their completion in order to incorporate more recent information. However, since new information and new drugs are announced almost daily, to sift and determine what is of permanent importance would tax the wisdom of Solomon. The sources of important information are therefore quoted in the text so that the reader, should he so wish, may refer to the original articles and form his own opinions. Even so, where new material has been included an attempt has been made to give as reasoned an evaluation as possible.

One of the difficulties encountered by students is the problem of relating information to its correct context, and for that reason, where necessary, the background of the subject under discussion has been sketched in with the intention of making it clear exactly where the information given fits into the field of disease therapy.

Structurally, the book consists of five sections in which is provided information on the essential physical, chemical and pharmacological characteristics of all the important drugs now in veterinary use in Great Britain; details of actions and uses, toxicity, dosages, and methods of administration are given prominence. Part I provides a general introduction, and includes the method of prescription building, which incorporates

the whole theory of prescribing, from the decision on which drug or drugs to use, up to the stage of administering the treatment to the patient. Part II details the drugs which are used to treat the imbalances and diseases of each system of the body and Part III covers the chemotherapeutic agents, mainly the antibiotics and the sulphonamides. Part IV is allotted to the vitamins, hormones (excluding the sex hormones) and the vaccines and sera. Pharmacy, which is dealt with only very briefly, and the Acts and Orders which concern the possession and use of drugs are grouped together in Part V. It is hoped that, in conjunction with the *British Veterinary Codex*, this book will meet most of the requirements of those who have been pressing for a book on these subjects.

I wish to acknowledge the help of all who have contributed advice and encouragement during my several years of travail. In particular I would mention Professor Burrow, Professor of Veterinary Medicine, Royal Veterinary College, University of London; the Principal of the Royal Veterinary College, who has allowed me to make use of its library; Mr. Charles J. Hewlett and the directors of C. J. Hewlett & Son Ltd., who have given me time, advice and encouragement; my secretaries, Mrs. Diana Clarke, who courageously typed almost the whole manuscript, and Mrs. Surridge, who has given invaluable help; Mr. Alexander Thomson, M.R.C.V.S., who read and criticized the mountain of typescript and galley proofs and who has advised on all professional aspects—he has besides my gratitude, my sympathy also; my publishers, for their kindness, advice and patience. To all I offer my sincere thanks. Finally I must mention my wife, who has agreed typescript with manuscript, advised on all matters of syntax and has nobly withstood the loneliness of the last few years; without her the book would never have been completed.

P. W. DAYKIN

ST. ALBANS,
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PART ONE

INTRODUCTION



CHAPTER 1

GENERAL INTRODUCTION

MEDICINES and salves are as old as history and many of the drugs mentioned in the earliest records continue to render good service. Numbers of loathsome remedies, mainly introduced by the charlatans of the Dark Ages, were also included in medical text books as recently as the middle of the nineteenth century and it was not until 1864, by virtue of the Medical Act of 1858 and of the Medical Council Act of 1862, that a reference book was published detailing all the officially accepted drugs: this book was entitled The British Pharmacopœia (B.P.). Superseding the three major pharmacopœias then in use, i.e. those of London, Edinburgh and Dublin, it gave detailed descriptions, stated the composition, established standards of purity, and provided human dosage rates for all the drugs considered by the Pharmacopœia Committee of the General Medical Council to be adequately tested and of known therapeutic value. At varying intervals since 1864 revised editions have been published as new drugs have been discovered and others have fallen from favour.

The British Pharmacopœia was, and is, of little direct value to the practitioner and in 1883 William Martindale published his Extra Pharmacopœia with the purpose of supplying practitioners and pharmacists 'with practical and up-to-date information on drugs and galenical preparations to supplement that contained in the British Pharmacopœia' . . .: so states the preface to the twenty-third edition published in 1952. That aim is continued with each succeeding edition, but the onus of production has been borne by the British Pharmaceutical Society since 1934 when the Society purchased the copyright after the death of William Martindale's son. In 1948 the Pharmaceutical Society also purchased the copyright of 'Squires Companion,' a similar work and a strong competitor of the Extra Pharmacopœia which had appeared first in 1864, some nineteen years before Martindale's first edition, but which lapsed on the death of Squire's second son shortly after publication of the nineteenth edition in 1916. Both are now produced as a combined edition in two volumes.

Neither Martindale's Extra Pharmacopœia nor Squire's Companion were accorded official recognition: the need for an official reference book for the use of those involved in 'the prescribing and dispensing of medicines' was recognized in 1907 when the Pharmaceutical Society published the first edition of the British Pharmaceutical Codex (B.P.C.). This book, besides giving details of manufacturing, physical and chemical characteristics and standards of purity in much the same manner as the B.P.

also contains monographs on actions and uses as well as details of toxicity and antidotal measures. Information is contained '. . . on all drugs and medicinal preparations in common use throughout the British Commonwealth and on all the principal substances which were official in the pharmacopœias of France, Germany and the United States of America.' It is now specifically stated that the inclusion of a drug '. . . is now regarded as an indication that it is of value or is an established constituent of a useful preparation'. These quotations are taken from the preface of the Codex of 1954. A number of the drugs detailed in the B.P.C. are not included in the B.P., either having been deleted or having been considered not sufficiently proved to warrant inclusion: the Codex has included them because of their wide usage and general clinical acceptance.

Both the B.P. and the B.P.C. are now republished once every five years to keep pace with the rapid advances in knowledge, but even so discoveries are numerous and five years between editions is too long. More frequent publication is uneconomical and therefore 'addenda' to the B.P. and 'supplements' to the B.P.C. are published as interim measures between the quinquennial revised editions.

These official and semi-official publications are the British milestones on the road of progress in the treatment of human diseases: the publication of the British Veterinary Codex in 1953, modelled on the British Pharmaceutical Codex and published by the same authority, is a similar milestone marking the advance of veterinary disease therapy.

These books of reference are widely accepted throughout the world and especially in the British Commonwealth. Most countries, however, produce their own pharmacopœias amongst which the United States Pharmacopœia (U.S.P.) and the International Pharmacopœia (I.P.) are of some importance. In the U.S.A., the National Formulary (N.F.), which is analogous to the B.P.C., establishes legal standards and formulations of accepted useful drugs: other American publications of importance are the New and Non-official Remedies (N.N.R.), which provides information, as its name implies, on newly discovered but adequately proven drugs, and the United States Dispensatory which is a huge volume incorporating information on all the drugs officially recognized in the U.S.P., B.P., I.P. and N.F. as well as many other new, not officially recognized drugs. It provides detailed commentaries on therapeutic theories and methods, with numerous references, in far greater detail than any similar semi-official publication and includes in the most recent edition a sizeable section on veterinary applications.

These books, then, establish the value of the majority of the drugs now in use, but it should always be remembered that the fight against disease is not entirely one of administering medicines to diseased animals, nor yet of applying surgical knowledge. The aim of all physicians, human or veterinary, is becoming increasingly directed towards the prevention of disease. In the last half century the application of hygiene to husbandry and the calculated use of mass vaccination, pest control and eradication

by slaughter, have achieved the complete elimination of some diseases from whole countries and large areas of continents. Vast herds of healthy animals can now be reared where previously a few weakly and diseased animals were all that vast tracts of land could produce. The attacks on rinderpest and trypanosomiasis in Africa, the elimination of rabies, glanders, rinderpest, bovine pleuropneumonia and of tuberculosis (anticipated for 1961) in Great Britain, are examples. The contagious abortion, and swine fever vaccination schemes, the wide use of canine distemper prophylactics and the anti-anæmia protective administration of intramuscular iron injections to new-born piglets are all signs of an increased awareness of the value of preventive medicine.

However, preventive measures are not always successful, and once disease has overtaken an animal curative measures must be applied. These may be surgical or medical, the latter being the concern of this book.

Curative medicine can be *rational* or *empiric*. By rational medicine is meant the use of therapeutic methods which are founded on a knowledge of normal physiological processes, of abnormal physiological processes (physiopathology), and on a knowledge of the pharmacological actions of drugs. Empiric methods, of necessity still used in practice because of our incomplete knowledge of many of the vital body processes, are not founded on a comprehensive understanding of the condition under treatment and the drugs in use, but on experience and tradition, which in themselves are excellent aids to correct diagnosis and treatment but are dangerous if unsupported by basic scientific principles. The endeavours of all physicians should be concentrated on a correct diagnosis of the disease or condition, followed by the application of specific remedial measures. Unfortunately, knowledge of disease processes and drug pharmacology is frequently incomplete and non-specific or symptomatic treatment must be applied: this treatment of symptoms alone verges on empiric therapy. Also, in veterinary medicine more than in human medicine, treatment is conditioned by economic factors, and although specific therapy may be possible, symptomatic treatment may be necessitated because of the high cost of the specific therapeutic agent.

It is important not to forget that drug therapy alone is rarely able to achieve an absolute cure without adequate and skilled nursing. In many cases, especially with small animals, meticulous and sustained nursing has achieved a cure when drugs have been of no value. On the other hand, unskilled and misguided nursing can equally destroy the good that rational therapy achieves. It is therefore important to impress upon owners the necessity of providing care and attention, and also to make sure that they understand what nursing is required and how it should be carried out.

When rational methods are applied to curative medicine there are several stages of examination, observation and deduction which must be passed through before reaching the point of drug administration. Each of these stages represents a whole field of study.

A correct diagnosis is the essential basis for correct prescribing. A knowledge of disease symptoms is, in turn, required before this diagnosis can be made, for symptoms betray to the trained physician the abnormalities of process and tissue which lie hidden under the skin. (*Symptoms* is a term used to describe the abnormalities reported verbally by the human patient, while the term *signs* was reserved for the visible indications of disease. In veterinary medicine these distinctions are obviously more academic than practical.) It follows that to trace the cause of these symptoms the physician must have an understanding of *tissue pathology*, changes of organ and cell structure, and also of *functional or metabolic pathology*. This pathological knowledge must itself be founded on a study of normal tissue—*macroscopic and microscopic anatomy*—and on a study of normal metabolism which is *physiology*. Anatomy and physiology in their turn are founded on a study of 'the basic' sciences, *biology*, *chemistry* and *physics*.

But all this knowledge is nothing unless it is allied to acute powers of observation, to an ability to appreciate and interpret the findings of manual examination but, above all, to an ability to correlate all the details discovered during examination of the patient and, with the aid of previous experience, to draw the correct conclusions: these attributes constitute the art which is the inseparable companion of the science of veterinary medicine.

When a diagnosis has been achieved the next decision to be made concerns the choice of treatment. This will incorporate measures which may fall within the sphere of *hygiene* and also of *animal husbandry*; the former discipline concerns the housing and control of the living conditions, whereas the latter relates to the feeding, breeding and rearing of animals. It will be seen that advice on nursing is closely concerned with these two subjects. And finally there must be a decision on the drug to be used and the method of administration, which are respectively the concern of the related subjects of *pharmacology* and *therapeutics*.

Pharmacology, or pharmaco-dynamics, is defined as the study of the effect of drugs on the structure and metabolism of normal tissues. The study of the actions of drugs under laboratory conditions has been termed *experimental pharmacology* whilst the study relating to the effects of drugs on normal and diseased humans and domestic animals has been termed *applied pharmacology*.

The pharmacology of a drug may be detailed in various sections which deal with both external and internal actions: details of absorption and also details of the incidence of certain pharmacological phenomena which are defined below.

1. *Cumulation* is a characteristic of all drugs which are excreted at a slower rate than they are absorbed; by this means, if administration of normal, or even low doses, of a cumulative drug is prolonged, there is a gradual build up of tissue and blood concentrations of the drug until

the levels reach toxic proportions. Cumulation is a normal attribute of drugs such as arsenic, strychnine and bromide, and prolonged administration of normal doses of any of these compounds will eventually lead to the incidence of toxic symptoms. However, if a slowing of the detoxication or excretion rates occurs due to inflammation of the liver (hepatitis) or kidney (nephritis), respectively, it is possible for almost any drug to assume cumulative characteristics: for this reason greater care should always be taken in assessing the size of the dose and the frequency of administration of any drug administered to an animal in which detoxication and excretion are impaired.

2. *Idiosyncrasy* is defined as an abnormal response of an animal following the administration of a therapeutic substance. This idiosyncrasy may be inherent or acquired; the latter is usually an individual idiosyncrasy, whereas the former may be common to a whole breed or species. Unusual reactions are exemplified by the hyperexcitability of cats following the administration of morphine, and by the allergic response of individuals to certain antibiotics.

Susceptibility is a type of idiosyncrasy in which an animal, breed, or species, exhibits a response which is exaggerated in degree but normal in character following the administration of normal doses of a drug. This may be a species susceptibility, as with rabbits and cocaine, or an individual susceptibility such as that shown by some dogs towards morphine or strychnine: an age susceptibility is typified by the prolonged narcosis which follows pentobarbitone sodium anæsthesia in very young calves (up to one month of age), whilst a conditioned susceptibility is shown by racing greyhounds which are anæsthetized by far less thiopentone sodium when in racing condition than when out of training and in fat condition.

Tolerance is an idiosyncrasy which may be inherited or acquired and consists of a reaction following administration of a drug which falls short of that normally anticipitated from the dose given. One of the best examples of inherent tolerance is that of rabbits to atropine and related alkaloids, which is due to rapid destruction of those alkaloids after absorption: the classical example of acquired tolerance is that acquired towards arsenic following prolonged oral administration of small doses, so that eventually even lethal doses can be administered by mouth without causing undue disturbance; this is reputed to be the result of a 'mucosal block' whereby the mucosa refuses to absorb the ingested chemical, for an animal immune to oral dosing is still susceptible to parenteral dosing.

3. *Synergism* is a pharmacological phenomenon relating to the activity of combinations of drugs. If, when two drugs are used together, the action of the combination is greater than would be given by either when used alone in an amount equal to that of the combination, the two drugs are said to be synergistic: this may be said to be a case of one plus one making three. *Summation*, which has been confused with synergism, is defined as the simple addition of the effect of one drug to that of another

where one and one make only two. An example of synergism is the combination of penicillin and streptomycin in which the addition of a small quantity of streptomycin enables penicillin to overcome the acquired resistance of certain bacteria, and the action of, say, 9·0 mg. of penicillin plus 1·0 mg. of streptomycin is superior to that of 10·0 mg. of either penicillin or streptomycin alone.

Summation occurs if sodium and magnesium sulphates are combined as saline purgatives, when one pound of magnesium sulphate may be expected to give approximately the same result as a combination of half a pound of each. The dividing line between summation and synergism is not very precise.

The reverse of synergism may be encountered: if, for example, penicillin and chloramphenicol are combined in the same manner as that quoted for penicillin and streptomycin, the result is not an increase but a decrease in activity, an equal quantity of either antibiotic being more effective than the combination.

Potentiation is a related term which is applied to the occasion when one drug protects another and allows it to continue its action. This may be illustrated by reference to the action of physostigmine (eserine), an alkaloid which blocks the destructive effects of the enzyme cholinesterase and allows the action of naturally produced acetylcholine to continue far longer than normally: physostigmine is therefore spoken of as a parasympathetic potentiating drug.

4. *Incompatibility* is a term applied to drugs which should not be combined because of a mutual antipathy. The incompatibility may be of three kinds:

(a) Physical incompatibility in which the physical characteristics are such that they will not mix unless assisted by a third compound. Oils and water are the classical example.

(b) Chemical incompatibility in which a chemical reaction occurs on mixing the two compounds. Acids and alkalis, oxidizing and reducing agents, iron and tannic acid, are examples. This reaction may not be detrimental to the pharmacological action of the compound, but, as with the last mentioned combination, it may make it æsthetically unacceptable as a therapeutic agent. Iron plus tannic acid, of course, makes a blue-black ink.

(c) Physiological and pharmacological incompatibility occurs when drugs with opposite actions are administered simultaneously. Thus a purgative and an intestinal astringent would not be pharmacologically compatible if given together: likewise the simultaneous administration of strychnine and pentobarbitone sodium is impracticable because of their mutual antagonism. These pharmacological antagonisms are utilized in the treatment of poisoning.

These are the terms which are frequently used in describing the actions of drugs.

Therapeutics is concerned with the application of drugs in the treatment

of disease. Such details as the choice of drug, the route of administration, the form in which the drug is applied, and the frequency of administration, all come within the scope of therapeutics.

Posology is that discipline concerned with dosage of drugs, whilst *metrology* is the study of the scales of weights and measures.

Both posology and metrology are integral parts of the wider subject of *pharmacy* which is concerned with the compounding, standardization and dispensing of drugs. Also associated with pharmacy, and an essential part of it, is *pharmacognosy* which, literally, is the study of the recognition of drugs; it relates to a knowledge of the chemical and physical characters and the sources of drugs.

The old term *materia medica* was widely applied to the study of all factors relating to drugs, including their actions, and frequently included therapeutics.

Pharmacognosy is becoming of less significance to the physician, as more and more pharmacy is performed by the manufacturing drug houses and less and less by the veterinary surgeon, and a general understanding is all that is required—whereas a detailed knowledge of dosage, weights and measures, pharmacology and therapeutics is essential if the opportunity provided by an accurate diagnosis is not to be wasted.

CHAPTER 2

WEIGHTS & MEASURES: PRESCRIPTION WRITING

Introduction

IT IS essential that there should be a standard language common to both prescribers and dispensers. Formerly, when it was considered inadvisable to disclose the ingredients of medicines, all prescriptions were written in Pharmaceutical Latin—a relic of the days when Latin was the written language of the Arts and Sciences. Much ignorance and charlatanism was disguised by this means, but, as it is now more usual to explain the treatment to clients, there is no need for secrecy and to-day English is more widely used in prescription writing. Latin is retained for certain parts of prescriptions, mainly for ease and speed in writing but partly because it is picturesque.

The student should not be hypnotized by the mention of Latin, for the Latin normally used consists of abbreviations only, so that the word endings which change and cause difficulties can be omitted. In any case it is now recommended that unabbreviated English should be used for the major part of all prescriptions.

Appendix I gives a list of commonly used latinizations, excluding, of course, those of the individual drugs. Should the student wish to probe more deeply into pharmaceutical Latin there are several reference books available which deal very thoroughly with the subject: e.g. Sollman's 'Handbook of Pharmacology'. A short book is Trease's 'Aids to Pharmaceutical Latin'.

The increase in the use of English in prescription writing has occurred since the change of the Imperial standard system of weights and measures in 1878 from the Apothecaries to the Avoirdupois system. More recently a further change over to the continental Metric system has been encouraged with a view to international standardization, but so far this system has not been officially accepted in Great Britain. The B.P., however, now gives dosages in the Metric as well as in the Avoirdupois standard system. This means that in practice three different systems of weights and measures may be met and therefore a knowledge of the relationship of these systems is essential, for the conversion of weights and measures from one system to another is now required daily. The key to these conversions are the equivalents:

1 Kilogram (kg.) = 15,432 Grains (gr.) = 2·2046 Pounds (lb.)

and 1 Litre (l.) = 1·7598 Pints (pt.)

or 28·412 Millilitres (ml.) = 1 fluid ounce (fl. oz)

WEIGHTS AND MEASURES

Imperial

WEIGHTS (mass)

AVOIRDUPOIS SYMBOLS		APOTHECARIES SYMBOLS	
1 gr.	grain (granum)	gr. j	
	scruple (scrupulus)	℈j	= 20 grains
	drachm (drachma)	ʒj	= 60 grains
1 oz. = 437½ grains	ounce (uncia)	ʒviij	= ℥j = 480 grains
1 lb. (standard) = 16 oz. = 7000 gr.	pound (libra)	lbj	= ℔xij = 5760 grains

MEASURES (fluid)

1 m.	minim		mj
1 fl. dr.	fluid drachm	= 60 minims	fl. ʒj
1 fl. oz.	fluid ounce	= 480 minims	fl. ℥j
1 pt. (octarius)	pint	= 20 fluid ounces	Oj
1 gal. (congius)	gallon	= 160 fluid ounces	Cj

Metric

WEIGHTS (mass)

1 gamma (γ)	= 1·0 microgram	(μg.)
1000 gamma	= 1·0 milligram	(1·0 mg.)
1000 milligrams	= 1·0 gramme	(1·0 g.)
1000 grammes	= 1·0 kilogram (standard)	(1·0 kg.)

MEASURES (fluid)

1 microl (λ)	= 1·0 microlitre	
1000 microls	= 1·0 millilitre	(ml.)
1000 millilitres	= 1·0 litre (standard)	(l.)

Approximate Imperial—Metric Equivalents

WEIGHTS (mass)

1 gr.	= 65·0 mg.	100·0 mg.	= 1½ gr.
60 gr.	= 4·0 g.	1·0 g.	= 15 gr.
1 oz. (avdp.)	= 28·0 g.	100·0 g.	= 3½ oz. (avdp.) = 3⅓ oz. (apoth.)
1 oz. (apoth.)	= 30·0 g.	1·0 kg.	= 2⅛ lbs. (avdp.)

MEASURES (fluid)

60 m.	= 3·5 ml.	1·0 ml.	= 15 m.
1 fl. oz.	= 28·5 ml.	100·0 ml.	= 3½ fl. oz.
10 fl. oz.	= 284·0 ml.	1·0 l.	= 1¾ pts.

Household Measures

A drop	= 1 minim	
A teaspoonful	= 60 minim	
A dessertspoonful	= 120 minim	
A tablespoonful	= 240 minim	= ½ fl. oz.
A wineglassful	= 2 fl. oz.	
A whisky or lemonade bottle	= 27 fl. oz.	

Weights and Measures

The Apothecaries' System (Imperial)

The wide use of the earliest of the three systems, the Apothecaries, persists mainly because the majority of pharmaceutical balances are supplied with apothecaries' weights. This type of weight, in various sizes from ¼ grain to 240 grains, is provided because the Avoirdupois system recognizes no denomination between one grain and one ounce.

It is important to indicate clearly, by the way in which the prescription is written, which system of weights and measures is intended. In the Apothecaries' system the weight denomination is usually expressed as a symbol and is followed by the number in Roman numerals. These numbers should have a line drawn over them and above this, to serve as a double check, a dot should be placed for each unit numeral. If the last numeral is a unit then it should be prolonged downwards to indicate that it is the last figure, viz.:—Eight Apothecaries' Ounces—$\overline{\overline{\text{ʒ viij}}}$. Fluid measures are similarly written except that the symbols are preceded by the letters 'fl.' viz.:—Seven fluid ounces—fl. $\overline{\overline{\text{ʒ vij}}}$.

Apart from the half grain which is written $\overline{\text{ss}}$, fractional quantities are written normally—gr. ⅛.

It should be noted that although the unit weight of one grain is identical in all Imperial systems (including the jewellers' Troy system) the Apothecaries' ounce and pound differ considerably from the corresponding Avoirdupois weights.

A recent official suggestion that arabic figures and letter abbreviations should be used in preference to Roman numerals and symbols, has added further complications.

The Avoirdupois System (Imperial)

The Avoirdupois system is the official system of weights and measures in the United Kingdom and is tied to the *standard pound*. This pound is equivalent to 7000 grains or 16 ounces. It will be seen that each ounce is therefore equivalent to 437·5 grains and is considerably smaller than the

Apothecaries' ounce. This is why it is so essential to indicate the system of weights in use when writing prescriptions. Avoirdupois weight numerals should always be written in arabic figures and these should be followed by the correct abbreviations:

One fiftieth of a grain (avdp.) = $\frac{1}{50}$ gr.
Sixty grains = 60 gr.
Two ounces = 2 oz.
Two pounds = 2 lb.

It is inadvisable to use other abbreviations than these.

Fluid measures are identical in both the Apothecaries' and Avoirdupois systems, but the rules relating to the positioning and types of symbols and figures used in prescription writing follow those for the weights of the corresponding system.

Note: American Standards are not the same as the corresponding Imperial Standards and consequently the weights and measures are not identical.

The Metric System

The Metric system is the Continental system of weights and measures which, it is suggested, should be adopted as the international standard system. Weights and measures are expressed in multiples of ten, the standards being the Kilogram and the Litre for mass and fluids respectively.

It is essential in the Metric system that the decimal point should be strongly indicated, the absence of numerals before or after the point being shown by a nought. The B.P. also recommends that in prescriptions a capital 'G' should be used to indicate 'grammes' so that confusion with 'gr.' for 'grains' should not arise. The 'ml—millilitre—$\frac{1}{1000}$ litre' has superseded the 'cubic centimetre—c.c.' in fluid measures. Numerals should always precede the weight or measure abbreviation:—

45·0 G.	or	45·0 ml.
2·0 kg.	or	2·0 l.
0·4 G.	or	0·4 ml.

Many wholesale and manufacturing chemists are converting to the Metric system and most new drugs have their dosages expressed in metric weights and measures

Approximate Equivalents

These are convenient for rapid conversion of quantities from the Imperial to the Metric system and vice-versa. They should not be used where toxic drugs are involved.

Household Equivalents

These measures are only very approximate, but are useful to indicate *fluid* quantities to a client, and dosages on labels are usually expressed in these household measures.

On no account should these equivalents be applied as estimates of *mass* — volumes of equal weights solids naturally differ considerably according to their individual densities.

Calculation of Percentage Solutions

The calculation of the quantities required to make percentage mixtures of either solids, liquids, or solutions, is easy if the metric system is in use, for 1 gramme or 1 millilitre of solid or liquid A with 99 grammes or millilitres of solid or liquid B will make a 1 per cent mixture of solids or liquids. If either solid or liquid is measured by weight, the percentage mixture is indicated as W/W (weight in weight): if liquids alone are used and measured by volume the percentage mixture is represented by V/V (volume in volume): if a solid, measured by weight, is dissolved in a liquid, measured by volume, the percentage mixture is indicated as W/V (weight in volume).

If the avoirdupois system is in use, the situation is more involved. Weight in weight mixtures are straightforward in that, if 4·375 grains of a solid C are made up to 437·5 grains with solid D, a 1 per cent W/W mixture of solid C in solid D is given. A V/V mixture is also straightforward in that 4·8 minims in 480 minims is a 1 per cent V/V mixture. On the other hand, as the fluid ounce contains 480 minims, a 1 per cent W/V mixture of solid C in liquid E requires 4·375 grains of solid C to be dissolved in a small quantity of liquid E of which, after the solid is dissolved, more is used to make up the volume to 1 fluid ounce (480 minims). This means that 1 grain is dissolved in approximately 110 minims (i.e. 480 ÷ 4·375). If the liquid is water, these same proportions hold good for W/W percentage solutions, for 1 fluid ounce of water weighs 437·5 grains.

Prescription Writing

With the extensive use of expensive modern drugs—sulphonamides and antibiotics in particular—'treatment by prescription' is becoming much more common in veterinary practice.

Although the deciphering of badly written and poorly expressed prescriptions is a skilled art very ably practiced by dispensing chemists, the *Poison Regulations* and *Dangerous Drugs Acts* (D.D.A.) lay down strictly defined requirements and recommendations. Veterinary prescribers should conform to these standards so that interpretation may be rapid, easy and correct, resulting in minimum delays for the client in obtaining the medicines. Writing should always be neat and legible.

Printed prescription forms are permissible and save a great deal of time. These will usually have as a heading the business name and address of the prescriber, and possibly the '℞' sign. At the bottom, the words 'For Animal Treatment Only' may be printed and other refinements may be added as the individual wishes.

Prescription Essentials

What are the details essential to a correctly written prescription?

1. The *Name* and *Address* of the *Prescriber* are required for reference in cases of doubt or mistakes.

2. The *Date* must be included for the same purpose, and a prescription reference number may also be included.

3. The *Superscription.* This is the symbol ℞ (the Roman symbol for Jupiter and originally intended to invoke his blessing and aid in the action of the drugs), which is now the symbolic order to the dispenser to 'take' the drugs indicated and is held to mean *recipe—take thou.* If full Latin names are used it should be noted that this symbol is followed by drug names in the genitive case where definite quantities are stated, and by the accusative where no definite quantity is stated e.g.:

Of powdered gentian 1 oz.—Pulveris Gentianæ 1 oz. or, Water up to 1 fluid ounce—Aquam ad 1 fl. oz.

4. *The Inscription.* This consists of the names and quantities of the drugs written in full English or, more quickly, in Latin abbreviations. Where an official preparation is to be dispensed this should be indicated by the letters (B.Vet.C.), (B.P.) or (B.P.C.) respectively. Indications of percentages and individual drug quantities are not then necessary e.g. Unguentum Sulphuris B.P.—Sulphur ointment. There would be no need to indicate that each kilogram of the ointment should contain 100·0 g. of sulphur and 900·0 g. of Unguentum Simplex (Simple Ointment), which in turn will consist of 50·0 g. wool fat, 100·0 g. of hard paraffin and 850·0 g. of white or yellow soft paraffin (petroleum jelly) per kilogram.

Where proprietary preparations are prescribed it is usual to state the proprietary name and the manufacturer.

> The prescriber can use whichever system of weights and measures he prefers *providing the dispenser sees exactly what is intended.*

It should, however, be remembered that the statutory system is the Avoirdupois, and this system should be used unless the drug is available only in metric quantities.

5. *The Subscription* is that part of a prescription which directs the dispenser during the compounding of drugs. Latin abbreviations are usual, although full English is not precluded: e.g. M. et div. in pulv. 12.—Mix and divide into twelve powders. Ft. pulv. 1. Mitt. 12.—Make one powder. Send twelve.

6. *The Signature*, symbolized by the abbreviation Sig. which is included on *all* prescriptions immediately below the subscription, is an anglicization of *signetur*—Let it be labelled. It will therefore instruct the dispenser in all the details to appear on the label as directions to the owner e.g.:

> Sig. *For Animal Treatment Only*
> *Powders For Cow: Ear No. H.E.* 9254
> One powder to be given twice daily in food.

Latin abbreviations may again be used but, where scheduled drugs (those controlled by the Poison Regulations and Dangerous Drugs Acts) are included, no latinization or abbreviation of '*For Animal Treatment Only*' is allowed. Latin translations of many directions are very involved, so that inaccuracies are more likely, and it is therefore recommended that, in all but the simplest of directions, unabbreviated English should be used.

7. *Prescriber's Signature and Qualifications.* These are needed for reference and to indicate the personal acceptance of responsibility in the prescribing of the drugs, for where 'controlled' drugs are incorporated a preparation may not be sold except on the direction of someone officially entitled to prescribe under the Statutory Regulations previously mentioned —the Poison Rules and D.D.A.

8. *Non-repet.* Where a prescription does not contain a controlled drug that prescription may be dispensed as frequently as the client wishes, *unless* instructions are included to prevent this. The Latin abbreviation *non-repet.*—let it not be repeated—will tell the chemist to impound the prescription, so preventing further dispensings. Should a number of repeats be advisable then the prescriber may indicate the number of repeats required, and if he so wishes, the interval between dispensings, or even specific dates.

For D.D.A. drugs special regulations are in force regarding repeat dispensings. These are indicated in the section of Part IV which deals with this Act.

The following prescriptions are examples incorporating the information given so far.

Practice Name and Address	A. Veteran & A. N. Other, M's.R.C.V.S. 270/272 High St., Manderton, Sussex.
Date	10.9.60.
Script Ref. No.	Ref. No. 1235
Superscription	R
Inscription	Acid Sodium Phosphate 120 gr. Sodium Chloride 2 oz.
Subscription	Fiat pulv. 1. Mitte 6.
Signature	Sig. For Animal Treatment Only Powders for Roan Cow, Ear No. H.125 One powder to be given as a drench in one pint of warm water morning and evening.
Veterinary Surgeon and qualifications	A. Veteran, M.R.C.V.S.
Client's Name and Address	L. Gentle, Castle Farm, Broadbeacli, Sussex.
Repetition instructions.	Non Repet.

Using Latinization and apothecary symbols this would appear as below:—

10.9.60.
Ref. No. 1235

A. Veteran & A. N. Other,
M's.R.C.V.S.,
270/272, High St.,
Manderton, Sussex.

℞ Sod. Acid. Phosph. $\bar{3}\ddot{i}\bar{j}$ or gr. 120
Sod. Chlorid. $\bar{3}\ddot{i}\bar{j}$ or oz. 2.

Ft. pulv. 1. Mitte $\bar{v}\dot{j}$
Sig. For Animal Treatment Only
Powders for Roan Cow, Ear No. H.125
Pulv. 1 in haust. $\bar{c}$ ʒ$\dot{j}$ aq. ferv. det. M. et N.

L. Gentle,
Castle Farm,
Broadbeach,
Sussex.

A. Veteran,
M.R.C.V.S.

Non Repet.

This form is only a recommendation which follows that given in the Poison Regulations and D.D.A., and need not be strictly adhered to providing the details mentioned are included, but it should not be forgotten that ease in reading and dispensing will be helped by uniformity of style.

CHAPTER 3

PRESCRIPTION BUILDING

(i) INSCRIPTION AND SUBSCRIPTION

Inscription.—The Choice of Drugs and Dosages

Choosing Drugs

THE hardest part of prescription building and the one which causes the student most trouble is the selection of drugs. This selection becomes easier with increasing experience. It should be based on a rational diagnosis of the disease according to a knowledge of disease physiopathology, correlated with a knowledge of the applied pharmacology of drugs. Assuming this knowledge and also a decision on the route and method of administration of the medicine, there are certain historical principles which are of use in choosing a correct combination of drugs, should a combination be required. Specific drugs, that is drugs which are particularly active against the causal agent of a specific disease, should be used if available, but where these are not available prescriptions should be as simple as possible.

It is usual to build an inscription on four main pillars:

1. *The basis* or main active agent of the prescription,
2. *The adjuvant* which has a complementary effect,
3. *The corrective* which counters any undesirable tendencies of the first two agents, and
4. *The vehicle* or excipient, usually a bulky agent but often therapeutically inert. It may, however, possess qualities which make a corrective unnecessary and often has a flavour if used internally. The flavour may disguise objectionable tastes and should be acceptable to the species to which the patient belongs, e.g. glucose, honey, treacle for dogs, cats and pigs; liquorice and aniseed for ruminants and horses.

These four guiding principles are based on a hypothesis attributed to Asclepiades, a Grecian physician who settled in Rome during the second century B.C. This hypothesis suggests that a medicine should '*Cure Quickly, Safely, and Pleasantly*'. These words correspond directly to the four divisions just mentioned.

An example of a prescription built according to these suggestions is that of a purgative horse ball, 'physic ball', in common use. This is an old prescription and the quantities are therefore expressed in the Apothecaries' system, as they were originally:

℞

Basis	Aloes Barb.	$\overline{3}\dot{\overline{iv}}$
Adjuvant	Hydrarg. Subchlor.	$\overline{3}\overline{ss}$
Corrective.....	Zingib. Pulverat.	$\overline{3}\ddot{ij}$
Vehicle	Sap. Moll.	q.s. (Quantum Sufficiens—a sufficient amount.)

Ft. bol. 1.

In this ball the aloes will do most of the work and will stimulate the large intestine after a delay of 12–18 hours. The adjuvant calomel–mercurous chloride—assists by immediate irritant stimulation of the small intestine and, if it reaches the large intestine in sufficient quantity, of that organ also.

Both these agents may intensify 'griping' or 'spasm' pain, which results from simultaneous contraction of circular and longitudinal muscles in the same length of intestine. This spasm, a common occurrence in 'colic', can be partially relieved by the corrective—ginger.

Soap is incorporated as a bulking vehicle but it may, by its irritant properties, act as a second adjuvant. This is a factor to be considered in southern England where it is accepted that horses are much more susceptible to aloes. The additional effect of the soap may result in excessive or 'superpurgation', a condition not easily countered.

Another example is that of a gastro-intestinal sedative very useful in the treatment of simple disturbances of the digestive system in dogs.

℞

Bism. Carb.	5 gr.
Sod. Bicarb.	3 gr.
Mag. Trisil.	10 gr.
Dextros.	20 gr.

Ft. pulv. 1.

Bismuth carbonate, a relatively slow acting antacid, is assisted by the rapidly acting bicarbonate. Both these, on meeting the acid in the stomach, release carbon dioxide gas which distends that organ. This distension results in the reflex secretion of further acid and other gastric juices. This is the so-called 'alkaline stomachic' action. To counter this secondary acid production, magnesium oxide or trisilicate can be included, both of which act as antacids without secondary stimulation. The trisilicate has other properties such as toxin adsorption and a mucosal protective action by mechanical coating. The glucose, besides adding bulk, has a sweet flavour, a soothing, protective and lubricant—demulcent—action. It is also a readily available source of energy.

Choosing Doses.

Drug dosage tables may be memorized, but this tedious task is unnecessary. It is far better to correlate the toxicity and activity of drugs with

certain dosage ranges. A very toxic or highly active drug will normally be administered in very small doses, whereas the dosages of the least toxic and inert drugs will often be determined by the volume of the drug that can be administered at one time. The majority of dosages will fall somewhere between these two extremes.

Using the horse as the standard animal most dosages of solid drugs will fall into four categories, the first for hypodermic injection, the others for oral administration.

1. Below 2 grains: Most pure alkaloids and their salts fall into this group: strychnine, arecoline, physostigmine and atropine.

2. 2–60 grains: Low in this range will come the less active pure alkaloids and the toxic minerals, whilst other less active plant derivatives and pharmaceutical extracts will be nearer the top of the range: morphine, codeine, arsenic and antimony, caffeine, dry and soft extracts containing toxic alkaloids, e.g. dry extracts of belladonna and opium.

3. 60 grains–1 oz. This group will incorporate the majority of drugs in common use such as the less toxic minerals and the crude unconcentrated vegetable compounds: ammonium carbonate, ferrous sulphate, tannic acid, aloes, powdered belladonna and ginger.

4. Over 1 oz. The relatively non-toxic drugs which will often act as vehicles and bulking agents will come into this group. The maximum for the inert insoluble powders is about 2 oz. but the doses of soluble drugs may be much higher: chalk, kaolin, fenugreek, magnesium sulphate, sulphur.

These groupings are obviously only an approximate guide to which there will be exceptions, but, with a knowledge of the relative toxicity and activity of a drug, its dosage range may be determined accurately enough to prevent dangerous overdosage, e.g.:

(a) *Powdered liquorice;* this is a crude insoluble powdered plant root with no real toxicity. Its dosage will therefore be in group 4, i.e. 1–2 oz.

(b) *Pilocarpine nitrate* is an extremely active pure alkaloidal salt and its dosage will therefore fall in group 1—less than 2 gr.

The dosages of drugs in regular use will soon become familiar, but should the use of a drug with an unfamiliar dosage be contemplated, reference to a posological table would be a wise precaution. Remember that, with few exceptions, low doses can always be increased, but an overdose of a drug may lead to its recovery by post-mortem analysis. Although this should not be used as an excuse for laziness, remember also that pharmacists are trained to scrutinize prescriptions carefully and to verify any abnormally high dose of a poisonous substance. Should such a dose be included intentionally in a prescription, it may be time-saving to indicate your intentions to the dispenser by following this dose by the letters Q.R. (*Quantum recte*—the correct quantity.)

Species Dosages. Having established the dose of a drug for the standard

animal it is possible to estimate the dosage for the other species by reference to the following table:

Horse ≡ 1 Cow ≡ $1\frac{1}{2}$ Sheep and Goat ≡ $\frac{1}{8}$ Pig ≡ $\frac{1}{8}$
Dog ≡ $\frac{1}{10}$ Cat ≡ $\frac{1}{32}$

These ratios are only approximate and must not be strictly applied to toxic drugs, particularly those to which certain species are susceptible:

Maximum oral dosage of strychnine hydrochloride for a horse = 1 gr.
Maximum oral dosage of strychnine hydrochloride for a dog—(susceptible species) = $\frac{1}{60}$ gr.

Factors involved in the establishment of species doses are numerous:

(1) *Size.* Obviously smaller species will usually need smaller doses, but those doses do not decrease in direct proportion to weight decrease. Dose calculations are said to be accurate when related to body volume, and therefore surface area. It is more convenient to work on a weight basis, but surface area is greater in proportion to weight in small species and the dosage of a drug will be correspondingly larger. The same factors influence breed dosage within a species and this provides an illustration for both groups. Pentobarbitone sodium dosage for small dogs may be estimated at a rate of $\frac{1}{4}$ gr. per lb. body weight, and for large dogs at $\frac{1}{7}$ gr. per lb. body weight. Thus a 50 lb. dog should need about 7 grains for general anæsthesia, whereas a 5 lb. dog should need about $1\frac{1}{4}$ gr. This latter dose is much larger than would have been estimated according to a common scale.

(2) *Alimentary anatomy.* The contents of ruminant stomachs cause great dilution of drugs and the relatively slow passage of food into the abomasum and intestines means that absorption of a drug dose will be slower but more complete. Providing that effective tissue concentrations of the drug can be achieved, this factor can be very helpful in maintaining continuous treatment and reducing the number of doses administered in a 24 hour period. This applies particularly to treatment with sulphonamides.

Oral doses of a drug are larger for cattle than for horses because of this dilution factor. Parenteral (i.e. hypodermic) doses are identical weight for weight.

(3) *Physiological variations* may be responsible for some differences between the species doses. Sodium chloride is not a suitable laxative or purgative for the vomiting species—pig, dog and cat, because the doses needed to achieve this action are considerably greater than those which produce emesis.

(4) *Susceptibility* has already been mentioned (see p. 7).

Individual Dosages. The dosage of a particular drug for the species having been established, the dose for a particular patient must be decided and it will be found that this will vary according to certain characteristics and circumstances of that individual:

1. *Weight*. Most doses are calculated according to weight but as has already been pointed out this is only for convenience and is not strictly accurate, though it is sufficiently so for ordinary purposes.

2. *Age*. In general young animals and old animals will need proportionately less than the prime adult, with a few exceptions. Factors similar to those described relative to size under '*species dosage*' are responsible for this, but susceptibility and, in certain cases, tolerance—vide purgatives in old animals—are also involved.

3. *Sex*. In human medicine it is usual to prescribe smaller doses for females, but this is mainly related to an average lower weight and in animals there is rarely any need to make any distinction.

4. *Physiological Variations*. It has already been pointed out that pregnant animals must not receive strong purgative doses. Choice of drug and dosage should also be carefully considered in lactating animals, partly because of the danger of milk taint and partly for fear of reducing milk yields. Purgatives and diuretics provide many examples. Working animals in hard condition will cope with larger doses than animals on poor diets and those out of training.

Oral doses will also be affected by the amount of food in, and the activity of, the stomach and intestines. Should a drug be administered immediately after a meal a larger dose will be needed to exert a rapid effect than if the intestines were empty, mainly because of the dispersal of the drug in the food and the consequent slowing of absorption.

Some drugs should not be administered orally immediately before or after meals, because the strong acidity of the stomach may destroy the drug. Pancreatic extract, hexamine and penicillin are examples of such drugs. The dosage of these, however, may be increased to allow for a moderate amount of destruction, though a delay of a few hours and administration when the pH is nearer neutral would achieve the same effect.

5. *Toxic State*. Animals in low condition and with advanced toxæmia should receive smaller doses than healthy normal animals. Their greater susceptibility is related to detoxication by the liver and elimination by the kidney, the function of both being materially reduced by toxæmia and septicæmia. There are important exceptions. With the majority of chemotherapeutics, and particularly with the sulphonamides, the more severe the illness the higher the dosage should be, providing the drug will not intensify the damage to liver and kidney. This is because the activity of these drugs is directly related to the number of bacteria present—more bacteria, more drug.

6. *Drug Form*. Should a drug be administered in solution, or a normally insoluble drug be given in a soluble form, absorption will be more rapid and complete. Dosages may need to be reduced to compensate for this, though frequency of dosing may have to be increased, for the sooner the drugs reach the tissues the sooner will they be excreted and the tissue concentrations fall below an effective level.

7. *Regional and Climatic Effects*. It is known that animals in northern

Britain are less affected by certain drugs than are those in the south. The effect of the purgative drug *aloes* is the accepted classical example.

Absorption and metabolism in tropical areas is more rapid and doses of toxic drugs in particular should be smaller, though administered more frequently. Similarly, drugs which depend on volatilization will achieve high vapour concentrations very rapidly in hot climates or in hot weather, but slowly in cold climates, although relative humidity is involved in addition to temperatures. The initial dosage of such volatile anæsthetics as chloroform and ether will in consequence be much less in hot climates.

Vehicle Quantities. All the factors so far mentioned will be involved in deciding the doses of the active solids and fluids detailed in the Inscription, but there are additional factors which will influence the quantity of vehicle needed.

Solid Vehicles or Bulking Agents. For *powders* the quantity of vehicle will be determined by the volume of powder capable of being swallowed by the individual patient. Any discrepancy between the volume of the active drugs and the optimum total volume for the species or individual will be made up by the necessary amount of vehicle.

The main species in which powders are administered directly and not in food are the dog and cat. In these species the approximate maximum weights are 120 grains and 30 grains respectively, though these are rare extremes, 30–40 grains and 10–15 grains being more normal. In cattle, powders of up to 4 ounces have been recommended.

Naturally the volume of a compounded powder will vary according to the specific gravities of the drugs included, but it is usual to determine the doses of the active drugs first and then add sufficient bulking agent to make each powder up to the desired volume. Obviously a powder containing light but bulky active drugs will need little if any bulking agent, whereas if the drugs are heavy with small volume, a much larger amount of bulking agent will be needed to bring the total powder up to the optimum size; e.g. light carbonate and oxide of magnesium need little bulking agent, but the heavy carbonate and oxide, being about 3½ times less bulky, need a proportionately larger amount of bulking agent.

Toxic drugs, which are administered in small doses, particularly to dogs and cats, always need large quantities of bulking agent to bring the volume up to an easily administered quantity, e.g.:

℞
Arsenic Trioxide $\frac{1}{100}$ gr.
Lactose to 5 gr.
Ft. pulv. 1.

For ointments the vehicle quantity will depend on the required concentration of the active ingredients.

Fluid Vehicles. With mixtures, the fluid vehicle quantity calculation is a little more complicated. The size of the container, which should always be completely filled by the medicine prescribed, rigidly controls the total bulk. These bottles are manufactured in ½, 1, 2, 3, 4, 6 and 8 fl. oz. sizes for general use, and 10, 12, 16 and 20 fl. oz. bottles are also available. The amount of vehicle used for each dose put into the bottle will therefore be determined by the number of doses to be dispensed, and by the volume of the insoluble solids or fluid medicines in each dose. The vehicle is used to bring up the volume to a suitable quantity for filling the container. It is usual to include extra doses of the medicine should those required for the treatment not fill the most suitably sized bottle. These extra doses will allow for wastage.

The volume of a dose of fluid for oral administration varies, maximum quantities for single doses being:

Horse and cow: ½–1 pint; sheep and pig: 2–4 tablespoonfuls;
dog: 1 tablespoonful; cat: 1 dessertspoonful.

It will be seen from this that small animal doses may be dispensed diluted, ready for administration, whereas it is more usual to dispense medicines for farm animals in concentrated form to be diluted by the owner before administration.

So far, single doses of individual drugs have mainly been considered, all of which, added together, make one dose of a compound medicine. The number of doses of the compounded drugs must now be decided, for until this has been done the Inscription cannot be completed nor the subscription or signature written. To complete the Inscription the frequency and duration of administration, which will be considered in the next chapter, must be determined and the individual drug doses must be multiplied by the number of doses of the compounded medicine needed. *This calculation must not be left to the dispenser.*

The Subscription

There are few complications in writing the subscription, for which there exists a restricted number of Latin phrases and words. It has been said earlier that these indicate clearly and concisely the manipulations to be carried out, the type of pharmaceutical preparation to be made and the quantity or number of packs to be sent. The latinizations are contained in Appendix 1.

CHAPTER 4

PRESCRIPTION BUILDING

(ii) THE SIGNATURE

THE Signature indicates to the dispenser what is to be written on the label. It will consist of the directions to the client: indication of the patient's identity, of the quantity of drugs to be given, in what form or by what medium, by what route, how often and for how long these drugs are to be given. Certain subsidiary information may also be included such as whether the medicine contains poison, or, should the prescription contain easily precipitated drugs, the words, 'Shake the bottle.'

These details must be considered individually.

Identity of the Patient

The words 'For Animal Treatment Only' are required by law to appear only on prescriptions containing 'scheduled drugs', but it is a wise precaution to include this in all '*signatures*', and hence on all labels. No confusion can then occur between human and veterinary medicines should the two groups be kept in the same cupboards, as they may well be where the animal involved is a household pet. Even greater safety follows if the particular animal is identified, e.g.:

Sig. For Animal Treatment Only.
Mixture for Fox Terrier.

The Quantity of Each Dose

This will have been decided as described in Chapter 3, and will appear on the label expressed in units easily measured by the client. Fluid and semi-fluid medicines will have doses expressed in household measures. Occasionally powders will also be expressed in terms of teaspoons or tablespoons, but unless mass therapy is involved, as with piperazine treatment of pigs and poultry, it is wiser to weigh and wrap each powder dose individually. No discrepancy can then occur due to misinterpretation of instructions; a level teaspoonful can contain widely differing quantities depending on whether the powder is packed closely or not.

Route of Administration

The choice of the route of administration will be governed by several factors.

Speed of Effect. Where a systemic disease is of an acute and severe nature rapidity in onset of drug action may be an important factor in

saving the patient's life. Rapidity of action can be considerably affected by variation of the administration route, although the solubility, absorption rate and similar properties of the drug itself will also have an important effect.

Drug absorption and distribution through the tissues take place more slowly following oral dosing than when administration is parenteral, particularly if intravenous injections are used. This is well illustrated by the simultaneous use of intravenous and oral administration of sulphonamides. The intravenous injection of a soluble sulphonamide gives immediately effective blood and tissue levels which are maintained by the drug absorbed later from the dose administered orally. Should the drug be administered only orally, effective blood and tissue levels would not be achieved until possibly six to eight hours after administration.

It follows that where treatment of systemic conditions is urgently required parenteral (hypodermic) injection is indicated, but where no urgency is involved dosing by other routes may be adequate.

Localized conditions, whether internal or external, are of course not included in this generalization.

Compatibility of Route and Drug. It must be remembered that some drugs may not be administered by certain routes:

(1) Because the drug may be dissociated and destroyed as with the oral administration of adrenaline, parathyroid extracts, unbuffered penicillin G., and insulin.

(2) Because absorption may not take place or may be insufficient and therefore ineffective. Streptomycin is not absorbed from the alimentary canal in amounts sufficient to affect the course of a systemic disease, nor is sufficient passed into the intestine from a parenteral injection to influence the course of an intra-alimentary disease. Many antibiotics are not absorbed from the alimentary tract of poultry.

(3) Because a drug may be toxic when administered by some routes.

(a) Potassium preparations are not normally given intravenously owing to the excessive stimulant action on the heart which may cause rapid death from heart failure due to paralysis.

(b) Chloral hydrate, formalin and soluble sulphapyridine are too irritant for any parenteral route but the intravenous one, and, should they be injected outside a vein, will cause tissue destruction and sloughing.

Compatibility of Route and Disease. The nature of some diseases precludes administration of drugs by particular routes. In no case of a respiratory disease should drugs be given orally except in the form of electuaries, for any further embarrassment of the animal's breathing will cause distress and the animal will struggle. There is then great danger that the patient will inhale some of the medicine and so cause gangrenous inhalation pneumonia, which is invariably fatal.

Compatibility with the Patient's Temperament. The patient may be frightened and wild so that it is impossible to apply restraint or dangerous

to attempt administration by a particular route. Thus it may not be possible to hand-ball a vicious horse or to give an injection by the intravenous route to a hysterical dog.

Convenience to Owner and Veterinary Surgeon. Administration by a particular route may suit neither the farm nor home routine, nor the practice routine of the veterinary surgeon. Few owners care to attend at a surgery three or four times a day nor would a practitioner relish a fifteen mile journey twice daily in order to give one injection on each occasion.

Economic Factors. A treatment which can be applied at home by an owner, supervised by infrequent visits of, or to, a veterinary surgeon will usually be far more economical in time and money to both owner and physician than daily or twice daily visits by the veterinary surgeon.

The Oral Route. This route of administration is probably the one most frequently used under normal conditions.

Its chief recommendations are the ease of owner administration, adaptability to farm and home routine, and the fact that no penetration of skin or mucosa takes place, which means that no introduction of bacteria into the tissues is possible.

The main drawbacks are (1) the possibility of 'choking' the animal and causing pneumonia if liquid preparations are used, and (2) the variability of degree and speed of absorption. Added to these factors is the danger of being bitten, though this should be a rare feature if animals are capably and firmly handled. Remember also, that certain drugs, examples of which have already been given, are destroyed by gastro-intestinal secretions, and should therefore be protected with buffering agents as with penicillin G., by enclosure in an acid resistant capsule which will not dissolve until it reaches the alkaline small intestine as with adrenaline, or by the administration of sufficiently large quantities to offset any acid decomposition as with hexamine.

Irritant drugs should always be administered either with a demulcent protecting agent or in a diluted form.

Pharmaceutical preparations available for administration by the oral route are numerous.

1. *Fluids. Mistura,* (Plural: misturæ)—a mixture. This is a fluid medicine for division into a number of doses, one single dose of which can be called a *haustus* (plural: hausti), a drench.

Each dose of a mixture may consist of either soluble solid drugs, insoluble solid drugs, or fluid drugs, or a combination of two or more of these, plus a vehicle. In some cases the fluid drug may act as the vehicle.

A number of official mixtures may be prescribed, such as:

Mistura Magnesii Hydroxidi B.P.	—Cream of magnesia.
Mistura Magnesii Sulphatis B.P.C.	—White mixture.
Mistura Alba, B.Vet.C.	

Drenches are of most value in cattle, sheep, goats, and dogs. They may be administered to cattle, goats and sheep from a bottle with a long neck which is introduced into the interdental space, but in dogs the dose is poured into the cheek pocket from a spoon or small bottle. Should the animal cough during the administration, time for recovery must be allowed before continuing. 'Drenching guns' are now widely used for the mass dosing of sheep, the special syringes often delivering directly into the œsophagus through metal, rubber or plastic nozzles.

Horses, pigs and cats are not easily drenched and this form of treatment is not recommended for these species, but fluid medicines may be administered to horses, cattle and also pigs, by the stomach tube. By this means the possibility of causing the restriction of breathing and inhalation pneumonia are both considerably lessened, providing the tube is passed correctly.

2. *Semi-Solids. Electuarium*, (Plural: electuaria)—an electuary or confection. These are semi-solid sticky masses usually with a base of treacle, malt extract, honey or glycerin, intended to be smeared on the tongue and teeth. They are extremely useful for the oral administration of drugs, particularly when drenching is contra-indicated or where lesions are present in the mouth and pharyngeal area. Horses and pigs are easily and safely dosed by this form of administration.

3. *Solids. Bolus*, (Plural: boli)—a ball or bolus. Used exclusively in the dosing of horses, the bolus usually consists of solid drugs mixed into a massing agent of glutinous consistency. In some cases where the main drug is of a resinous nature, such as aloes, this is melted in a water bath and the other drugs stirred into it as it cools and resolidifies.

The massing agents commonly used are: Common ball mass, which consists of equal parts of treacle and linseed meal; glycerin; soap; and soft yellow paraffin.

The hand made bolus has now largely been superseded by glycogelatin capsules into which the drugs can be packed. Besides being more convenient, these are preferred because disintegration and drug dispersal are rapid. These are attributes which could not often be applied to the old type of horse ball.

Pilula, (Plural: pilulæ)—a pill. The compounding of pills by hand is now as much a past art as is that of dispensing horse-balls. Pills are round and usually sugar-coated. They are used in treating dogs and cats but have been mostly superseded by sugar-coated or plain tablets.

Tabella, (Plural: tabellæ)—a tablet. The majority of these are circular, flattened, compressed masses of drugs weighing up to about 10 gr. but larger, elongated tablets weighing about 5·0 G. are made specially for dosing calves, sheep and goats. The latter are often administered by balling gun.

The tablet is the most popular form of drug administration for small animals, antibiotic administration excepted, though formulations are

appearing which allow even penicillin to be successfully administered by mouth.

Pulvis, (Plural: pulveres)—a powder. Powders of varying granule size for oral dosing may be administered directly onto the back of the tongue as with the dog and cat, mixed in the food, which is a method suitable for all species but most frequently used in farm animals particularly for herd and flock dosing, or dissolved in drinking water. Drugs intended to be administered as a drench are often dispensed in powder form, with instructions for their solution or suspension included in the signature.

Powders for mixing in food should be either tasteless or incorporate flavouring and disguising agents suitable to the species for which they are intended.

The Parenteral Routes. Administration by these routes involves the introduction of therapeutic agents into the body by piercing the skin. The agents, following the skin penetration, may be deposited in one of a number of anatomical sites. Examples are subcutaneous, intramuscular, intravenous and intraperitoneal injections.

Which of these routes is chosen on a particular occasion will be decided by the factors mentioned in the introductory section of the chapter, such as the necessity for speed of action, accuracy of dosage, compatibility of route and disease, compatibility of route and drug.

Arranged according to the speed with which effective blood levels are most rapidly achieved the intravenous and intracardiac routes are followed by the intramuscular, the intraperitoneal and intrathoracic, and lastly, the subcutaneous routes. This generalization is not absolute, and there are exceptions, of which slow penicillin absorption across the pleural and peritoneal membranes is one.

All parenteral injections should be sterile. Normally only aqueous solutions will be injected intravenously. Oleaginous solutions and suspensions are often given by the other routes although mainly intended for intramuscular injection.

For all parenteral injections the patient must be adequately controlled and the site of injection as immovable as possible.

Intravenous Injection. Drugs are administered by this route for the following reasons:

(1) *In emergency.* Where an animal is suffering from an acute and severe bacterial disease, or where an acute metabolic disturbance has resulted in a deficiency of some factor essential to life such as calcium or magnesium in milk fever, at least the initial treatment should be administered by the intravenous route. Because of the speed of dispersal the effect on the condition is almost immediate.

(2) *Irritant drug administration.* Where drugs are irritant to subcutaneous and muscle tissue the intravenous route may be used. Such drugs are given slowly and the blood flow removes them from the site of injection.

immediately dispersing and diluting them at the same time. Should repeated injections of an irritant drug be made at approximately the same point, or should seepage occur into the vessel wall during insertion or removal of the needle, inflammation of the vein wall and clotting of the blood may occur—thrombophlebitis. To avoid this such solutions as chloral hydrate, sodium sulphonamides, formalin and certain organic arsenic preparations should be well diluted and the blood allowed to flow freely from the needle before and after injection. This ensures correct needle placement and the washing of irritant solutions from the needle before its removal.

(3) *Accuracy of dosage.* Intravenous administration is the only method of any value where accurate blood and tissue concentrations are essential. These may be necessary either to produce a predetermined effect as with barbiturate (e.g. Nembutal) anæsthesia, or because the effective dose of a drug is close to the toxic dose and can only be determined by the individual's reaction during administration, as with all non-volatile anæsthetics.

The *site* of injection will depend on the preference of the veterinary surgeon and the species involved.

In the *horse, cow, sheep and goat* the jugular vein is the vein of choice, though in cattle the milk vein is often used. In the *pig* the ear veins are the most convenient, providing the injection is made near the base of the ear where shaking of the head will not materially effect clotting at the puncture site. The subclavian route is not to be recommended as the calibre of needle required often causes a puncture from which fatal hæmorrhages can, and often do, occur. The veins most suitable in the *dog and cat* are the radial on the fore-leg, the recurrent tarsal on the hind leg and the tongue vein, which can be particularly useful for the injection of heart and respiratory stimulants during anæsthetic collapse.

The *technique* of giving intravenous injections is, in its essentials, the same for all species. The clipping of the site is a considerable help, although not always carried out. The vein should be 'raised'—made to fill up with blood so that its position becomes obvious,—by applying pressure on that side of the injection site which is nearest the heart. This may be done manually or by ropes and rubber tourniquets. A solid object in the jugular furrow will greatly assist raising that vein when pressure is applied by a rope. Swabbing the clipped injection site with spirit will, apart from cleaning and slightly disinfecting the area, make the hair lie flat and accentuate the raised vein. If the operator then tenses the skin over the site the vein will be partially fixed in position so that the needle, with its bevel upwards, may be inserted through the skin and into the vein. This may be carried out with two distinct movements, the first designed to penetrate the skin and the second the vein. Alternatively, the needle may be thrust through the skin and into the vein in one movement. Do not incline the needle too steeply or it will tend to transfix the vein. Blood should flow freely from the vein before starting to inject, particularly if irritant solutions are to be administered. Injections should be given

slowly following the release of the vein-raising pressure and, if large volumes are to be given, the fluid should be at body temperature.

When removing the injection apparatus blood should again be allowed to flow freely through the needle. Pressure applied over the injection site when removing the needle helps to prevent extravasation of blood and the formation of a hæmatoma. In small animals pressure can be applied for a few hours by a cotton wool pad strapped on with adhesive tape.

Intramuscular Injection. This route is used for:

(1) *Routine injections.* After injection the drug is absorbed and dispersed to the tissues more slowly than by the intravenous route. Intramuscular injections can therefore be used where no emergency is involved or where secondary continuation injections are required following initial treatment by intravenous injection.

(2) *Irritant drug administration.* Though very irritant drugs may be given only by intravenous injection, those which are slightly less irritant, such as organic mercurial preparations, may be given by deep intramuscular injection. Drugs which have a powerful vasoconstrictor action like adrenaline and pituitrin should also be administered by this route as well as those which have a base which is slowly metabolized such as ethyl oleate. The good blood supply to muscle tissue is responsible for the removal of the substances in a reasonable time so that the irritation, the vasoconstriction, and the semi-inert 'foreign body' respectively, are not present long enough to cause a marked reaction and the formation of a permanent scar.

(3) *Accuracy of dosage.* Where accurate blood and tissue levels are not required but where a reasonable level must be maintained over a period, drugs in a semi-inert base may be injected intramuscularly forming a depot from which absorption may continue for as long as 24–48 hours. Given subcutaneously absorption might be so slow that no satisfactory blood level would ever be reached, although absorption would continue for a longer time.

The *site* for intramuscular injections in the *horse* is usually in the thick muscles of the middle of the neck, but sometimes the triceps are used. In *cattle* the neck or the large semimembranosus and semitendinosus muscles are used. With the *smaller species* the semimembranosus and semitendinosus are the muscles of choice, although in the pig that part of the neck just behind the ear is often chosen.

Care must be taken to make sure that deep intramuscular injections are not made into intermuscular fascia, blood vessels, nerves or even into joint capsules. Damage to the sciatic nerve can easily occur in the smaller species, particularly in cats and small dogs where little muscle belly is available.

The *technique* is fairly straight forward and is much easier than for intravenous injection. The route is often preferred for this reason. Intramuscular injections can be extremely painful and minimum calibre needles

should be used, remembering always that muscular contractions can break needles off at the shoulder. Injections should always be made slowly. A muscle under tension, particularly from fear, will resist injections more strongly than will a relaxed muscle, and the separation of fibres as the volume of injection increases will then cause more pain. This pain may persist for several days. Pain will not be so marked a feature in large animals unless the volume injected is proportionately greater.

The muscle into which the injection is to be made should be identified and the site cleaned with spirit. Fixing the muscle may be difficult in the cow where subcutaneous tissue is plentiful and muscles loosely bound, but in the pig and horse connective tissue is relatively sparse and muscles are less mobile. Fixation of muscles between fingers and thumb should be easy in smaller animals.

Two techniques are used for inserting the needle into the muscle. Where the animal is very nervous and is loosely held a smooth, firm gliding technique is probably the better method. The animal is not then alarmed by the sudden and necessarily jerky movement which is involved with the second technique. This consists of almost throwing the needle into the muscle with a stabbing action. It is of most use in pigs, particularly when they cannot be restrained and are milling around in the stye, but it can be used quite successfully in most species of farm animals.

Subcutaneous Injection. Until the advent of intramuscular antibiotic injections the subcutaneous route was the most widely used of all parenteral routes. It is used for:

(1) *Routine injections.* Where speed of drug dispersal is even less important than when intramuscular injections are given, the subcutaneous route can be used. The blood supply to subcutaneous tissue is far less than to muscle tissue. Consequently most substances deposited subcutaneously will be only slowly removed from the site of injection. Most doses for the continuation of treatment are given by this route.

(2) *Irritant drug administration.* Only relatively innocuous drugs should be injected subcutaneously. Fluids with a high or low pH, strongly hypertonic solutions, irritant chemicals and vasoconstricting agents should not be administered subcutaneously. Nor should drugs such as liquid paraffin and oleates, which are slowly metabolized, be given by this route, for the substances remain in the tissue for long periods and are treated by the tissues as if they were foreign bodies. Foreign body reactions occur which, though sterile, are accompanied by fluid extravasation and local swelling.

(3) *Accuracy of dosage.* If rapidly achieved and predetermined blood levels are required the subcutaneous route should not be used. Pentobarbitone sodium in a dosage theoretically sufficient to give anæsthesia, if injected subcutaneously, will probably never reach a blood and tissue level sufficient to give more than light narcosis. This is a stage of central nervous system depression a little deeper than normal sleep levels, from

which the patient can be roused only with difficulty. Similarly with penicillin long-acting suspensions, though absorption may continue for several days, the rate of absorption will be insufficient to maintain levels already achieved by intravenous or intramuscular injections.

The *sites* for subcutaneous injections are essentially the same in all species. Wherever the skin is fairly thin and subcutaneous tissue plentiful, solutions, suspensions or even solid drugs may be injected. In the *horse* the principle is modified, for no site may be used where harness is likely to chafe, so that the middle of the neck is probably the commonest site. In *cattle*, *sheep* and *goats* subcutaneous injections may be made almost anywhere on the body but the normal sites are behind the shoulder, either just below the withers but often in the axillary fold, in the neck, and also in the precrural fold. In cattle which are restrained in the byre by yokes and neck chains the neck should obviously not be used. These sites are all positions where normal movements of the animal will help in dispersing the drug—another prerequisite for a normal subcutaneous injection site. In *pigs* the amount of subcutaneous connective tissue is limited by the large amounts of fat. The precrural and axillary folds are useful but perhaps the commonest site used for the injection of small quantities is an inch or two behind the ear, where the skin is thin and more easily penetrated. It must be remembered that certain injections *must* be made subcutaneously to achieve the right effect. Swine fever crystal violet vaccine is one of these, for when injected into fat insufficient absorption occurs to ensure adequate antibody formation, and immunity is not satisfactory. In *dogs* and *cats* all the usual sites are suitable. The site behind the shoulder is perhaps the most valuable because adequate dispersal is assured as the animal walks. The neck, though frequently used is not the site of choice because the skin is so loose that muscle movement gains little purchase and cannot move the fluid, which then tends to gravitate to the brisket and is absorbed over a period of days rather than hours.

The *technique* is simple and very little restraint is necessary, though some is advisable in most cases. The skin at the chosen site should be cleaned and a small fold lifted up from the underlying structures. The needle, which should be sharp, as with all injections, can then be gently but firmly pressed through the skin at the base of the fold. Injection should be slow to allow the fluid to percolate through the subcutaneous tissues; if large volumes are given, this process, and the stretching and lifting of the skin from the underlying tissues, will cause pain. Consequently, small volumes may be given at any site where a skin fold can be lifted, but large volumes must be given only at sites where the subcutaneous space is adequate and where essential movements will aid dispersal.

Intraperitoneal Injection. This route is mainly used for the administration of relatively large volumes of a restricted range of solutions.

(1) *Routine injections.* The speed of absorption for the majority of solutions is approximately that of intramuscular injections. There are

exceptions, of which penicillin is the best example. Penicillin is only very slowly absorbed through the peritoneal membrane, although the rate is somewhat faster in peritonitis when the membrane is inflamed and the blood supply therefore greater.

(2) *Irritant drug administration.* Irritant drugs may be administered by this route. Chloral hydrate and the sodium sulphonamides have been given in this way.

(3) *Accuracy of dosage.* The intraperitoneal route has the same disadvantages as all other routes, except the intravenous one, in that once a dose has been administered by the route no further control of blood and tissue levels is possible. Idiosyncrasy cannot be determined and allowed for. Thus, following the administration of a non-volatile anæsthetic such as pentobarbitone sodium, a normal dose can result in no effect at all, mild hypnosis (depression at about the level of normal sleep), or a fatal overdosage with bulbar paralysis. Which of these effects will result depends on several pathological and physiological factors.

Pregnancy and *pyometra*, whilst increasing the possibility of accidental intravenous injection because of the enlargement of uterine vessels which occurs in these conditions, also provide tissue masses and fluid into which the injection may be accidentally made. *A distended bladder or stomach*, *ascites* (dropsy), and *tumours* provide similar masses, all of which will markedly interfere with absorption rates and therefore blood and tissue levels.

The route is not popular in Great Britain except in single-handed practices where, so long as the practitioner keeps the contra-indications well in mind, it provides amongst other indications an easy and safe means of inducing anæsthesia and euthanasia in small animals.

The *technique* is essentially one for young farm and small animal treatment. The animal is restrained preferably on its back, but sometimes on its side. In these positions the intestines and other organs tend to drop away from the site. The site, which is from half to two inches, depending on animal size, lateral to, and approximately level with, the umbilicus, is clipped and cleansed. Local anæsthetic may be infiltrated on the path along which it is proposed to insert the needle. The needle itself should be of medium to fine bore and from one to two inches in length, depending on the species and size. It should be inserted forwards and diagonally inwards so that each tissue layer is penetrated at a point slightly in front of that in the preceding layer. Some operators prefer to penetrate the skin and then turn the needle parallel to the surface through the subcutaneous tissues for a short distance before directing it through muscle layers and peritoneum into the abdominal cavity. These techniques aim at closing the needle puncture so that leakage from the abdomen cannot occur.

Intrathoracic and Intracardiac Injections. Neither of these routes is frequently used for anything but the euthanasia of dogs, cats and young farm animals.

(1) *Speed of absorption.* Absorption from the lung is slightly faster than from intramuscular injections and, providing small volumes of warm sterile aqueous solutions are used, emergency injections can be made quite safely. Five to ten millilitres of solution will cause little deleterious effect on the lung. Intracardiac injections provide the quickest means of obtaining effective blood and tissue levels, but the technique frequently involves pain and loss of blood through wounds torn in the wall as the heart beats. There is no justification for the belief that puncturing the heart will kill the animal, but emergency and euthanasia injections only are indicated.

(2) *Irritant drugs.* No irritant drugs should be given by intrathoracic injection as alveolar tissue is very susceptible to such drugs and pneumonia may result. Intracardiac injections may be considered on the same basis as intravenous injections but irritant drugs will not from choice be administered by this route.

(3) *Accuracy of dosage.* No predetermined level of activity can be achieved by intrathoracic injections and though it is possible to administer doses by the intracardiac route which can be varied according to individual response, it is not usual to do so.

The *site* for an intrathoracic injection should be high on the chest wall between two ribs which lie somewhere about the centre of the chest. The distance from the midline will vary with the species but should be lateral to the psoas and latissimus dorsæ muscles. This is where the lungs are thickest and dispersal of the injection will be aided by gravity.

The *site* for intracardiac injections should not be determined by counting the number of ribs and choosing a point between any two ribs from the fourth to the seventh on a level with the elbow. It is far easier to feel for the apical beat of the heart—where the strongest beat can be felt on the chest wall—and introduce the needle an inch or more diagonally above and anterior to this apical beat.

The right side or the left may be used for both types of injections but the right side is often chosen for intracardiac injections owing to the thinness of the myocardium and to the less frequent occurrence of lung penetration.

The *technique* used is essentially the same for both routes. The aim is to introduce the needle across the anterior border of the rib immediately behind the site. Less damage and pain will be caused providing neither the rib nor its periosteum are touched, for it will be remembered that the intercostal vessels and nerves run along a channel in the posterior border of each rib.

The intracardiac needle is about $\frac{1}{16}$th inch in bore and four inches long, but intrathoracic injections may be made with a fine bore needle about $1\frac{1}{2}$ inches long.

Both types of injections should be made with the animal standing.

No special precautions are attached to intrathoracic injections apart from those already mentioned. Correct administration is usually indicated by slight coughing.

Intracardiac injections should be made by pressing the needle firmly through the intercostal muscles altering direction slightly forwards after penetration. The needle should be pushed in until the firmness and movement of the heart is felt. A further half-inch or so penetration will be followed by a spurt of blood from the needle indicating that a heart chamber has been entered. If the route is employed for euthanasia in the client's house be sure either that the thumb is over the needle mount or, better still, before insertion attach the syringe to the needle. Adequate restraint is essential for intracardiac injections.

The technique for carrying out subclavian injections or blood sampling is related to that for intracardiac injections. The subclavian technique is mainly used for taking blood samples in young pigs, although fatalities are not infrequent. The animal is firmly restrained on its back and an intracardiac needle is inserted just lateral to the midline in the pit between the first rib and the base of the neck. It is directed downwards at an angle of 30°–40° from the horizontal and slightly towards the midline. Blood is drawn from, or an injection made into, the great vessels just before they enter the heart. There is a great danger of 'oversticking' when blood, escaping from the puncture, floods into the pleural cavity. Death may follow, usually from shock and asphyxia. Subcutaneous and intrathoracic hæmatomata frequently develop following the use of this technique.

Injections Associated with the Central Nervous System. These parenteral injections are mainly associated in veterinary surgery with local anæsthesia. Techniques have been developed for the intraspinal injection of radio-opaque substances, for the collection of cerebrospinal fluid and for other similar purposes, but these are mainly confined to small animal work and are not yet universally adopted.

Epidural Injection. This type of injection is very frequently used in cattle practice for restraining abdominal and uterine contractions during parturition, prolapse of the uterus and similar conditions. Desensitizing of the skin and related structures in the hind quarters can also be achieved by this type of anæsthesia, but epidural injections are used less commonly for this purpose. Excess anæsthetic may cause loss of control of the hind legs and recumbency. Application of this method of anæsthesia to other species is possible, but not popular.

In cattle the *site* for injections is between the first and second coccygeal vertebræ. A similar site is used in the horse, but for other species the lumbosacral space is used.

Intrathecal Injection. Administration by the intrathecal route involves the penetration of the dura mater and arachnoid mater, and the route is not used frequently in veterinary practice. The penetration and injection into the cysterna magna of radio-opaque substances, which assist in the determination of the site of 'prolapsed disc' in dogs, has been developed

in recent years. The technique is a specialized one and fraught with considerable danger to the patient's life. It is not very widely used.

Injections Associated with the Peripheral Nervous System. Entirely associated with local anæsthesia, classification of these injections is concerned only with technique.

Paravertebral anæsthesia is a technique which involves the 'blocking' of certain nerves as they emerge from the foramina of the spinal column. It is used in cattle for desensitizing the skin and abdominal wall on the left side prior to a rumenotomy operation. (This operation involves the opening of the abdomen and rumen and is necessary, in traumatic reticulitis, for the removal of foreign bodies which are often found penetrating the reticulum wall.) It is also used for Cæsarian section. The local anæsthetic is infiltrated around the trunk of the nerves as they leave the spinal foramina and before they branch, so that the whole area supplied by these nerves is desensitized.

The technique of blocking nerves by infiltration around the nerve trunk is applied not only to paravertebral anæsthesia, but is also used used for blocking the nerves which supply the horns of cattle prior to dehorning operations, for blocking nerves which supply the limbs at various levels to determine the site of lesions causing lameness in horses, for blocking nerves to the teeth prior to removal; in fact it is used for the desensitizing of any area prior to operation when the route of the nerve trunk or trunks is known and is sufficiently superficial to be reached by hypodermic needles.

Where the area or structure to be anæsthetized is supplied by several nerves of small size and irregular routing, a method known as *field anæsthesia* is used. The method consists of creating a barrier around the operation area. It should be sufficiently remote from the site so that whenever possible no tissue involved in the wound healing shall be directly in contact with the anæsthetic, for local anæsthetics tend to retard healing. This can be done by 'line injection' where anæsthetic wheals are created by a number of injections in line, each succeeding penetration of the needle taking place just inside the area desensitized by the previous injection. A second method consists of partially withdrawing the needle several times and then redirecting it so that a large fan shaped wheal is created underneath the operation area. If this is repeated from the opposite pole of the site the whole area can be anæsthetized with only two skin penetrations.

The actual introduction of the anæsthetic solution into the tissues may be carried out either by inserting the needle to its fullest extent and expressing the fluid during withdrawal of the needle, or by slowly inserting the needle expressing anæsthetic ahead of the needle point. This latter method would seem to be more humane as there should be no further pain once the initial skin penetration has been achieved.

All these methods and techniques for applying local anæsthetics are

very fully described in J. G. Wright's text book on 'Anæsthesia' and students are recommended to use this book for further information on this subject.

Drip Techniques. Some drugs may achieve optimum results when administered in a dilute but continuous stream. 'Blood expanding' agents used for maintaining blood volume after loss of blood during operations or after accidents, or to maintain circulatory volume during a shock phase, are preferably administered by this technique. Antibiotics, anticoagulants and general anæsthetics may also be applied in this manner.

Drip techniques have been used experimentally in large animals, but so far they have been applied clinically only to small animals as it is essential that movement shall be minimal and that the patient shall not voluntarily attempt to dislodge the apparatus. To achieve this the animal is best anæsthetized, or at least narcotized.

Intravenous, intramuscular, subcutaneous, and intramedullary (injection into the medulla of a long bone) injections are the routes most commonly adopted for the application of drip techniques, but most routes are suitable.

Anticoagulant aids are essential if drip techniques are to be used successfully. These may consist either of anticoagulants incorporated in the injection fluids, or atraumatic coating of needles and tubes. Polythene tubes inserted and passed for considerable distances up inside the veins are frequently used in human surgery, and are being more frequently used in veterinary work.

Diffusing Agents. With the discovery of hyaluronidase, and the knowledge of its character of promoting very rapid intercellular diffusion, very large volumes of fluid can now be given subcutaneously without discomfort and with little obvious lifting of the skin. Over 100 ml. may be given subcutaneously to a dog within ten minutes without causing any marked discomfort. The injection fluid rapidly disperses and is quickly absorbed so that the possibility of chemical irritation and sloughing is vastly decreased. Calcium borogluconate, local anaesthetics, saline, and glucose injections particularly, are given subcutaneously to all species, using small amounts of hyaluronidase to aid dispersion and absorption.

The Rectal Route. This route is rarely used in veterinary practice for any other purpose than local action on the rectum and lower colon, but glucose, digested proteins, and anæsthetics are very occasionally administered by high colonic irrigation to obtain systemic effect.

Enema (Plural: enemata)—a clyster or enema. An enema consists of an infusion of fluids into the rectum or lower colon which usually aims at the evacuation of the contents of these organs. When used for this purpose enemas contain irritant and lubricant substances such as soap or glycerin. Occasionally an enema may be given as an anthelmintic: infusions of

quassia or solutions of sodium thiosulphate are sometimes used against Oxyuris, the false whipworm, of the horse.

Suppositorium (plural: suppositoria)—a suppository. These are elongated cone-shaped masses with a glycogelatin or theobroma oil base, both of which are solid at room temperature but fluid at body temperature. The suppository is sometimes used as an alternative to an enema for promoting defæcation in the dog, cat and pig. It weighs approximately 1–2 grammes and may contain a number of active ingredients. Suppository of glycerin is the commonest example. Preputial suppositories known as 'bull cones' are available for treating preputial infections of the bull. They are much larger than ordinary suppositories and may weigh up to one ounce. The active ingredients vary but most commonly sulphonamides and antibiotics are incorporated.

The Vaginal Route. Local treatment of conditions affecting the vagina and uterus may be achieved by the use of pessaries or irrigation.

Pessus (Plural : pessi)—a pessary. Pessaries are cone-shaped masses with bases similar to those of suppositories. They are shorter and broader than suppositories. The modern trend is toward types which do not have a base that liquefies at body temperature and which are prepared in much the same way as tablets; they are often called intra-uterine tablets. Sizes and weights vary considerably but the largest are approximately half an ounce in weight. They dissolve in the uterine fluids.

Intra-uterine and *intra-vaginal irrigations* are frequently used in cows as antiseptic infusions, but sometimes as irritants to stimulate uterine activity. In the latter category irrigation with diluted Lugol's iodine solution was used extensively before World War II as a treatment for bovine infertility; in this context intra-vaginal irrigation was apparently as effective as intra-uterine irrigation.

All solutions should be warm when administered.

Intramammary Infusions. With the availability of sulphonamides and antibiotics, the use of udder infusions through the teat canal in cattle has increased considerably. Warm infusions of substances such as acriflavine and mineral oil compounds were used for many years with fluctuating success but penicillin brought with it a new era in mastitis treatment. In the early days of antibiotic mastitis treatment warm aqueous solutions of 100,000 units of penicillin G in 50·0 millilitres of sterile distilled water achieved spectacular success. Penicillin remains the antibiotic of choice for universal use though later antibiotics such as streptomycin, oxytetracycline, and chlortetracycline all have their place for the treatment of resistant infections. These antibiotics are now injected from small collapsible tubes in a form which has come to be known as a *cerate*. This name is derived from the Latin *cerum* meaning *wax* and was adopted because the bases of most of these preparations originally consisted of oil and wax compounds. Water miscible bases are being increasingly adopted so that

mixing with the milk is more rapid, and penetration into the tissues possibly more efficient.

External Application. Preparations may be applied externally for either a superficial effect or for one which follows penetration of the skin and reaches subcutaneous tissues and underlying structures.

For superficial effects inert or semi-inert vehicles should be used, such as liquid paraffin and the related hard and soft paraffins (petroleum jelly). Aqueous solutions of most drugs do not penetrate deeply; if drugs are applied as dusting powder little more than surface action can be expected.

Where penetration is required, alcohols, volatile oils, and animal fats such as lard and lanolin will help considerably; even greater penetration can be achieved with volatile compounds if bandaging is used to delay evaporation, and to open up the pores by retaining heat.

Great care should be taken in choosing the base of an application and also in deciding on the size and position of the area to be dressed if drugs which are toxic when absorbed are to be used. If drugs are incorporated in bases which aid penetration, if large quantities are applied to small areas or normal quantities applied to large areas, or if ingestion results from licking the area, then either acute or chronic poisoning can occur. Many cases have been reported of poisoning subsequent to drugs being misapplied in these ways.

All dressings which are applied to wounds and eyes should be sterile. In veterinary practice less attention is paid to this feature than is observed in human medicine, except for operation dressings. This is mainly a matter of convenience, for accident wounds and abrasions are so frequently contaminated with fæces, dirt and hair, that a few extra bacteria and spores are successfully ignored. All containers of external applications should be labelled clearly with 'For external use only' or a similar phrase. Bottles should be distinctive in shape and colour, so that a warning is conveyed by sight and touch. Pharmacists use green or brown, hexagonal and/or fluted bottles for poisons and also for external applications, but in veterinary practice such recommendations are rarely followed and it is usual to rely on the label instructions.

Applications to Mucous Membranes. There are several therapeutic forms specifically intended for application to the eyes, the ears, the nose and the mouth.

1. *The Eyes.* Drugs may be applied to eyes in several different forms, some of which have an effect lasting for several hours, whilst others have a relatively transient effect. Preparations should always be sterile.

Oculentum (Plural: oculenta)—an eye ointment. These are semi-solid preparations with an official oculentum base. Unofficial oculenta are now prepared with a tear miscible base which greatly assists application and dispersal, but which decreases the persistence of any action, as the tears

wash the preparation away. Because of this washing action it is essential that antibacterial oculenta should be applied at least three times daily. Where drugs with peculiar and specific actions, such as atropine, are incorporated, the frequency of application will naturally be restricted.

Examples are Eye Ointment of Penicillin, B.Vet.C and eye ointment of sulphathiazole. The base must be sterile and should contain specified proportions of soft and hard paraffins, and lanolin. Ingredients which are heat stable should be added before sterilization but those drugs, such as the antibiotics, which are destroyed by heat may be added to the base under aseptic conditions after it has been sterilized.

Eye ointments are reputed to be unstable but this is a somewhat academic view for the majority of those not containing antibiotics should keep with reasonable activity for at least one year.

Collyrium (Plural: collyria)—an eye lotion. These preparations are intended for bathing the eyes to wash out pus and foreign bodies, and to soften and remove incrustations on the lids. They may have an aqueous or oil vehicle. Boric acid lotion at a strength of 5 per cent, is very widely used, but normal saline is to be preferred. Castor oil and liquid paraffin are frequently used to help in extracting foreign bodies from the conjunctival sacs. Aqueous eye lotions should not be used too frequently as they tend to make the area around the eye very wet and unhealthy; loss of hair may also occur giving the animal a most unsightly appearance. Rubbing and scratching follow which intensify the initial soreness and infection of the eye.

Gutta (Plural: guttæ)—an eye drop. The composition of eye drops is similar to that of eye lotions but the drops are intended for repeated application using a few drops at a time—sufficient to fill the conjunctival sacs and cover the eye. Aqueous and oily drops of cocaine are available. Besides these many other guttæ are available which incorporate such drugs as silver nitrate, zinc sulphate and most of the antibiotics.

Lamella (Plural: lamellæ)—an eye tablet. Ocular tablets have a base of glycogelatin and are used where maximum drug concentrations are required. Their use in small animals is relatively difficult compared with eye drops owing to the small size of the tablet—2–3 mm. diameter. Larger lamellæ are available for use in large animals and are very easily applied; these larger ones have also been successfully used in small animals, although the usual temporary discomfort is greater in these species.

Penicillin, oxytetracycline, cocaine and atropine are frequently applied in this form.

2. *The Ears.* In small animal practice a considerable amount of time is spent in dressing the ears of dogs and cats. Ear dressings therefore assume some importance in the treatment of small animals, but in large animals external ear conditions are relatively rare.

Alkaline aqueous solutions are frequently used for the injection of human ears, but dogs, and particularly cats, resent the instillation of cold

aqueous solutions. They will, however, tolerate the use of lotions and ointments with a propylene glycol, oil or fat base, and these are therefore the bases most commonly chosen. Oil based lotions are very useful for the removal of wax and debris impactions, as they penetrate through the mass, loosening it and floating the pieces out of the ear. No aqueous solution is as effective.

Where serous exudates occur, as in eczematous otitis in the dog, an exception is made and warm aqueous astringent lotions may be applied in addition to the use of antihistaminics.

Dusting powders are frequently but very misguidedly used by pet owners as a treatment for 'canker'. This powder treatment of otitis, in unskilled hands, often aggravates the condition, as the powder adheres to the wax and blocks the canal. More powder then completes the impaction and pressure is built up against the tympanum producing vertigo and inco-ordination of the hind legs. In extreme cases the pressure on the tympanum, particularly if swabs on orange sticks and forceps are pushed into the ear, causes rupture of the membrane.

3. *The Mouth and Nose.* The use of mouth and nasal washes—*collutoria* and *collunaria* respectively—is less in veterinary practice than in human medicine. Mouth lotions are sometimes used in small animal practice as an adjunct to systemic therapy of such conditions as canine leptospirosis, where large ulcers may form on the tongue and gums. These ulcers respond very well to treatment with penicillin lotions. Hypochlorite lotions are useful for cleaning the teeth and gums following teeth scaling.

Approximately isotonic solutions are used as nasal washes in small animals. They are often dispensed in a concentrated form to be diluted with warm water. Penicillin lotions are very useful in nasal catarrh in cats, and for loosening nasal incrustations which develop in distemper and allied conditions, warm normal saline is of great value.

Applications to the Skin. Preparations may be applied to the skin either to achieve a local and superficial effect or for the purpose of penetrating through the skin and affecting underlying structures. Emollients which soften and soothe the skin, such as lanolin and glycerin, and parasiticides such as derris which destroy fleas and lice on the skin surface, are examples of agents having a superficial action. Counter-irritants such as mercuric iodide and iodine which are frequently applied to affect bones and glands under the skin are examples of penetrating applications.

1. *Solid Applications. Conspersus* (Plural: conspersi)—a dusting powder. Rarely more than superficial in their action, dusting powders, which must be finely divided, can be used in all species, though the sparse bristles of the pig do not retain the powder very well. All types should be sterile when applied to wounds and abrasions. Large quantities of toxic powders should not be left where the animal can lick them off and swallow them;

in such cases the coat should be brushed half an hour or more after dressing. Dusting powders may have a *skin sedative* action, an *astringent*, an *antibacterial* or a *parasiticidal* action.

Skin sedation by the use of dusting powders may be achieved in a mechanical way by the application of, for example, starch, kaolin, or chalk, but the addition of slightly absorbed local anæsthetics such as amethocaine and benzocaine considerably increases their sedation value.

Astringents when applied to the skin are intended to have a local and superficial drying action. The sulphates of iron, zinc, copper and aluminium are frequently used.

Antibacterial or *antiseptic action* is achieved by adding bacteriostats and bactericides such as sulphanilamide, penicillin, organic mercurial compounds, chlorine compounds, iodoform and many other drugs. This type of dusting powder is frequently used as a wound dressing.

Parasiticidal dusting powders are very useful in the treatment of parasitic infestations of all species. They are of most use in treating superficial infestations of ticks, keds, lice, fleas and harvest mites. Baths are more effective but may not be desirable or practicable. In the cat bathing is not an easy operation, though on rare occasions a necessary one, and dusting powders are therefore preferred in this species. In small animals no concentration of derris, benzene hexachloride, dicophane (DDT) or similar parasiticides, should be left in the coat where licking may result in large and toxic quantities being swallowed.

Dispersible bath powders are sometimes mistakenly used as dusting powders. Should an animal so treated be soaked with rain, strong mixtures of the powder will run down the skin causing 'burns' which ulcerate in vertical stripes causing considerable trouble. The damage is mainly caused by the irritant action of the concentrated wetting agent. Only dusting powders which are specifically designed for this purpose should be used.

Dusting powders containing drugs such as iodoform which are likely to cause 'taint' should not be used on cattle which are in milk.

2. *Liquid Applications. Lotio* (Plural: lotiones)—a lotion. Intended for external application without friction, lotions usually have water as a vehicle. They may contain spirit where a drying, cooling or penetrating action is required, and glycerin is often incorporated where persistence and a softening emollient action is needed. Oils are sometimes used as vehicles in veterinary lotions. In no circumstances should gums be used as suspending or emulsifying agents, for they serve only to glue the hair together and produce a matted coat. Lotions are usually applied by swabbing.

Official examples are:

Lotion of Zinc Sulphate and Lead Acetate, B.Vet.C.—Lead lotion, white lotion.

Lotion of Salicylic Acid, B.Vet.C.

Linimentum, (Plural: linimenta)—a liniment.

Liniments are liquids with a wide range of viscosities intended for application to intact skin with friction. The preparations may have an oily or spirit base; frequently the preparation is an emulsion.

The majority of liniments contain counter-irritants and frequently incorporate drugs with analgesic properties;

Linimentum Alba, White Liniment, B.Vet.C.

Linimentum Camphoræ Ammoniatum, Ammoniated Liniment of Camphor, B.Vet.C.

Liniments are widely used for sprains and strains of horses and dogs and are commonly referred to as 'rubbing oils'.

3. *Semi-Solid Preparations*. These can be subdivided again into preparations for which bandaging is optional and those for which bandaging is essential. Ointments, including creams and pastes, comprise the first group, whilst plasters and poultices comprise the second.

Unguentum (Plural: unguenta)—an ointment. This is essentially a semi-solid substance with a base containing either a wax, a fat or a fixed oil, and is intended for external application with or without friction. The term is usually retained for those preparations which are oil miscible, although the majority incorporate some lanolin which permits the addition of small quantities of aqueous solutions. This is because the lanolin will adsorb up to twice its own weight of water.

In veterinary practice many ointments are dispensed which contain only yellow soft paraffin (petroleum jelly) as a base. This provides a non-penetrating emollient base suitable for superficial action. Where a penetrating effect is required an animal fat such as lard or lanolin is necessary. By varying the proportions of these two groups of substances actions ranging from a mild and local surface action to a severe and deeply penetrating action are obtainable. It is most important to remember this when compounding severe counter-irritant ointments—'blisters'.

Cremor (Plural: cremores)—a cream. A subdivision of ointments, creams are intended for external application without friction. Their main attribute is miscibility with water, for they are essentially semi-solid emulsions. Simple cream, given the official Latin name of *Unguentum Emulsificans Aquosum*, consists of emulsifying wax, white soft paraffin, liquid paraffin and a large quantity of water.

This miscibility with water means that creams will readily mix with all body fluids and exudates. When applied to wounds, ulcerated tissues, mucous membranes and wet oozing lesions, the preparations adhere more easily than ointments, which they are rapidly replacing.

Antihistaminic creams applied to 'wet eczema' patches in the dog and the analogous condition in the horse, 'summer itch', admirably illustrate the value of this type of preparation.

Pasta (Plural: pastæ)—a paste. The composition of pastes is similar to that of ointments but the consistency is much firmer due to the higher pro-

portion of solid ingredients. They are unpopular, for they are not easy to handle, and most of them must be bandaged on. Only one paste has any significant place in modern practice:

Pasta Bismuthi et Iodoformi—Paste of Bismuth and Iodoform, B.P.C. (B.I.P.P., Bismuth, iodoform and paraffin paste.)

Its use is mainly confined to dirty pocketing foot wounds of the horse.

Cataplasma (Plural: cataplasmata)—a poultice. Poultices are applied to maintain heat at the site of a chronic or subacute inflammation. The heat, in addition to any action which incorporated drugs may have, is responsible for opening up the capillaries in the area and increasing the blood supply. This in turn provides a rapid and increasing concentration of the body's defences—antibodies, macrophages, etc.—at the site, increased nutrition and an improved metabolite removal rate. All anti-infection processes are hastened, the formation of pus is speeded and, following opening of the abscess and evacuation of the pus, healing processes are improved.

Veterinary poultices are frequently home-made non-pharmaceutic preparations which are often æsthetically unacceptable. They are prepared with hot water and have the disadvantage of producing wet unhealthy tissue when applied. Bread, bran and linseed poultices are of this type. Kaolin poultice, however, possesses the characteristics necessary to achieve good therapeutic effect without the disadvantages of the wet poultice, and is widely used in small animal practice. Expense makes it less popular for use on farm animals, although it is ideal for poulticing sheep, pigs, calves and foals.

Poultices should be as hot as can be borne, and may be applied as a sandwich between two layers of bandage, or on squares of lint, as with kaolin: some are packed into a bag into which the foot is thrust and tied, as with bran and linseed. (It is the foot or lower limb which is most frequently poulticed in farm animals). Whatever the method of application the aim should be to restrict heat loss.

Prior to maturation of abscesses, kaolin poultices may be renewed at 24–48 hour intervals. Bran and similar poultices, which lose their heat rapidly, should be renewed at least once daily though the best results are achieved with this type of poultice if it is renewed as soon as it is cold.

Once abscesses have matured and opened, poultices should be changed as soon as they become saturated with discharge. Kaolin poultice needs infrequent changes—once daily is often sufficient, as the high glycerin content is capable of absorbing a large amount of fluid before it loses its 'drawing' or 'lymph lavage' action. Other poultices need more frequent changes.

Hot fomentations are often used in place of poultices. They are useful in applying heat to areas which cannot be poulticed, but may cause mild scalding with loss of hair from the application area.

Emplastrum (Plural: emplastra)—an adhesive plaster or 'charge'. These have a base of adhesive substances such as pitch, resin and beeswax

into which can be incorporated various types of drugs e.g. antiseptics, astringents and counter-irritants. According to the base employed they may be either soft, or hard and brittle at normal temperatures. Plasters should be applied to a clipped site as an even layer spread on a bandage, lint or chamois leather. The hard resin based types must therefore be melted on a water bath and spread evenly on the dressing material. They should be applied whilst still warm and soft. Sometimes the site, which is commonly a limb joint, is first bandaged and then moulten plaster is smeared onto it. A further bandage layer is applied overall. This latter method ensures easy removal, for direct application sticks the plaster onto wool and hair.

Adhesive plaster bandages, sometimes elasticated, have largely replaced medicated 'charges'. Where adhesive bandages are used drugs may be applied directly to the site, but it is more usual to interpose a layer of medicated gauze between the adhesive bandage and lesion. Adhesive bandages do not allow the skin to breathe and, when applied over large areas, 'breathing' spaces must be left to allow moisture to evaporate.

Counter-irritant charges are still used occasionally as the ultimate treatment for chronic fibrous, or even osseous, joint and tendon inflammations in large animals.

Administration Vehicles

Vehicles used in the administration of drugs must be compatible chemically, physically and therapeutically: obviously no client should be advised to mix aqueous solutions into oil or oily solutions into water. It is less obvious that liquid paraffin should not be used for parenteral injections or that sodium fluoride must be administered to pigs in dry or nearly dry food, and not in water or swill.

Frequency of Administration

Frequency of dosing will depend on a number of factors, each of which must be considered when making a decision:

(1) *The Character of the Disease.* If the disease is very acute and severe, then, with due regard to toxicity considerations, frequent massive doses are indicated to save the animal's life. Where subacute conditions are involved less urgent and heroic measures are necessary, and, providing adequate tissue levels are achieved, high and frequent dosage is not necessary.

(2) *The Character of the Drug.* Some drugs are absorbed and excreted more rapidly than others and the dosage of these drugs must be sufficiently frequent to maintain adequate tissue concentrations: aqueous solutions of penicillin are an example. Toxicity of the drug also has a bearing on dosage frequency, for it is usual to give doses of sulphonamides frequently for the first two days, when the disease is at its height; subsequently, for a further two or three days, the dosage frequency can be decreased as the tissue levels are stabilized and the disease controlled. This decrease in

frequency is necessary as excretion of the sulphonamides is slow and toxic levels would soon be built up if a high frequency of dosage were maintained.

(3) *Animal Physiology*. This may affect frequency. Ruminants, by virtue of the depot mass in the rumen, need only twice daily oral dosage but parenteral dosage follows normal practice.

(4) *The Ability of the Owners to Administer the Drug at the Required Interval*. This also affects dosage frequency. The owner may be away all day, or assistance may not be available except for morning and evening dosage.

This correlation of the dosage frequency with the owners daily routine is an important factor, particularly in farming, where working hours are often governed by weather and daylight. Interference with farming routine should be as little as possible, otherwise dosing will be neglected and the results of treatment erratic and unpredictable.

Duration of Treatment

It is usual in both small and large animal practice to revisit routine cases approximately every third day. With acute and psychologically disturbing conditions, such as colic in horses and epileptiform fits in dogs, it may be necessary to revisit the case after only a few hours. In chronic conditions such as thyroid alopecia (baldness) in dogs and cats, or wooden tongue in cattle, weekly or even fortnightly attendances may be satisfactory.

The number of doses will vary accordingly but a sufficient number to allow for wastage and flexibility of revisiting should be prescribed. No client should be left short of drugs between visits or there may develop a feeling that attention is inadequate and unplanned. This should be avoided at all costs, for the confidence of the client is the essence of good treatment. Sound diagnosis and correct prescribing may fail to cure owing to incorrect nursing and drug administration by a client who, through lack of confidence, fails to co-operate.

CHAPTER 5

VEGETABLE DRUGS

THEIR ACTIVE PRINCIPLES, ASSAY AND PRESENTATION

SINCE the earliest days of medicine, plants have been the main source of therapeutic agents, and it is only in the last two decades that chemotherapeutic synthesis has begun to provide safer and more active compounds. Even now the search for new chemotherapeutic agents frequently begins with a study of an active principle derived from a plant, and in many cases the plant extract cannot be improved upon. As an illustration digitalis, which contains glycosides derived from the purple foxglove, has no superior as a 'heart tonic', whilst morphine, derived from opium, itself a product of certain species of poppy, is still one of the most effective analgesic and narcotic drugs although related compounds have been synthesized which have fewer side actions.

The active constituents of plants vary in chemical characters, structure, potency and concentration. By far the most important group of substances derived from plants are alkaloids, such as morphine, aconitine and nicotine: the glycosides, such as digoxin and digitalin from the foxglove, sinigrin from mustard, and linimarin, a cyanogenetic glycoside from linseed, are also a very active and important group. As the concentration of these active principles varies in different parts of the plant, being most concentrated in the seed as a rule, and, as the content varies according to the time of the year or stage of plant development, each batch of drugs produced from such plants must be standardized. This is done by various specific assays according to the action and chemistry of the active constituents. Thus, with curare, a skeletal muscle relaxant, the alkaloids are biologically assayed by the 'head drop' method in rabbits, whereas digitalis is assayed by heart block methods using pigeons, cats or frogs, for, though chemical methods have been tried, they have so far proved unreliable. Other alkaloids such as those in Belladonna Herb, B.Vet.C., (Belladonna Leaf, U.S.P.) are estimated chemically, in this particular instance either in terms of hyoscyamine or atropine.

The active constituents of many plants may be extracted, purified and used as the pure alkaloid, glycoside, or similar principle. These purified active principles are often extremely potent and toxic; they must therefore be given in very small and accurately measured doses, so that many prefer to use the less exacting but relatively crude plant products such as powdered root, stem, or leaves, liquid, soft or dried extracts, infusions,

or tinctures, which must be assayed and standardized if accuracy in dosage and safety in treatment are to be achieved. However, not all drugs derived from plants rely for their effect on such potent active principles, and in these cases purification is pointless, although increasing the concentration of the principles may prove helpful.

Plant Structures Used in Pharmacy and Medicine

Active principles are usually found in all plant structures, but the concentrations are often high in one particular part. These structures which contain the higher proportions of active ingredient are therefore used more frequently for pharmaceutic and therapeutic purposes. The structures used are specific to each plant and sometimes the principle is specific to a particular structure also, as will be seen from the following descriptions:

Root (Radix): The roots of some plants are dried, 'skinned,' and cut into short rod-like lengths. These lengths may be ground and used as a powder, or crushed and extracted with various solvents to produce tinctures, infusions, and extracts. Examples are Belladonna Root, B.Vet.C.; Gentian, B.Vet.C.; and Ipecacuanha, B.Vet.C. Some roots have tuberous swellings in which food reserves are accumulated in concentrated form: Jalap, B.Vet.C., is an example.

Corms (Colchicine, B.P.), *bulbs* (Squill, B.Vet.C.), and *rhizomes* (Rhubarb, B.Vet.C., Ginger, B.Vet.C.), are all used for similar purposes.

Bark (cortex): Several important and highly active compounds are prepared from the bark of shrubs and trees. Of these Jesuit's bark or Cinchona, B.P.C., is possibly the most important, but Cascara Sagrada, B.Vet.C., and Cinnamon, B.P., are also known and widely used.

Wood (Lignum): Perhaps the best example of wood used in pharmacy is that of Quassia, B.Vet.C., which consists of the wood chips from a tree native to the West Indies. Tar, B.Vet.C., (Stockholm Tar) and wood turpentine are both prepared from the wood of species of pine.

Leaves (Folia): Cocaine, B.Vet.C., is prepared from the leaves of a shrub *Erythroxylum coca;* Digitalis Leaf, B.Vet.C., and Buchu, B.P.C., are other examples. Herb is a term which usually indicates the use of both leaves and other aerial parts of a plant as with Belladonna Herb, B.Vet.C.

Flowers (Flos): The flowering tops of certain plants are of therapeutic value, Pyrethrum Flower, B.Vet.C., being an excellent example.

Fruit: These are also used: Prune, B.P.C., and Anise, B.Vet.C., (Aniseed) are fruits which are commonly used in pharmacy and therapeutics.

Seeds (Semen): In plants containing potent principles, the greatest concentration is usually located in the seed and may be extracted in relatively high concentration. *Nux vomica* seeds, Areca (nuts), B.Vet.C.,

are used and physostigmine, linseed oil and castor oil are extracted from beans or seeds.

Active Principles of Plants

The most active constituents of plants are alkaloids and glycosides. Resins, saponins and tannins are also found in plants along with proteins, fats and oils, carbohydrates, enzymes, vitamins, acids, inorganic salts, pigments and probably hormones.

Alkaloids. Members of this group of compounds, widely distributed throughout the plant kingdom, consist chemically of nitrogenous organic bases which react with acids to form salts. The structure of these alkaloids is usually most complex and includes many organic ring structures of which the following are examples:

Pyridine (nicotine)



Piperidine (pethidine-synthetic)



Pyrrolidine (cocaine, atropine and nicotine)



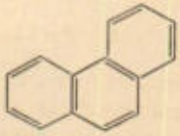
Quinoline (quinine)



Isoquinoline (narcotine and papaverine)



Phenanthrene (morphine)



Alkaloids have the following characteristics:

1. They are usually white crystalline substances which are relatively non-volatile. Exceptions, usually those not containing oxygen in their structure, are liquid and volatile at normal temperatures and pressures. Examples of the former are atropine ($C_{17}H_{23}O_3N$), physostigmine ($C_{15}H_{21}O_2N_3$) and cocaine ($C_{17}H_{21}O_4N$), whilst nicotine ($C_{10}H_{14}N_2$) and coniine ($C_8H_{17}N$) are liquid.

2. Alkaloids are almost insoluble in water, but usually more soluble in alcohol and freely soluble in ether, chloroform and oils. Exceptions occur.

Strychnine (water 1 : 7,000, alcohol 1 : 250, chloroform 1 : 6, but ether—almost insoluble); atropine (water 1 : 400, alcohol 1 : 3, ether 1 : 60, and freely soluble in chloroform); and cocaine (water 1 : 1300, alcohol 1 : 10, ether 1 : 4, chloroform 1 : 0·5), may be cited as examples.

3. They form salts with acids, the halogen acids forming hydrochlorides, hydrobromides, etc. These salts have a reverse solubility, being soluble in water and alcohol but insoluble in other organic solvents.

4. Both alkaloids and their salts are incompatible and are precipitated by tannic acid, alkalis, heavy metals and their salts, particularly mercury, gold and silver salts.

5. Alkaloids are now distinguished by the termination of their names with the letters—INE. On latinization this becomes—INA. This is the agreed international suffix, as shown below:

Cocaine - cocaina	:	Ergotoxine - ergotoxina.
Morphine - morphina:		Codeine - codeina.
Emetine - emetina	:	Physostigmine - physostigmina.

Glycosides. The members of this group of compounds, also sometimes known as glucosides, vary considerably in their chemical composition but have in common the production of a sugar and another substance, known as a *genin* or *aglycone*, on enzyme or acid hydrolysis. The genin may be an alkaloid, a tannin, or compounds of unknown structure, collectively called *neutral* or *bitter principles*. Some glycosides, following enzyme hydrolysis, produce hydrocyanic acid, and are therefore known as *cyanogenetic glycosides*. Those which have a specific action on the heart are known as *cardiac glycosides*.

The ester-like linkage of the sugar and genin may be illustrated by reference to the simplest glycoside:

$$CH_2OH.\overbrace{CH(CHOH)_3CH}^{O}.OH + CH_3OH$$
$$= CH_2OH.\overbrace{CH(CH.OH)_3CH}^{O}.OCH_3 + H_2O.$$

In this way methyl glucoside is formed i.e., glucose plus methanol. If the sugar were galactose or mannose, the glycosides formed would be known as methyl galactoside or methyl mannoside, respectively. Isomeric forms exist.

By substituting other substances which contain hydroxyl groups, or will react to produce the hydroxyl grouping, other glycosides varying from simple alkyl compounds to complex aromatic and heterocyclic compounds can be formed.

Glycosides are usually soluble in water and aqueous-alcoholic solutions. They are not precipitated by lead salts and do not reduce Fehling's until after hydrolysis. Pharmacologically the main activity of the glycosides rests in the genin or aglycone, the sugars modifying their absorption and

general metabolism. They may be distinguished in literature by the internationally agreed English suffix of—IN, and the Latin—INUM. Examples are:

Digitalin	: digitalinum
Digoxin	: digoxinum
Saponin	: saponinum
Linimarin	: linimarinum.

Saponins. These are now classed as a sub-group of the glycosides, the group characteristic being the ability to cause foaming when shaken with water. They are sometimes used as emulsifying agents e.g. Quillaia, B.P., which contains a large proportion of saponins has been used frequently as an emulsifying agent for volatile oils. Saponins frequently occur along with other glycosides, as in digitalis, and increase their absorption rate. There are some saponins which are extremely toxic and are known as *sapotoxins*.

Most saponins are neutral, but a few are slightly acidic and a few are basic.

Tannins. These are a heterogenous group of compounds, some of which are glycosides. They have certain chemical and pharmacological characteristics in common, such as astringency, producing inks with iron salts, and the ability to precipitate certain heavy metals and some alkaloids, but neither *cocaine*, *nicotine*, *morphine*, *atropine and physostigmine*, nor *arsenic*, *antimony and mercury*.

The tannins are widely distributed throughout the plant kingdom and are usually named after their source, e.g. *gallotannin* from oak galls, *catechutannin* from catechu, and *quercitannin* from oak trees.

Tannins are usually water soluble.

Carbohydrates. *Cellulose* is the main constituent of the cell walls of plants, but in older plants and trees it is modified by the introduction of lignin (wood) or suberin (cork). Cellulose is an isomer of starch but may undergo modification into gums or pectin.

Starch is also a large constituent of the cells of plants and forms one of the main reservoirs of energy. It is hydrolysed to dextrin and then to glucose.

Sugars are also a reservoir of plant energy. They are more quickly mobilized than starch and may be monosaccharides such as glucose, or disaccharides such as maltose. Polysaccharides, such as starch and cellulose, already mentioned, are less easily converted into energy.

Gums are complex carbohydrates, often glycosides, which form viscous adhesives with water. *Pectins* are similar carbohydrates derived from fruit.

Tragacanth and acacia are official examples of gums.

Fats and Fixed Oils. These are, respectively, solid and liquid esters of fatty acids and glycerin. They are found in the most concentrated form in

the seeds of plants but may occur throughout the structure. They have certain characteristics, as follows:

1. They are coloured (yellow or brown), fairly viscous oils or solid fats.
2. They are insoluble in water but soluble in organic solvents.
3. They saponify with alkalis to give soaps and glycerin.
4. They stain black with osmic acid, leave permanent grease marks on paper, are permanent lubricants. Vegetable oils tend to go rancid on keeping but they keep far longer than animal fats or oils which have, otherwise, similar characteristics.
5. Fats differ from oils in having high proportions of the more solid fatty acids—palmitic and stearic acids.
6. Those obtained from the seeds and beans are usually extracted by cold expression.

Waxes are similar in consistency and character to fats but differ chemically in being esters of fatty acids and alcohols other than glycerin.

Volatile Oils. These are also referred to as Essential, Aromatic or Ethereal oils. They are obtained usually by steam distillation. Chemically they are mixtures of aldehydes, esters, ketones, alcohols and terpenes. They are volatile, have a characteristic odour specific to each oil, are colourless, highly mobile liquids which leave no permanent greasy mark on paper and are non-lubricant. They are only slightly soluble in water, but miscible with fixed oils and organic solvents. On cooling they usually separate to give a supernatant liquid or *elæoptene*, and a solid or *stearoptene*.

Volatile oils have, until now, had a distinct nomenclature and were always referred to as "Oil of . . . ", whereas fixed oils were named '. . . oil.' Examples of both are:

Fixed oils: Olive Oil, B.Vet.C.
Castor Oil, B.Vet.C.
Linseed Oil, B.Vet.C.
Theobroma Oil, B.Vet.C.

Volatile Oils:
Oil of Aniseed—Anise Oil, B.Vet.C.
Oil of Chenopodium—Chenopodium Oil, B.Vet.C.
Oil of Peppermint—Peppermint Oil, B.Vet.C.
Oil of Turpentine—Turpentine Oil, B.Vet.C.

Unhappily the Veterinary Codex has cancelled this nomenclature and this distinguishing feature is therefore obsolescent.

Resins. These compounds are brittle, amorphous compounds mainly derived from the oxidation of the terpene components of volatile oils. In many cases their chemistry is unknown: some resins are esters or ethers of organic acids and complex alcohols known as *resinols* or, where they have similar reactions to tannins, *resinotannols*. Other resins consist mainly of acids or acid anhydrides.

Resins fracture giving smooth, shiny surfaces; they are insoluble in water but soluble in most organic solvents and oils. Examples are Podophyllum Resin, B.Vet.C., and jalap resin.

Oleoresins are mixtures of volatile oils and resins. Turpentine Oil, B.Vet.C., is the best example in veterinary use.

Balsams are oleoresins which contain benzoic and, or, cinnamic acid or their derivatives.

Balsam of Peru, B.P.C., and *Balsam of Tolu*, B.P., are well known constituents of skin dressings and cough mixtures, respectively.

Assay Methods

Any drug which contains a potent active ingredient mixed with inert or less active substances in proportions which vary according to the source, quality, and manufacturing batch, should be assayed. This is necessary in order to determine the amount of the active ingredient in a stated quantity of any sample of the compound, so that a physician may know the exact quantity of the active ingredient which he is giving to an animal.

The official pharmacopœia and similar official volumes lay down standards for all recognized drugs, and manufacturers must conform to these standards, reinforcing samples that have a low assay with samples that have a high content of active ingredient, and *vice versa*.

Where chemical assays are allowed, the method is relatively straightforward, but where chemical methods are not satisfactory, or not available, biological assay must be resorted to. By this is meant that living organisms or parts of living organisms, whether they be bacteria, protozoa, or cats, birds, mice, guinea pigs and other laboratory animals, are used as 'indicators' of potency. In most cases chemical assay allows greater accuracy and the limits of inaccuracy are very narrow, whereas with biological assays the limits of accuracy are often very wide, approaching ± 25 per cent in some cases. This inaccuracy is due to the variable response of individual animals, and large numbers of test animals must be used to minimize the variability. This makes the tests both laborious and expensive.

The principle with all standardizations not dependent on chemical assay, is to compare the results obtained using a known quantity of the compound under test with the results obtained using a known amount of a standard preparation of the same compound. In many cases the standard preparation is kept at a national standards laboratory from which samples are distributed as and when required for testing. Normally manufacturers are expected to maintain their own standards, which are initially assayed against the national standard. Where the compound is used internationally, the national standards are assayed against the international standard.

The assay of *digitalis* may be taken as an example. The tests may be carried out on frogs, guinea pigs, cats or pigeons, the last two being the animals most commonly used. In brief, the test consists of injecting

known dilutions of the standard and the test compound intravenously, under standard conditions, into a minimum of six individuals for each preparation. The cats or pigeons are of known weight and condition, and are lightly anæsthetized prior to the test. Equal dilutions of standard and unknown are injected in quantities of 1.0 ml. per kg. body weight at intervals of five minutes until the heart stops. The average number of injections must be not less than 13 and not more than 19. From these results the lethal dose for each individual is calculated and the results statistically analysed, average errors being calculated and the test repeated if the errors fall outside the allowed limits. If the averages fall within the limits, the potency of the test compound is calculated by dividing the average of the standard by that of the unknown. With cats the allowed inaccuracy is ± 20 per cent. Some of the details vary according to the species used for the test, but the principles are the same.

Biological assays applying to the antibiotics are discussed in the Introduction to the Antibiotics, p. 442 et seq.

Pharmaceutical Preparations of Plant Origin

Before the roots, seeds, leaves and other plant structures can be administered as medicines they are subjected to various pharmaceutical procedures. By these processes the active ingredients may be extracted and concentrated, or the plant structures may merely be ground into a powder which is then sieved to ensure a uniformity of granule size. These various products are then standardized.

Powders. The simplest plant preparations are the powders. They are obtained from plants by drying the required portion of the plant and grinding to a fine powder. If the powder is subsequently assayed and standardized to contain a specified amount of active ingredient, the resulting powder is referred to as '*Prepared.*' If the powder is not adjusted to contain a standard quantity of active ingredient it is referred to as '*Powdered.*'

To illustrate this, the powders obtained from Belladonna Herb, B.P., may be quoted. Powdered Belladonna Herb, B.P., consists of the dried aerial parts of *Atropa belladonna*, including the leaves, ground to a fine powder: it must conform to the B.P. specification, which includes a minimum alkaloid content of 0·3 per cent expressed as hyoscyamine; no upper limit is specified. Prepared Belladonna, B.P., is the same powder assayed, and the alkaloid content adjusted up or down to contain 0·3 per cent total alkaloids expressed as hyoscyamine (limits 0·28–0·32 per cent). It follows that the powdered compound may vary considerably in potency from batch to batch, whereas the prepared compound should be of relatively unvarying potency. In dispensing, the prepared compound is always used.

From the powdered drug various other presentations can be prepared. The most important of these are: the extracts (liquid, soft and dried), the infusions (concentrated and fresh), and the tinctures.

Extracts. There are three types of extracts, but all are prepared initially by subjecting the powdered plant structure to one of several types of pharmaceutical extraction procedures—decantation, maceration, or percolation, using water with or without alcohol and other organic fluids as solvents. The resulting solutions are concentrated by evaporation and, depending on the degree of evaporation, the three extracta are produced—the liquid extract, which is the least concentrated, the soft extract, which retains a proportion of solvent, and the dry extract, which is evaporated to dryness and therefore contains the highest proportion of active ingredients. In practice the extracts are usually adjusted to standard active ingredient concentrations.

Examples are:

Liquid Extract of Belladonna, B.P. (from the root)
Green Extract of Belladonna, B.P. (a soft extract from the herb)
Dry Extract of Belladonna, B.P. (from the herb).

Infusions. These are now rarely used in veterinary practice but nevertheless are still used pharmaceutically in the preparation of various mixtures. Infusions are usually prepared by aqueous exhaustion of the powdered plant structures, using maceration processes. If the resulting solution is unconcentrated and intended for immediate use it is known as a *Fresh Infusion* (Infusum Recens), but if the solution is evaporated down and concentrated to $\frac{1}{5}$ of its original volume it becomes a *Concentrated Infusion* (Infusum concentratum). If diluted by the addition of seven times its own volume of water, the concentrated infusions become equal in strength to the fresh infusion.

Examples are:

Concentrated Infusion of Rhubarb, B.P.C.
Fresh Infusion of Rhubarb, B.P.C. 1949

Tinctures. This group of pharmaceutical preparations includes some very important and frequently used examples. Tinctures are solutions prepared by alcoholic extraction of vegetable drugs, usually by the process of maceration or sometimes percolation. The standard tincture is usually a *Strong Tincture* from which a *Weak Tincture* is prepared by dilution.

Examples are:

Strong Tincture of Ginger, B.Vet.C.
Weak Tincture of Ginger, B.Vet.C. (20 per cent of the Strong Tincture in 90 per cent alcohol).
Tincture of Opium, B.Vet.C.
Tincture of Nux Vomica, B.Vet.C. is an exception prepared by diluting the Liquid Extract with 45 per cent alcohol.

Other pharmaceutical preparations, not necessarily associated with vegetable drugs are:

1. *Waters* or aquae, which consist of solutions of volatile substances in water: e.g. Chloroform Water, B.P., used as a vehicle for many mixtures dispensed as human medicines.

2. *Spirits* or spiriti, which are solutions of volatile substances in alcohol e.g. Aromatic Spirit of Ammonia, B.Vet.C.

3. *Solutions* or liquores, which are solutions usually of non-volatile substances in water, e.g. Solution of Adrenaline Hydrochloride, B.Vet.C.

4. *Syrups* or syrupi, which consist of sugar, water, and a water soluble drug e.g. Syrup of Chloral, B.Vet.C.

5. *Honey compounds* or mellita, consist of a drug mixed with honey, and sometimes glycerin, e.g. Honey of Borax, B.P.C.

6. *Elixirs* or elixiria, consisting usually of syrup, alcohol and an aromatic drug are now rarely used in veterinary medicine.

7. *Glycerins* or glycerina, which are solutions of drugs in glycerin, e.g. Glycerin of Alum, B.Vet.C.

8. *Vinegars* or aceta, which are rarely used in veterinary medicine, contain drugs dissolved in acetic acid. Vinegar of Squill, B.P.C., is an ingredient of many compound cough mixtures.

9. *Oxymels* or oxymellita, which are mixtures of honey, acetic acid and a drug. Oxymel of Squill, B.P.C., is also a constituent of many proprietary cough mixtures.

10. *Collodions* or collodia, which are compounds containing alcohol, ether, pyroxylin, other solvents and drugs. They are intended for external application, the volatile solvents evaporating off to leave a protecting cellulose film over the area of application (pyroxylin is a nitrated cellulose). Collodion of Antimony Trichloride, B.Vet.C., is the commonest veterinary example.

Pharmaceutical Methods Applied to Vegetable Drug Extraction

In the preparation of extracts, tinctures and infusions various extraction processes have been mentioned. The following are brief explanations of some of the processes used.

Decantation. The solvents are poured onto the crude drug or powdered drug, stirred vigorously and allowed to settle. The supernatant fluid is then run off and more solvent added. The process is repeated until the soluble ingredients are all extracted. The solution is then evaporated and concentrated to a suitable strength for pharmaceutical use. Some extracts have been prepared in this manner.

Maceration. This is similar to decantation in that the solvent or *menstruum* is mixed into the crude drug or powder and allowed to stand at room temperature for a given time. Subsequently the fluid is strained and filtered. Processing at a temperature of 30–40°C. produces a fluid called a *digestion*, and if the drug is boiled with solvents the term used is *a decoction*. Infusions and some extracts are prepared by these methods.

Percolation. In this process the solvent is passed through the crude drug or powder packed into a column. After sufficient solvent to extract all the soluble ingredients has passed down the column the fluid is bulked and standardized. The resulting fluid is known as a *percolate*. Many tinctures are prepared in this way.

PART TWO

SYSTEMATIC MATERIA MEDICA

the whole theory of prescribing, from the decision on which drug or drugs to use, up to the stage of administering the treatment to the patient. Part II details the drugs which are used to treat the imbalances and diseases of each system of the body and Part III covers the chemotherapeutic agents, mainly the antibiotics and the sulphonamides. Part IV is allotted to the vitamins, hormones (excluding the sex hormones) and the vaccines and sera. Pharmacy, which is dealt with only very briefly, and the Acts and Orders which concern the possession and use of drugs are grouped together in Part V. It is hoped that, in conjunction with the *British Veterinary Codex*, this book will meet most of the requirements of those who have been pressing for a book on these subjects.

I wish to acknowledge the help of all who have contributed advice and encouragement during my several years of travail. In particular I would mention Professor Burrow, Professor of Veterinary Medicine, Royal Veterinary College, University of London; the Principal of the Royal Veterinary College, who has allowed me to make use of its library; Mr. Charles J. Hewlett and the directors of C. J. Hewlett & Son Ltd., who have given me time, advice and encouragement; my secretaries, Mrs. Diana Clarke, who courageously typed almost the whole manuscript, and Mrs. Surridge, who has given invaluable help; Mr. Alexander Thomson, M.R.C.V.S., who read and criticized the mountain of typescript and galley proofs and who has advised on all professional aspects—he has besides my gratitude, my sympathy also; my publishers, for their kindness, advice and patience. To all I offer my sincere thanks. Finally I must mention my wife, who has agreed typescript with manuscript, advised on all matters of syntax and has nobly withstood the loneliness of the last few years; without her the book would never have been completed.

P. W. DAYKIN

ST. ALBANS,
January 1960

ZOOLOGICAL GARDENS CALCUTTA 467N

PREFACE

Wallis Hoare's *Veterinary Materia Medica and Therapeutics* served the veterinary profession well for over 50 years, but changing ideas and requirements, combined with increases in both the number and types of therapeutic agents, made it progressively more difficult to compile each succeeding edition within the framework of the original book. Whole new classes of drugs have been discovered and many of the older drugs have been re-assessed since the publication of the last edition; in consequence, abandonment of the old book and an entirely new approach to the whole subject became imperative.

With the increase in importance attached to the teaching of Experimental Pharmacology and related subjects there has been a considerable decline in the teaching of drug characteristics and their clinical applications; the need for a modern text book of Applied Pharmacology and Therapeutics has thereby been made more urgent. In these circumstances, and making use of personal experience as a practitioner, teacher, examiner and technical adviser, an attempt has been made in this new book to provide the student with the maximum possible help. It is also hoped that teachers and practitioners may find the book of value.

To cover twenty years of new material and yet to retain what among the older therapeutics is still of use has been a task of considerable magnitude, and it has been necessary to modify the original form of several chapters after their completion in order to incorporate more recent information. However, since new information and new drugs are announced almost daily, to sift and determine what is of permanent importance would tax the wisdom of Solomon. The sources of important information are therefore quoted in the text so that the reader, should he so wish, may refer to the original articles and form his own opinions. Even so, where new material has been included an attempt has been made to give as reasoned an evaluation as possible.

One of the difficulties encountered by students is the problem of relating information to its correct context, and for that reason, where necessary, the background of the subject under discussion has been sketched in with the intention of making it clear exactly where the information given fits into the field of disease therapy.

Structurally, the book consists of five sections in which is provided information on the essential physical, chemical and pharmacological characteristics of all the important drugs now in veterinary use in Great Britain; details of actions and uses, toxicity, dosages, and methods of administration are given prominence. Part I provides a general introduction, and includes the method of prescription building, which incorporates

which are more frequently used than the parent alkaloid. The incompatibilities of atropine are also those of a typical alkaloid: atropine will be precipitated from alcoholic solutions such as tinctures, by the addition of water; also salts of heavy metals, particularly silver, lead, mercury and zinc, tannic acid and related acids, will precipitate atropine and its salts.

In addition to the pure atropine salts used in the form of injections, the alkaloid is commonly used as the relatively crude belladonna-plant preparations. The more popular preparations are the powdered leaf, the tincture and a soft extract. The green, soft extract of belladonna, for example, is frequently used to prepare electuaries for the alleviation of symptoms in 'broken-winded' horses.

Actions and Uses. The actions of atropine are equivalent to an increase in sympathetic activity, for the peripheral activity of the parasympathetic system is paralysed at the myo-neural junction, thus allowing the sympathetic system undisputed action in the body. The mechanism of parasympathetic paralysis is one of antagonism of acetylcholine effects. It does not prevent the formation of acetylcholine following nerve stimulation, but prevents it from acting on the cell (Cushny).

External actions are confined to the effect of atropine on the eye, with the exception of some slight dulling of peripheral sensory receptors (Cushny). This ocular effect is well known, for atropine has long been used by oculists to dilate the pupil, enabling the retina and other deep structures of the eye to be easily identified and examined. This dilatation of the pupil or *mydriatic* action is due to paralysis of the oculomotor nerve and hence of the circular muscles of the iris. This allows the radial, sympathetic innervated muscles to respond to the impulses which are normally present, and which are responsible for maintaining tonus. (The iris gives a perfect illustration of the balanced control which is exerted over all involuntary muscle by the two divisions of the autonomic nervous system. In many cases the two act on the same muscle fibres but here that is not the case.)

As a result of this dilatation of the pupil, the muscles of the iris become localized at the periphery of the chambers and must consequently bulge at right angles to the radius. This fills in the filtration angle of the eye and constricts the spaces of Fontana which drain into the circular canal of Schlemm. In the normal eye this is of no significance for the effect usually passes off within two to three days, although exceptionally it may persist for up to a week, and no more than a temporary slowing of aqueous humour circulation occurs, with no ill effects. In eyes where there is any tendency to *glaucoma*, (high intra-ocular pressure) the extra pressure resulting from the iris collapse may be sufficient to cause closure of the spaces. This closure becomes permanent owing to the building up of a pressure which is too great to allow the iris to return to its normal position following dispersal of the atropine effect.

The Alkaloidal Bitters. Many plants contain alkaloids, but the majority of these agents are toxic in very small doses, and it is suggested that the intensely bitter taste is intended as Nature's way of discouraging animals from eating such plants and poisoning themselves. It is not true, however, to say that all plant poisons are alkaloidal and have a bitter taste.

This group of bitters is adequately represented by the preparations of Nux Vomica, B.Vet.C., which are the most frequently used examples of reflex alkaloidal sialagogues. The tincture and powder are the preparations most commonly used; their *dosage* scales are:

The powder:	Horse and Cow:	30–120 gr. (2·0–8·0 G.)
	Sheep and Goat:	10–20 gr. (0·6–1·3 G.)
	Pig:	10–15 gr. (0·6–1·0 G.)
The tincture:	Horse and Cow:	½–1 fl. oz. (16·0–32·0 ml.)
	Sheep and Goat:	15–60 m. (1·0–4·0 ml.)
	Pig:	5–20 m. (0·3–1·3 ml.)

Extracts and Infusions are also available.

The popularity of nux vomica preparations is not entirely due to their bitter action, for the two alkaloids, which are the bitter principles, *strychnine* and *brucine*, have a powerful action on the spinal cord and peripheral nerves once they are absorbed. Brucine is much less active than strychnine but similar in effect. The effect of strychnine is to speed up the progress of nerve impulses, particularly at nerve junctions, so that the general tone of the whole body is improved. In pharmacological terms the alkaloid causes 'facilitation of nerve impulses across the synapses'.

The combined bitter and 'nerve tonic' actions of nux vomica are widely used in the treatment of convalescents by both human and veterinary physicians.

Antisialagogues or Antisialics

These are drugs which reduce the flow and fluidity of saliva. There is often a reduction at the same time of all respiratory and alimentary gland secretions.

The therapeutic aim of antisialagogues is to reduce salivation, particularly during a period of excessive salivation such as may occur during inhalation anæsthesia with ether or chloroform, and also during morphine narcosis. Although there are several agents which will either mechanically, or by their astringent properties, reduce salivation—kaolin and alum are respective examples, only atropine and related alkaloids such as hyoscine and hyoscyamine have much practical value.

Atropine

Derived primarily from *Atropa belladonna*, deadly nightshade, and in lesser quantity from related solanaceous plants such as henbane and thorn apple, atropine is a typical alkaloid; it is therefore a white crystalline solid which is odourless when pure, insoluble in water but soluble in alcohol, and reacts with acids to form salts, e.g. atropine sulphate and hydrochloride,

typical of convulsants or analeptics of which picrotoxin, and leptazol are further examples.

Excessive overdosage produces cortical and medullary depression, coma and death.

2. The action on the *peripheral nervous system.*

This is one of paralysis of the parasympathetic part of the autonomic nervous system. The paralysis is not complete when single therapeutic doses are used, but even partial blocking of the parasympathetic impulses allows greater action of the sympathetic system. The major effects are:

(i) Removal of vagal tone, which results in:

(a) An increase in heart rate equivalent to the amount of vagal depression previously exerted.

(b) Relaxation of intersphincter intestinal muscles and constriction of sphincters.

(c) Shutting down of the splanchnic circulation, which turns large quantities of blood into the circulation.

(d) Shutting down of the alimentary secretory glands, including the pancreas, following the lack of blood supply and digestive activity.

(e) Salivary secretion is proportionately controlled.

(ii) Cutaneous circulation is usually increased, even by therapeutic doses, but sweating is suppressed so that the temperature may rise in those species which rely on the production of sweat for some heat loss. The dog is one species in which the lack of normal sweat glands is responsible for no temperature variation following atropine administration.

(iii) The respiratory rate, and sometimes the depth, is increased. This is associated with a relaxation of the bronchi and suppression of bronchial secretions.

Uses. The main internal uses of atropine are: 1. The alleviation of pulmonary emphysema, (broken wind in horses) in the form of belladonna electuaries, e.g.:

Green Extract of Belladonna, B.P.C.	10 gr.	0·6 G.
Prepared Nux Vomica, B.Vet.C.	30 gr.	2·0 G.
Powdered Gentian, B.Vet.C.	120 gr.	8·0 G.
Excipient	q.s.	q.s.

2. The restriction of salivation and bronchial secretions during anæsthesia, especially with ether and chloroform. This is of particular value in protracted anæsthesia of horses, when copious amounts of saliva and bronchial exudates may be drawn into the lungs and produce pneumonia. Atropine sulphate injections are given subcutaneously 15–20 minutes before induction of anæsthesia using the following *doses*:

Horse and Cow:	$\frac{1}{4} - \frac{1}{2}$ gr. (15–30 mg.)
Sheep:	$\frac{1}{16} - \frac{1}{8}$ gr. (4–8 mg.)
Pig:	$\frac{1}{30} - \frac{1}{16}$ gr. (2–4 mg.)
Dog:	$\frac{1}{200}$ gr. up to $\frac{1}{100}$ (0·3–0·6 mg.)
Cat:	$\frac{1}{200}$ (0·3 mg.)

Besides affecting the iris, the ciliary muscles which control the accommodation, or focus, of the lens by pulling on the suspensory ligaments, are also affected; the lens surfaces become maximally convex and the eye then has a fixed long distance focus. This ciliary paralysis also materially affects filtration.

Eserine, or physostigmine, has been used to reverse the atropine effect where paralysis of the iris for 24–48 hours was contra-indicated. Eye Ointment of Physostigmine, B.Vet.C., (0·125 per cent.) and Eye-drops of Physostigmine, B.Vet.C., (0·5 per cent.) were used for this purpose, but the effect was not completely satisfactory and a synthetic agent was devised similar in effect to atropine. This is *homatropine*. Used in the form of 1–2 per cent. eye drops or eye ointments, homatropine effects which, like atropine effects, are maximal in about 30 minutes, last for, at the most, 24 hours and any hyperactivity can be adequately controlled and reversed (cancelled) by physostigmine. Indeed, where there is a danger of iris adhesion, alternate dilation and constriction of the pupil can be achieved by the alternate use of homatropine and physostigmine. The iris is thus in constant movement and adhesions are less likely.

The mydriatic action of atropine is responsible for the Latin name for deadly nightshade—*Atropa belladonna*. An extract of this plant was used by fashionable ladies of the Roman and pre-Roman eras as a means of dilating their pupils and giving them a luminescent and alluring appearance, hence bella donna, beautiful lady.

Atropine has no other external uses but preparations of belladonna are occasionally used externally.

The tincture and liniment of belladonna are frequently incorporated in udder 'rubbing oils'. The use of this type of preparation is no longer popular since antibiotics have provided rapid control of many acute cases of mastitis, but the rationale of this type of treatment was quite sound. The massage mechanically expressed infected milk and debris from the infected area into the milk well, from whence they could be removed by frequent stripping. Some of the alkaloids present in belladonna, including atropine and hyoscyamine, have a local anodyne action and gave relief from pain in inflamed superficial tissues and the distended skin.

Absorption of atropine from an infection site or from a mucous membrane is rapid but appreciably less absorption occurs through intact skin unless alcoholic solutions are used.

Internal actions. Following absorption the effects of atropine can be divided into two groups—the effects on (1). The central nervous system, and (2). The peripheral nervous system.

1. The action on the *central nervous system.*

In normal therapeutic doses no cerebral effect is apparent. Intravenously in small over-doses atropine has a stimulant and sometimes convulsant action on the cerebral cortex. Larger doses will excessively stimulate the medulla and still larger doses will affect the spinal cord. This sequence is

bitters'. The 'bitter principles' of these drugs vary considerably and only those which contain an alkaloid (an organic nitrogenous base which reacts with acids to form salts) can be grouped according to the chemical nature of the drug which gives them their bitter taste. The others called the 'simple bitters' are divided according to whether or not the preparations made from the plant possess a characteristic odour. There are thus *aromatic simple bitters* such as orange or lemon peel, and *non-aromatic simple bitters* such as gentian, calumba and quassia.

Because they act locally on the taste buds of the tongue all bitters must be administered orally in the form of a powder, drench, or electuary. Tablets, pills, capsules, boluses or administration by stomach tube are useless, for the drugs in these forms do not contact the taste buds or mucosa of the mouth and pharynx.

In order to achieve their full effect bitters should be administered either 5–15 minutes before feeding or actually mixed in with the food.

The value of bitters as therapeutic agents has been questioned in recent years, but, though their use in the smaller species has justifiably lapsed, cattle drenches and horse powders containing gentian and nux vomica are still extensively employed. They are relied upon by experienced practitioners to stimulate and improve the digestion of convalescent cattle and horses. The opponents of therapy with bitters claim that these two species dislike these drugs, but horses, well known for their selective feeding habits, will take them mixed in bran mashes and 'chop'. So readily are they taken that the best of the simple bitters, gentian powder, in spite of its relatively high cost, is frequently used as a bulking and disguising agent for less acceptable drugs.

Dogs and cats object to the taste of bitters, particularly in tincture form. Meat and meat extracts are far more useful salivary and gastric stimulants for carnivorous species.

The Simple Bitters. The preparations of gentian are representative of those of the whole group of simple bitters. These are: a powder, Powdered Gentian, B.Vet.C.; a compound tincture, Compound Tincture of Gentian, B.Vet.C.; a soft extract, Extract of Gentian, B.P.C.; a compound strong, or concentrated, infusion, Concentrated Compound Infusion of Gentian, B.Vet.C.; and a weak, or fresh, compound infusion,

The greenish brown powder and the green tinged brown compound tincture are the two preparations commonly used. Their toxicity is non-existent and the *dosage*-level, which is the same for all the simple bitters therefore falls into the fourth group mentioned in chapter four.

The powder:	Horse and Cow:	½–2 oz.
	Sheep and Goat:	60–120 gr.
	Pig:	40–100 gr.
	Dog and Cat:	not used.
The tincture:	Horse and Cow:	½–2 fl. oz.
	Sheep and Goat:	½–1½ fl. oz.

CHAPTER 6

THE ALIMENTARY SYSTEM

(i) THE MOUTH AND PHARYNX, THE ŒSOPHAGUS, THE STOMACH

To assist in classification the alimentary system has been divided into four sections: (a) mouth and pharynx, (b) œsophagus, (c) stomach and (d) intestines. Obviously there will be some drugs which will have an effect on more than one section but, as in other chapters, each drug will be placed in that section where its most important action is exerted. The importance of the action will be determined from a therapeutic view-point.

The Mouth and Pharynx

Sialagogues or Sialics

These are drugs which are used to increase the volume and fluidity of saliva. This definition excludes any drug which effects an increase in only one of these characteristics; it particularly excludes sympathetic nerve stimulants which, though they cause a slight increase in volume, tend to decrease the fluidity. Also excluded are those agents not specifically used to create salivation and agents such as were used by Pavlow, which induce salivation by means of psychosomatic reflexes.

The aim of all sialagogues is to improve a patient's digestion and appetite by increasing saliva production. In addition to causing salivation these drugs usually increase gastric secretion and for this reason some may also be classed as stomachics or gastric stimulants.

Sialagogues may be divided into two groups according to the means by which salivation is induced.

1. *Reflex sialagogues* are those which, by stimulating the taste buds on the tongue, initiate a reflex which results in salivation. Gentian, calumba, quassia and nux vomica preparations are commonly used examples of this group.

2. *Direct sialagogues* are those which by-pass the sensory half of the salivary reflex and cause salivation by direct stimulation of the parasympathetic nervous system. Carbamylcholine, arecoline, pilocarpine and physostigmine are examples, but not one of these drugs is used solely for this purpose. (See neuromuscular purgatives).

Reflex Sialagogues. These are most commonly referred to as 'the

The Alkaloidal Bitters. Many plants contain alkaloids, but the majority of these agents are toxic in very small doses, and it is suggested that the intensely bitter taste is intended as Nature's way of discouraging animals from eating such plants and poisoning themselves. It is not true, however, to say that all plant poisons are alkaloidal and have a bitter taste.

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Extracts and Infusions are also available.

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Atropine

Derived primarily from *Atropa belladonna*, deadly nightshade, and in lesser quantity from related solanaceous plants such as henbane and thorn apple, atropine is a typical alkaloid; it is therefore a white crystalline solid which is odourless when pure, insoluble in water but soluble in alcohol, and reacts with acids to form salts, e.g. atropine sulphate and hydrochloride,

which are more frequently used than the parent alkaloid. The incompatibilities of atropine are also those of a typical alkaloid: atropine will be precipitated from alcoholic solutions such as tinctures, by the addition of water; also salts of heavy metals, particularly silver, lead, mercury and zinc, tannic acid and related acids, will precipitate atropine and its salts.

In addition to the pure atropine salts used in the form of injections, the alkaloid is commonly used as the relatively crude belladonna-plant preparations. The more popular preparations are the powdered leaf, the tincture and a soft extract. The green, soft extract of belladonna, for example, is frequently used to prepare electuaries for the alleviation of symptoms in 'broken-winded' horses.

Actions and Uses. The actions of atropine are equivalent to an increase in sympathetic activity, for the peripheral activity of the parasympathetic system is paralysed at the myo-neural junction, thus allowing the sympathetic system undisputed action in the body. The mechanism of parasympathetic paralysis is one of antagonism of acetylcholine effects. It does not prevent the formation of acetylcholine following nerve stimulation, but prevents it from acting on the cell (Cushny).

External actions are confined to the effect of atropine on the eye, with the exception of some slight dulling of peripheral sensory receptors (Cushny). This ocular effect is well known, for atropine has long been used by oculists to dilate the pupil, enabling the retina and other deep structures of the eye to be easily identified and examined. This dilatation of the pupil or *mydriatic* action is due to paralysis of the oculomotor nerve and hence of the circular muscles of the iris. This allows the radial, sympathetic innervated muscles to respond to the impulses which are normally present, and which are responsible for maintaining tonus. (The iris gives a perfect illustration of the balanced control which is exerted over all involuntary muscle by the two divisions of the autonomic nervous system. In many cases the two act on the same muscle fibres but here that is not the case.)

As a result of this dilatation of the pupil, the muscles of the iris become localized at the periphery of the chambers and must consequently bulge at right angles to the radius. This fills in the filtration angle of the eye and constricts the spaces of Fontana which drain into the circular canal of Schlemm. In the normal eye this is of no significance for the effect usually passes off within two to three days, although exceptionally it may persist for up to a week, and no more than a temporary slowing of aqueous humour circulation occurs, with no ill effects. In eyes where there is any tendency to *glaucoma*, (high intra-ocular pressure) the extra pressure resulting from the iris collapse may be sufficient to cause closure of the spaces. This closure becomes permanent owing to the building up of a pressure which is too great to allow the iris to return to its normal position following dispersal of the atropine effect.

Besides affecting the iris, the ciliary muscles which control the accommodation, or focus, of the lens by pulling on the suspensory ligaments, are also affected; the lens surfaces become maximally convex and the eye then has a fixed long distance focus. This ciliary paralysis also materially affects filtration.

Eserine, or physostigmine, has been used to reverse the atropine effect where paralysis of the iris for 24–48 hours was contra-indicated. Eye Ointment of Physostigmine, B.Vet.C., (0·125 per cent.) and Eye-drops of Physostigmine, B.Vet.C., (0·5 per cent.) were used for this purpose, but the effect was not completely satisfactory and a synthetic agent was devised similar in effect to atropine. This is *homatropine*. Used in the form of 1–2 per cent. eye drops or eye ointments, homatropine effects which, like atropine effects, are maximal in about 30 minutes, last for, at the most, 24 hours and any hyperactivity can be adequately controlled and reversed (cancelled) by physostigmine. Indeed, where there is a danger of iris adhesion, alternate dilation and constriction of the pupil can be achieved by the alternate use of homatropine and physostigmine. The iris is thus in constant movement and adhesions are less likely.

The mydriatic action of atropine is responsible for the Latin name for deadly nightshade—*Atropa belladonna*. An extract of this plant was used by fashionable ladies of the Roman and pre-Roman eras as a means of dilating their pupils and giving them a luminescent and alluring appearance, hence bella donna, beautiful lady.

Atropine has no other external uses but preparations of belladonna are occasionally used externally.

The tincture and liniment of belladonna are frequently incorporated in udder 'rubbing oils'. The use of this type of preparation is no longer popular since antibiotics have provided rapid control of many acute cases of mastitis, but the rationale of this type of treatment was quite sound. The massage mechanically expressed infected milk and debris from the infected area into the milk well, from whence they could be removed by frequent stripping. Some of the alkaloids present in belladonna, including atropine and hyoscyamine, have a local anodyne action and gave relief from pain in inflamed superficial tissues and the distended skin.

Absorption of atropine from an infection site or from a mucous membrane is rapid but appreciably less absorption occurs through intact skin unless alcoholic solutions are used.

Internal actions. Following absorption the effects of atropine can be divided into two groups—the effects on (1). The central nervous system, and (2). The peripheral nervous system.

1. The action on the *central nervous system.*

In normal therapeutic doses no cerebral effect is apparent. Intravenously in small over-doses atropine has a stimulant and sometimes convulsant action on the cerebral cortex. Larger doses will excessively stimulate the medulla and still larger doses will affect the spinal cord. This sequence is

typical of convulsants or analeptics of which picrotoxin, and leptazol are further examples.

Excessive overdosage produces cortical and medullary depression, coma and death.

2. The action on the *peripheral nervous system.*

This is one of paralysis of the parasympathetic part of the autonomic nervous system. The paralysis is not complete when single therapeutic doses are used, but even partial blocking of the parasympathetic impulses allows greater action of the sympathetic system. The major effects are:

(i) Removal of vagal tone, which results in:

(a) An increase in heart rate equivalent to the amount of vagal depression previously exerted.

(b) Relaxation of intersphincter intestinal muscles and constriction of sphincters.

(c) Shutting down of the splanchnic circulation, which turns large quantities of blood into the circulation.

(d) Shutting down of the alimentary secretory glands, including the pancreas, following the lack of blood supply and digestive activity.

(e) Salivary secretion is proportionately controlled.

(ii) Cutaneous circulation is usually increased, even by therapeutic doses, but sweating is suppressed so that the temperature may rise in those species which rely on the production of sweat for some heat loss. The dog is one species in which the lack of normal sweat glands is responsible for no temperature variation following atropine administration.

(iii) The respiratory rate, and sometimes the depth, is increased. This is associated with a relaxation of the bronchi and suppression of bronchial secretions.

Uses. The main internal uses of atropine are: 1. The alleviation of pulmonary emphysema, (broken wind in horses) in the form of belladonna electuaries, e.g.:

Green Extract of Belladonna, B.P.C.	10 gr.	0·6 G.
Prepared Nux Vomica, B.Vet.C.	30 gr.	2·0 G.
Powdered Gentian, B.Vet.C.	120 gr.	8·0 G.
Excipient	q.s.	q.s.

2. The restriction of salivation and bronchial secretions during anæsthesia, especially with ether and chloroform. This is of particular value in protracted anæsthesia of horses, when copious amounts of saliva and bronchial exudates may be drawn into the lungs and produce pneumonia. Atropine sulphate injections are given subcutaneously 15–20 minutes before induction of anæsthesia using the following *doses*:

Horse and Cow:	$\frac{1}{4} - \frac{1}{2}$ gr. (15–30 mg.)
Sheep:	$\frac{1}{16} - \frac{1}{8}$ gr. (4–8 mg.)
Pig:	$\frac{1}{30} - \frac{1}{16}$ gr. (2–4 mg.)
Dog:	$\frac{1}{200}$ gr. up to $\frac{1}{100}$ (0·3–0·6 mg.)
Cat:	$\frac{1}{200}$ (0·3 mg.)

These doses can be used in cases of ptyalism—excessive salivation—which may occur in some types of poisoning such as lead and mercury poisoning, in diseases of the salivary glands such as strangles in horses, and in severe affections of the oral mucosa and tongue particularly if swallowing is affected, as in 'wooden tongue' of cattle.

3. The use as an *antispasmodic* where excessive parasympathetic stimulation is responsible for 'tonus rings' or circular muscle spasm. This applies to all smooth muscle of hollow organs, of the uterus, ureter, bronchioles, but particularly of the intestines. Whenever parasympathetic stimulants such as carbamylcholine are administered as purgatives to horses, atropine should always be available to counteract excessive stimulation. The quantity of atropine necessary is not proportional to the level of overstimulation but is a fairly constant proportion of the animal's weight, 2–3 mg. per cwt., that is ½–1 gr. per animal.

Demulcents

These are agents which are used to lubricate, soothe and protect an alimentary mucous membrane, but the term is usually applied only to those affecting the mouth, pharyngeal, œsophageal and gastric mucosæ.

Demulcents serve several purposes in that they may be used to protect mucosæ prior to, and during, administration of irritant substances; to allay irritation and inflammation already caused either by chemical or bacterial action; to act as innocuous bulking agents for more active drugs; and to act as sweetening, flavouring and disguising agents: some are also easily digested foods, *vide* the carbohydrates and the animal proteins.

They consist of several groups of compounds which differ very widely in their chemical structure.

(1) The sugars: This group includes sucrose, lactose and related carbohydrates such as honey, treacle (molasses), malt extracts, starch, flour, and linseed mucilages.

(2) The gums, such as acacia and tragacanth.

(3) Animal proteins such as gelatin and egg albumen.

(4) Vegetable oils and glycerol.

(5) Miscellaneous compounds such as liquorice powder, the hydrocarbon liquid and soft paraffins, and colloid forming compounds such as bentonite (a hydrated aluminium silicate *q.v.*) and carboxymethylcellulose.

Groups 1, 2, and 3 and liquorice powder can be conveniently mentioned at this point, but the other groups will be mentioned elsewhere—see Index.

The Sugars. All the sugars, in solution, and their relatives, starch, flour and linseed, in gruel form, have good demulcent properties. For this reason *sucrose* in the form of Syrupus, B.Vet.C., a 66⅔ per cent. sucrose solution in water, is used as a vehicle and bulking agent for many official and unofficial syrups, the active ingredients of which are often quite irritant. Syrup of Squill, B.P.C., is used as an irritant expectorant in both medical and veterinary cough mixtures. Its sweet disguising taste is very

useful in this type of preparation, and also in those containing alkaloids, such as Syrup of Codeine Phosphate, B.Vet.C. Honey, treacle, and malt have similar characteristics but their semi-solid nature makes them especially useful as electuary bases for both small and large animals.

As a food, *malt* has advantages over other demulcent carbohydrates for, besides various sugars, it contains diastase, an enzyme which is capable of converting large quantities of starch into easily assimilated sugar. It also contains appreciable proportions of the B complex of vitamins. As a convalescent treatment *doses* of up to 1 oz. may be given to dogs, calves, and foals, but large doses tend to have an aperient effect and it is this which controls dosage in any particular individual.

Treacle is frequently used as an electuary base, for it is a readily available household food and the owner is able, in an emergency, to make his own electuary from powder left by the veterinary surgeon. The sugar content of treacle and molasses has been used as a treatment of acetonæmia in cattle and pregnancy toxæmia in ewes but it has, in recent years, been established that these remedies aggravate the conditions. This is because the main fermentation product of treacle, or even glucose, in the rumen is β-hydroxybutyric acid which, when absorbed, is added to that already present in the blood. As the high level of this organic acid in the blood is partially responsible for the symptoms, and as the acid cannot be converted by the tissues into energy-providing carbohydrates, the acetonæmia is in no way improved. Moreover, continued dosing with molasses or treacle in the quantities recommended in the past soon produces scouring.

Dextrose, B.Vet.C., formerly known as glucose, is not so useful as a sweetening agent, for neither lactose nor dextrose are markedly sweet. This is often an advantage, for dextrose is more acceptable to small animals, enabling larger quantities to be given as a food and as a *gastric sedative* or *antemetic*. *Dosage* is limited only by the amount accepted by the individual. Parenterally, dextrose, either in a 20 per cent. solution subcutaneously or 40 per cent. intravenously, supplies carbohydrate for the treatment of debility or acetonæmia. It is not advisable to use the 40 per cent. concentration subcutaneously, for the osmotic pressure is high and abscess formation may occur. Dextrose is also used as a food and partly as a blood volume maintaining substance in the form of 'glucose-gum-saline,' which contains 5 per cent. dextrose and 6 per cent. gum acacia in normal saline. (This is no longer considered a safe blood-volume expander.) Glucose saline is a similar preparation. These are available for the treatment of shock and debility in all species.

The physical and mechanical characteristics of these carbohydrates are made use of in various ways. *Sucrose* in concentrations of about 66 per cent. in water is used to increase the density of fluids prepared from fæces and skin scrapings, so that worm eggs and skin parasites will float up to the surface of these fluids from whence they are easily removed and prepared for microscopic examination. This is the so-called sugar-flotation

method for preparing diagnostic specimens. *Lactose* is frequently used as an inert bulking substance for tablets, and *starch* is commonly used as a disintegrating substance for incorporating in tablets. (The B.P. gives a standard disintegration time for official tablets.)

The Gums. Acacia, B.Vet.C., commonly known as 'Gum Arabic', and Tragacanth, B.Vet.C., or 'Gum Dragon', which are shrub exudates, are of less importance than formerly. They are useful in the making of emulsions *for internal use only* in animals (they matt the hair too much for external use); they combine emulsifying and demulcent properties. Mucilage of Acacia, B.Vet.C., is useful as a suspending agent in drenches containing heavy powders such as heavy magnesium oxide. Tragacanth is used in 'barium meal' as a suspending agent for barium sulphate; the meal is used as a radio-opaque diagnostic drench.

The use of acacia to increase the viscosity of blood volume expanding injections is not now so popular, for the gum-saline containing 6 per cent. gum acacia remains in the blood for a relatively short period. Some workers claim that gum-saline may even hurry on collapse and death. This is attributed partly to interference with liver function, for the acacia is removed rapidly from the blood and stored in the liver, where it remains for a long time. The danger of exceeding the maximum circulatory volume and damaging the 'capillary bed' is always present when treating shock by intravenous injection.

Liquorice. Powdered Liquorice, B.Vet.C., an aromatic brown powder, is used as a demulcent, flavouring and bulking agent for powders to be administered in the food of farm animals. It contains, besides the sweet glycerin, a cortisone-like substance, glycyrrhetinic acid, which is used as a cortisone substitute. As a demulcent and diluent the *dosage* varies from about 40 grains (2·6 G.) for the dog, to 3 oz. (85·0 G.) for the horse and cow.

Aniseed. Powdered Anise, B.Vet.C., is sometimes used instead of liquorice, for its stronger flavour is more readily accepted by animals, and its lower dosage of 1 oz. maximum for horses and cattle is useful where large powders are not required. It has no demulcent properties, but is carminative and antispasmodic in the stomach and intestine. Anise Oil, B.Vet.C., has a strong odour which has suggested its use as a fly repellant, although it is not very efficient for this purpose. Some slight expectorant action occurs during excretion.

Gelatin, B.Vet.C., and *egg albumen* are extremely good demulcents but the latter is the only one used to any marked degree in veterinary practice. If egg albumen is whipped up with a little glucose a very good demulcent and nutritional supplement is made. A teaspoonful administered every hour or so will alleviate emesis of local, but not central, origin in dogs and cats.

The Œsophagus

In ruminants, the closure of the œsophageal groove is an important factor in therapy, particularly against helminth parasites, for this closure directs fluids straight into the abomasum, the home of some of the most important ruminant worms. The groove in young calves and lambs is closed by stimulation with milk or water, but adult sheep require 1 per cent. copper sulphate or merely a crystal rubbed on the oral mucosa. Adult cattle show no œsophageal reaction to copper, but it has been shown that 2 fl. oz. (60 ml.) of a 10 per cent. sodium bicarbonate solution will give rapid closure. There are indications that the closure reflex can be conditioned. Investigations on the species difference and the conditioning possibilities are continuing.

Parasympathomimetic drugs such as arecoline or pilocarpine have been used in ½ gr. (30 mg.) doses to stimulate salivation and increase œsophageal peristalsis for the relief of choke in the cow and horse; choke may be caused by foreign bodies such as potatoes, pieces of turnip, sugar beet pulp etc. in the œsophagus. Carbamylcholine is more frequently used nowadays in small doses repeated at 6–12 hourly intervals (1–2 ml. of 1 : 1,000 solution, i.e. 1·0 to 2·0 mg.).

The Stomach

The drugs which act on the stomach are classified into carminatives, antispasmodics and antizymotics, emetics and antemetics (or gastric sedatives), amongst which are included the antacids.

Carminatives

These are drugs which, when administered orally, cause the expulsion of gases from the stomach, politely known as eructation. They have also been used in flatulent colic to assist evacuation of gases from the large intestine.

They are mainly volatile compounds. There are thus compounds which contain volatile oils such as powdered aniseed and ginger, pure volatile oils such as oil of turpentine and oil of peppermint, and substances derived from volatile oils by cooling, the stearoptenes camphor and menthol. Certain volatile anæsthetics and related compounds also have a carminative action: chloroform, ether and alcohol are examples.

These compounds in the correct dosage cause mild irritation of the gastro-intestinal mucosa which results in vasodilatation. This is probably responsible for the well known 'warm' feeling which follows the swallowing of these compounds. Other actions which result are the relaxation of gastro-intestinal musculature, but particularly the cardiac sphincter of the stomach, for a period of up to 30 minutes, which probably plays a large part in releasing gases from the stomach.

The antispasmodic action of some of these drugs, particularly ginger, is due to the same factors which give the carminative effect. The rhythm and tone of peristalsis may be initially increased, but this is often followed by a decrease of movement which will help in relaxing colic spasms. (Atropine and homatropine which exert the effect by a parasympatholytic action have already been mentioned as antispasmodics, see ref. p. 67. Hyoscine and hyoscyamus have a similar effect.) Pethidine also has a marked antispasmodic action.

The carminative actions of these drugs are not constant and their use for this specific purpose is decreasing, particularly in small animals. Many of these drugs are retained for other purposes. For example, ginger is used in horse and cattle practice as an antispasmodic which can also be used as a flavouring and bulking agent, whilst turpentine is used as an antizymotic and antispasmodic for horses and cows as well as for its external counter-irritant action. Where carminative action does occur this is often a useful adjunct.

Ginger

Zingiber, familar to all as root, stem, and powdered ginger, is still widely used in horse and cattle practice. The yellow-brown powder is used in *doses* of ½–2 oz. (15·0–60·0 G.) for horses and cattle, incorporated in powders for oral use. Where cattle are drenched, the ginger can be included in the form of either the strong tincture or, better than this, the weak tincture, the *dose* of which for horses and cattle is ½–2 fl. oz. (15·0–60·0 ml.) For small animals the *doses* are 5–60 m. (0·3–4·0 ml.) of either the weak tincture or the syrup prepared from the strong tincture; these are not frequently used.

The use of ginger is restricted to internal administration as a flavouring and bulking agent, and as a carminative and antispasmodic. Typical combinations would be:

1. A horse physic ball:

Aloes, B.Vet.C.	240 gr.	16.0 G.
Powdered Ginger, B.Vet.C.	120 gr.	8·0 G.
Soft Soap, B.Vet.C.	q.s.	q.s.

The powdered ginger is incorporated essentially as an antispasmodic to relieve the griping spasms produced by the strongly irritant aloes.

2. A carminative and tonic:

Powdered Nux Vomica, B.Vet.C.	30 gr.	2·0 G.
Ammonium Carbonate, B.P.C. '34.	120 gr.	8·0 G.
Powdered Ginger, B.Vet.C.	240 gr.	16·0 G.

This powder would actually be administered suspended in a pint of warm water, twice daily for three or four days. It would be used during the convalescent period following an attack of 'indigestion'—often an upset in rumination due to unidentified causes.

Antizymotics.

Strictly defined, these agents are drugs which prevent or decrease bacterial or enzyme fermentation. Their use is aimed at the prevention of further gas production in tympany and bloat in ruminants, and flatulent or tympanitic colic in horses. These conditions occur only occasionally in other animals and treatment follows the same principles as in the larger species. The two conditions in cattle are the ones of greatest importance.

Bloat and tympany in ruminants have historically been treated, irrespective of ætiology, with volatile oils, especially turpentine, with formalin, phenol, and with phenolic compounds such as salol, cresol and lysol. Chloroform, chloral hydrate and ethyl alcohol have also been used (the last of these often in the form of gin, whisky or ale!).

More recent research has indicated the need for accurate diagnosis of both the *exciting* cause of ruminal distension and also the *immediate* cause.

The *exciting* cause is usually ruminal stasis, which may be due to one of several circumstances: œsophageal obstruction, too little or too much bulk in the rumen, too high or too low a pH, abnormal diet, and foreign bodies in the reticulum are some examples.

The *immediate* causes can be divided into three groups.

1. Free gas in the rumen (tympany),
2. Gas locked in the bubbles of a frothy mass (bloat),
3. Mechanical distension by abnormal food eaten in quantity following accidental access.

The treatment of groups 1 and 3 are similar and follow the historical methods, but frothy bloat must be treated as specifically as possible, and for this there are new agents which may be listed as 'surface tension increasing/decreasing' or 'antifrothing agents'.

Free gas may be removed by stomach tube or trocar and cannula. If a cannula inserted through the left flank is used, it is usual to leave it in place for 12–24 hours: a longer period predisposes to æration and a change of ruminal flora. Although this period of change may be short-lived it can aggravate the existing condition.

Following removal of the gas, and therefore any danger of asphyxia by diaphragmatic pressure, the next procedure will depend on the initial or 'exciting' cause. Where the cause requires surgical interference, such as œsophageal obstruction and foreign bodies in the reticulum, the treatment is obvious. Where no histopathological factors are involved, and by this is meant such pathological changes in structure as those caused by actinomycosis of the rumen and œsophagus or enlargement of mediastinal lymph glands, some attempt at diagnosing the physiological and pathological changes must be made before rational treatment can be applied. The history of the case will often indicate dietary causes, and a clinical examination will help to assess the volume of ruminal contents and diagnose the milk fever and febrile conditions. By a process of elimination

a hard core of undiagnosable cases will be left. This nucleus of cases is treated empirically.

Where dietary causes are involved the remedy is obvious, but with more abstruse physiological causes, pH changes, etc., the diagnosis and treatment is more difficult. In the United States it is common practice with all these cases to remove a regurgitated bolus from the mouth of a normal ruminating cow and administer it immediately to a non-ruminating animal: modifications of this treatment are the administration of 24-hour samples of ruminal fluid from slaughtered normal animals or exciccated ruminal contents. Extremely good results are reported, but the mode of action of the treatment is as yet undetermined, though claims are made on the basis of readjustment of pH and also on the basis of re-establishment of normal bacterial strains.

In Britain this method of treatment is not popular. Reliance for the reinstatement of ruminal movement in cattle is placed on such drugs as powdered nux vomica in 30–90 grain doses (1·0–3·0 G.) by mouth, liquor strychninæ hydrochloridi (1 per cent. solution of strychnine hydrochloride) in 4·0–6·0 ml. doses subcutaneously, and barium chloride in 15–30 gr. doses by mouth. (This last treatment is not recommended.) Perhaps the most popular treatment, however, is the subcutaneous injection of 1–3 ml. of carbamylcholine, Carbachol, B.Vet.C., 1 : 1,000 injection. This injection, repeated at one or two hourly intervals until rumination is re-established, is probably the best available for restarting ruminal movement. Two or three injections are sometimes required.

If the fermentation processes still continue, it is usual to administer an antizymotic; 1 fl. oz. of turpentine in ½–1 pint of linseed oil (15·0–30·0 ml. in 300–600 ml.) is the basic formula of most cattle drenches used. These may be given by stomach tube, as a drench or, if a trocar and cannula are used, they may be injected directly into the rumen through the cannula. In the last case care must be taken to ensure that the cannula has not been displaced by abdominal movements lest the fluid is introduced into the peritoneal cavity. A three inch, wide-bore needle is very often used. In sheep the doses will be smaller: 60–120 m. in 2–10 fl. oz. (4·0–8·0 ml. in 60–300 ml.). Formalin in doses of 60 m. (4·0 ml.) three times daily for cattle in ½ pint of water, or 10–15 m. (0·6–1·0 ml.) in a few ounces of water for sheep have also given good results. The use of phenol, lysol and similar agents is not recommended nowadays.

The treatment of conditions in Group 3 is complicated, for several factors must be considered: the distension of the rumen by the swelling mass of material, which leads to pressure paralysis of the muscle; the possibility of these substances—sugar beet pulp, potatoes, wheat and barley, fermenting and producing gas; and the danger of asphyxia, particularly as the animal is usually recumbent.

The distension and asphyxia can be relieved only by rumenotomy, and the practitioner must decide when a dangerous degree of distension has

been reached. The fermentation and further swelling of grains can be controlled within limits by formalin solutions and by restricting fluid intake, respectively.

Frothy bloat is typified by the inability to relieve the ruminal distension by stomach tube, probang, or trocar and cannula. All that exudes from any of these instruments is a small amount of fluid and bubbles. The condition often appears and matures very rapidly, and what is known as 'jack-knife' therapy in the United States is resorted to by the more courageous owners. With less courageous owners this incision of flank skin, muscle, and rumen, is shirked and the animal dies unless the veterinary surgeon arrives quickly. Where this emergency 'operation' is performed, peritonitis often follows and it should therefore be avoided wherever possible.

The bubbles are thought to result, in many cases, from a high intake of saponins and similar compounds which only slightly reduce or even increase the surface tension of the fluid within the rumen (Nichols *et al.*, 1956, 1957), and produce a high viscosity foam (Johns, 1958). It has been observed for centuries that bloat occurs most frequently on lush clover pastures. All clovers, and alfalfa particularly, have a high saponin content. Other exciting causes such as lack of roughage in the diet and toxic substances causing ruminal stasis are also implicated.

The rational treatment for this high viscosity foam is to reverse the process by diffusing throughout the rumen agents which cause a reduction in surface tension. Turpentine and paraffin (kerosene) have been in use for many years but more recently organic silicones, particularly methylsilicone in a fine state of division, have been added to these. Fixed oil-detergent mixtures have been sprayed on pastures and administered orally, with fairly good results (Johns, 1958; Southcott *et al.*, 1958). Complex organic ethylene oxide, other emulsifying agents, and penicillin in 50–200 mg doses are also used successfully (Johns, 1956, 1958).

Oil of Turpentine. (Oleum Terebinthinæ.) This is the most important volatile oil in veterinary medicine, and its characteristics are often quoted as typifying the group characters. It has a typical odour, is a colourless mobile liquid which yellows with age, is insoluble in water but miscible with organic solvents including alcohol, benzol, chloroform and fixed oils. The characteristic odour is capable of tainting flesh and milk, and turpentine therefore should neither be administered within 4 days of slaughter, nor given to animals where the milk is to be sold. Its irritant properties make a demulcent vehicle essential for oral administration.

The preparations of turpentine include a sulphonation product *terebene* which is used primarily as an inhalant, Liniment of Turpentine, B.P., or 'compound camphor liniment,' and White Liniment, B.Vet.C., or white oils. The first liniment contains turpentine 65 per cent., camphor 5 per cent., soft soap and water to 100 per cent., whilst the second consists of 8·33 per cent. oleic acid, 4·5 per cent. dilute solution of ammonia, 1·25 per

cent. ammonium chloride, 25 per cent. turpentine oil, and 62·5 per cent. water. A widely used but unofficial formula consists of turpentine oil 1 fl. oz. (30·0 ml.), ammonium carbonate 120 gr. (8·0 G.), soft soap ½ oz. (15·0 G.), and water to 6 or 8 oz. (180–240 ml.).

Dosage. The horse and cow will need from ½–2 fl. oz. (15–60 ml.) and ½–3 fl. oz. (15–90 ml.) respectively, the sheep up to 180 m. (12·0 ml.) and the pig up to 60 m. (4·0 ml.)

Actions. The *external* action of importance is that of counter-irritation (see Agents used on the Skin, p. 365). The two degrees of counter-irritation can be achieved: a rubefacient or reddening effect by application in liniment form with friction, and vesication or blistering by preventing evaporation, which is achieved by bandaging. Severity of action in both cases can be varied by shortening or lengthening the period of rubbing. It is well known that horses are, as a species, susceptible to turpentine and ammonia vesication so that extra care must be taken with these animals, particularly thin skinned blood stock.

The strong odour of turpentine is sometimes utilized as a disguising agent in ointment compounding.

Internally turpentine acts before absorption as a reflex sialagogue, a carminative, and an antizymotic, when it is administered mixed in linseed oil. A representative formula for a horse colic treatment administered by stomach tube would be:

R Chloral hydrate	½ oz. (15·0 G.)
Oil of turpentine	1 oz. (30·0 G.)
Linseed oil to	1 pint (600 ml.)

Further actions of less importance are (1) an *anthelmintic* effect on roundworms in the horse when it has been combined with oil of chenopodium—oil of turpentine 1 fl. oz. (30 ml.), oil of chenopodium (American wormseed) 120 m. (8·0 ml.), and linseed oil to 1 pint (600 ml.).

An action has been claimed against lung-worms when intratracheal injection is made but the whole principle of these injections is not recommended.

(2) A reflex cardiac and respiratory stimulant from gastric irritation.

Absorption from the intestine is quite rapid, and circulation in the blood causes no change in the constitution, nor is any therapeutic effect seen at this stage when dosage is normal.

Excretion is typical of all volatile oils and commences quite soon after administration. The general effect is that of stimulating all secretions, due to irritation of the various glands and organs which provide excretory routes—the salivary glands, the lungs, the milk, urine and sweat glands. Thus an expectorant effect occurs in the bronchi, and the breath has an odour of turpentine by which undisclosed therapy can be confirmed.

Diuresis results from dilation of the renal blood vessels due to irritation, and also resorption by the tubules is decreased. An odour, classically described as that of violets, is given to the urine. During excretion by the skin irritation of the sweat glands occurs, along with dilation of the blood vessels and sweating (diaphoresis)—hence turpentine can be classed as a mild diaphoretic.

Overdosage will give symptoms which one would expect from a powerful irritant—severe gastro-enteritis, liver damage, and nephritis, with an increased flow of dark, and possibly bloodstained, urine initially, followed by a decrease, and possibly a cessation, of urine excretion. Nervous excitement symptoms are also reported. Treatment is symptomatic, as for most chemical poisons—gastro-intestinal sedatives, urinary sedatives, cardiovascular diuretics, sugar to build up the glycogen reserves, and decreased nitrogen (protein) intake to restrict the work of the liver and the build up of nitrogen compounds, particularly urea, in the blood.

The Silicones. These are organic compounds of silicon with a basic structure of alternating silicon and oxygen atoms. The silicon atoms have attached to them various organic groups such as methyl and phenyl groups. It is those silicones which possess methyl groupings which are of importance in veterinary work because of their important property of increasing surface tension of fluids when added in very small amounts. Their action in bloat is probably one of decreasing foam stability.

Polymerized Methyl Silicone is a viscous translucent liquid which is non-volatile and chemically inert, tasteless and non-toxic. It is used for the treatment of bloat in concentrations of 2–5 per cent. in fluid hydrocarbons such as purified kerosene. *Dosage* varies from 100 ml. of the lower concentrations to 50 ml. of the higher ones. Administration is by stomach tube or drench, diluted with water, or more rapidly by injection directly into the rumen using a cardiac needle or fine cannula.

Other silicones are used for coating glassware from which complete fluid evacuation is required as with antibiotic and similarly expensive and active drugs. When syringe plungers are coated certain silicones will act as almost permanent lubricants. The lubricant, non-reactive and coating properties are also utilized when coating needles and cannulæ which are intended to remain inserted within blood vessels for long periods. This coating smooths the needle surfaces so well that fibrin will not deposit on the surface of the metal and clotting will not therefore take place in contact with, or inside the needle.

Emetics

True emesis is not possible in the horse, ruminants and rats. Regurgitation of stomach contents sometimes occurs in all these species particularly in young ruminants, but where it occurs in adults the animal seldom lives long after the event. Any regurgitation in the horse occurs via the nose. True emesis is, of course, described as a reflex in which the pylorus and

the pyloric area of the stomach contract, the fundus relaxes and the cardia opens; abdominal contraction allied with thoracic and diaphragmatic relaxation drives the stomach contents into the œsophagus; the œsophagus and thorax then contract, forcing some of the material back into the stomach and the rest into the mouth.

Emesis may be caused reflexly by irritation of the stomach mucosa, or centrally by the stimulation of the vomiting centre situated in the medulla just below the third ventricle.

Reflex Emetics. The irritant substances used are mainly inorganic salts, sodium chloride, sodium carbonate (washing soda), copper and zinc sulphates; mustard is also used. Many other substances such as powdered digitalis, aspirin, ipecacuanha, and antimony and potassium tartrate can also induce vomition; the last two examples were once used as emetics, but they are unreliable and dangerous, particularly the last, 'tartar emetic', and are no longer in use for this purpose.

The sodium salts and mustard are usually available in the home, and are therefore always at hand when an emergency treatment is necessary.

The chloride of sodium can be used in crystalline form as half a teaspoonful thrown onto the back of the tongue or as a solution, when 1–2 teaspoonsful may be dissolved in half a cupful of tepid water and given as a drench. The carbonate is used in the form of one sizeable crystal pushed over the back of the tongue. Copper sulphate is used in the form of a 1 per cent. aqueous solution of which up to half a cupful may be required. The zinc sulphate is similarly administered but the mustard requires ½–1 tablespoonful in ½–1 cup of tepid water.

Vomition usually occurs within 15 minutes of administration, but most of these drugs are unreliable as emetics. For this reason the sodium salts are preferred as no deleterious effect results from non-emesis, whereas purgatives or gastric lavage are needed if vomition does not follow the administration of copper or zinc salts, which are all toxic following absorption.

Central Emetics. Apomorphine hydrochloride, and more recently carbamylcholine chloride, (Carbachol, B.Vet.C.) are used to stimulate the vomiting centre in dogs and to cause emesis.

1–2 ml. doses of carbamylcholine chloride 1 : 1,000 injection have been used in dogs to produce emesis by central effect. This is ten times the dose required for purgation. Its value has yet to be confirmed.

Apomorphine Hydrochloride

This is an alkaloid derived from morphine by reaction with hydrochloric acid. It has all the properties of alkaloids, and though derived from opium it is, for obvious reasons, not included in the D.D.A.

Actions and Uses. The actions of apomorphine are peculiar in that the initial stimulatory properties of morphine are intensified, whereas the secondary depressant effects are minimal. The stimulatory effect is almost

entirely specific to the vomiting centre, and, following administration, vomition occurs within two or three minutes, preceded by nausea and salivation; emesis may continue for 5–15 minutes depending upon the size of dose and susceptibility of the individual. Exhaustion is often quite marked and is intensified by the depressant after-effects of the apomorphine.

The use of this drug is indicated where poisons have been recently ingested or where smooth foreign bodies have been swallowed. It should not be used in advanced poisoning cases for the additional shock may kill the patient.

Administration should not be repeated if the first dose fails in its object, for excess first causes excitement and subsequently marked depression, coma and death.

Dosage. For the dog the dose varies from $\frac{1}{40}$–$\frac{1}{8}$ gr. (1·5–7·5 mg.) subcutaneously, with an average of $\frac{1}{20}$ gr. (3·0 mg.) Oral dosages are approximately twice these quantities, but less reliable effects are achieved by this route.

Antemetics

Drugs which assist in suppressing emesis can be classified under several headings.

(1) *Demulcents* which coat, protect, lubricate and soothe the gastric mucosa:

(2) *Local gastric sedatives*, which include the groups of antacids and alkaline stomachics and act either by acid neutralization, by coating the gastric mucosa, or by local nerve sedation.

(3) *Central gastric sedatives*, such as hyoscine which exert their effect by depressing the vomiting centre.

The aim of antemetic administration is to suppress the vomiting reflex, so conserving the animal's strength and the chloride content of the stomach, blood and tissues. Continued vomiting is extremely exhausting and causes severe shock. This must be avoided but gastric sedation should not be used to over-ride essential vomition, for this is nature's way of removing irritant and poisonous materials from the stomach before digestion and absorption can take place. Once this material has been removed, the reflex should be suppressed as soon as possible. Where emesis is initiated centrally the cause must be diagnosed and treated, for in such conditions as nephritis with uræmia no amount of local gastric sedation, and only rarely central sedation, will prevent vomition.

1. Demulcents. These have already been mentioned and amongst them dextrose, and possibly glycerin, are the most effective antemetics in this group.

2. Local Gastric Sedatives. These may be divided into antacids, inert coating agents, and local nerve sedatives.

Antacids. These are widely used in both human and veterinary medicine for the neutralization of the hydrochloric acid of the stomach. Although gastric hyperacidity does occasionally occur in small animals, it is doubtful whether wide use of antacids is justified, for it is usually only a symptom of far greater disturbances. In ruminants the effect of pH on rumination is only just becoming known, but the long established use of bicarbonates and carbonates—both ammonium and sodium salts—can often be justified where excessive carbohydrates have been fed or where such conditions as ketosis are present.

Rapid acting compounds are those normally soluble in water, such as sodium bicarbonate and ammonium bicarbonate (ammonium carbonate consists of a mixture of bicarbonate and carbamate and constantly evolves ammonia. The bicarbonate is stable and almost odourless yet retains the activity of the other compound). The slower acting antacids are the less soluble compounds such as the carbonates of calcium and magnesium, the hydroxides and oxides of these, and the even less soluble silicates of aluminium and magnesium. Aluminium hydroxide gel and, more recently, the amino-acid co-ordination compounds of bismuth and aluminium—bismuth and aluminium glycinates for example—have been developed.

The antacid effect of carbonates is only temporary, as the carbon dioxide released by the chemical reaction collects in the cardia, distends the stomach before it is released by sphincter relaxation, and in doing so causes a reflex secretion of acid and digestive enzymes. This is the so-called '*alkaline stomachic*' action.

It is usual, where true neutralization is required, to combine the rapidly acting sodium bicarbonate with the slower acting oxides, carbonates or trisilicate of magnesium, and kaolin (a hydrated aluminium silicate). The choice of slow acting drugs depends on whether a laxative or antidiarrhœic action is required in the intestines, where the basic ion is of more importance than the acid radical. Calcium, bismuth and aluminium tend to have an antidiarrhœic action, whereas magnesium is laxative (though the trisilicate dissociates so poorly that the ions are relatively inactive and mechanical coating effects superimpose themselves to give an antidiarrhœic action. This effect is aided by the adsorptive forces which attract and fix toxins present in the intestines. This toxin adsorption property is also possessed by kaolin, but to a lesser degree).

A gastric sedative, antacid, and antidiarrhœic powder for a dog would be:

℞	Sod. bicarb.	5 gr.	0·3 G.
	Calc. carb.	10 gr.	0·6 G.
	Mag. trisif. }	aa 15 gr.	aa 1·0 G.
	Dextrose }		
	Fiat pulv. 1.		

This prescription combines the demulcent activities of dextrose with the rapid and slow acting alkaline stomachics, sodium bicarbonate and

calcium carbonate respectively, and lastly the slow antacid and coating effect of the trisilicate. The coating effect of excess calcium carbonate and the trisilicate will be noticed in the intestines also.

For the treatment of most gastritis conditions the glycinates and trisilicates are superior to the alkaline stomachic type of preparation.

Local Mucosal Nerve Sedatives. Where irritation of the gastric mucosa is excessive, local nerve sedatives may be used to assist the demulcent and mechanical coating agents. These consist mainly of less soluble, topically applied, local anæsthetics such as benzocaine and amethocaine, used for small ar[illegible] in doses of about 5 gr. (0·3 G.) three times daily. Chlorbutol is also u[illegible]ilar dosage. In general this method of dealing with the problem [illegible]ly satisfactory.

3. Central Gastric Sedatives. Many central nerve sedatives will suppress the vomiting centre in the medulla along with other centres and brain areas. Chlorbutol (Chloretone) has already been mentioned for its local effect on the gastric mucosa, but, following absorption, this drug also has a central sedative effect, including depression of the vomiting centre. The compound has thus been widely, and often effectively, used in human and veterinary medicine as a travel sickness remedy, which, as with most central antemetics, must be administered 15–30 minutes before starting the journey. Further investigation into central antemetics has shown that hyoscine, in doses up to $\frac{1}{100}$ gr. (0·6 mg.) and its near relatives, and, more recently still, chlorpromazine, have definite antemetic properties superior to the older compounds. Frequently these central emetics are only efficient against centrally induced vomiting; chlorpromazine in particular will not prevent locally induced vomiting, although it will effectively suppress any response from injection of apomorphine when administered subcutaneously in a dose of 1·0 mg./kg. Oral dosing is equally efficient although the dosage must be larger.

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CHAPTER 7

THE ALIMENTARY SYSTEM

(ii) THE INTESTINES

THE drugs used expressly for action on or in the intestines are divided into a number of groups—(1) Purgatives and laxatives, (2) Astringents and antidiarrhœics and (3) Antiseptics. The anthelmintics have been given a complete chapter of their own in view of the increasing importance accorded to these drugs.

Intestinal Stimulants—Purgatives and Laxatives

A *purgative* is a drug which causes marked intensification of intestinal activity and results in the expulsion of intestinal contents from the colon and rectum. The terms *aperient* and *cathartic* are also used to describe this group of compounds.

A *laxative* causes a similar action but the effect is milder and rarely results in more than a slight intensification of intestinal activity. Frequently a laxative action is achieved by small doses of drugs which in larger doses will cause purgation, but there are some agents which will only produce a laxative effect no matter how large the dose. Liquid paraffin is one of these.

Superpurgation may follow overdosage of, or idiosyncrasy to, purgatives. It consists of extreme and continued intestinal activity indicated by frequent and painful evacuation of fluid and possibly dysenteric (blood-stained) fæces. This causes shock and dehydration which may result in collapse and death. It is a difficult condition to treat and mortality is fairly high. Horses are more susceptible than other species and less responsive to treatment.

It follows that purgatives must be used intelligently and only when necessary. At one period of medical and veterinary history purging was, apart from bleeding, the only remedy for the majority of illnesses, but this position happily no longer exists and the frequent use of these drugs is not justified.

Before prescribing or administering purgatives, particularly in small animals, the veterinary surgeon must be certain that purgation is required, for owners frequently are unable to distinguish between the straining due to constipation and that which follows diarrhœa (frequent evacuation of fluid, or semi-fluid, fæces).

There are a considerable number of purgatives, and classification is essential for a clear understanding. The four main groups of intestinal stimulants are:

(1) Mechanical laxatives.		Liquid Paraffin White and Yellow Soft Paraffin
(2) Bulk purgatives.	a: Simple:	Agar-Agar Psyllium Sodium Carboxymethylcellulose Wheat Bran
	b: Saline:	Sodium Chloride. Magnesium Oxide, Carbonate, and Sulphate. Potassium and Sodium Tartrate
(3) Irritant purgatives.	a: Direct:	Mercury compounds, Sulphur, Phenolphthalein, Vegetable oils.
	b: Indirect:	Anthracene compounds—Aloes, Senna, Cascara, Rhubarb, Synthetic anthraquinones.
	c: Drastic:	Jalap, Colocynth, Scammony, Podophyllin, Croton oil, Barium Chloride.
(4) Neuromuscular purgatives:		Parasympathomimetic drugs—Carbamylcholine, Arecoline, Physostigmine, Pilocarpine.

Mechanical Stimulants. The drugs which comprise this group have a laxative rather than purgative action, for their effect is entirely mechanical. The chemical and physical characteristics of these drugs governs their activity. They are long chain hydrocarbons which are extremely resistant to chemical and physiological reactions, and particularly digestion. This ensures that once administered they remain almost entirely unchanged and unabsorbed throughout the length of the alimentary canal; their oily and lubricant character is therefore used to the maximum throughout. This oily property enables the drugs to coat the mucosa and intestinal contents, and so smooth the passage of fæcal material.

These compounds have a number of disadvantages: (1) As the intestinal contents are essentially aqueous, there can be little mixing of inert hydrocarbon and fæces. Chronic constipation or impactions will not benefit or may even be aggravated by the oil, for the coating of the mucosa decreases the effect of any irritant action the intestinal contents may have. This decrease in irritability may result in the further slowing of intestinal movements.

(2) Coating of the mucosa prevents contact with food in the intestine so that absorption may be hindered. Not only normal protein, carbohydrate and fat absorption, but that of essential supplements, particularly the fat soluble vitamins, may be radically affected. Consequently continued use, especially in young animals, is contra-indicated.

(3) Undue reliance is sometimes placed on the degree of activity of

these compounds when mild purgation is required. This may result in dangerous and severe affects. A good example is the use of liquid paraffin with oil of chenopodium for worming young puppies. The paraffin is insufficient to expel either the excess of the worming mixture or the worms, but more important still, the excess chenopodium is absorbed and causes poisoning. Some of the 'patent remedy' worming mixtures have in the past been guilty of this error.

(4) In small animals, liquid paraffin may actively encourage the continued existence of fæcoliths, for the oil aids the passage of soft material past the solid mass. The owner—and sometimes the veterinary surgeon—can be misled by the fact that the animal continues to defæcate.

Liquid and the soft paraffins, white and yellow, are the main examples of this group. Of these, liquid paraffin is the most widely used.

Liquid Paraffin, B.Vet.C. (Paraff. Liq.)

This is a clear, 'water white' fluid residue from petroleum distillation, of varying density, with no odour, but a bland oleaginous 'taste'. There are available two grades, heavy and light. The fluid is often referred to as mineral oil.

Internally liquid paraffin has a demulcent action in the mouth, œsophagus and stomach. In the intestines it is a typical lubricant laxative. It has the disadvantages of the group but, additionally, large doses or continuous administration will result in anal seepage and the soiling of bedding, furniture and carpets when administered to small animals. Some slight absorption is reported to produce a benign tumour of the intestine when administration is continued over a long period.

Dosage. The pig with a dose of 2–10 fl. oz. (60–300 ml.), and the dog 60 m.–1 fl. oz. (4·0–30·0 ml.), are the animals in which liquid paraffin is most frequently used.

No matter by how much the dose is increased, the laxative action cannot be increased to one of purgation.

Externally the drug has very wide *emollient* uses (an emollient is almost equivalent to a demulcent but the term is used in Great Britain only to describe agents applied externally. In the U.S.A. the term covers demulcents as well). A wide variety of pharmaceutical preparations use liquid paraffin as a base: creams, emulsions, pastes and suspensions.

Cream of Penicillin, B.Vet.C., Kaolin and Liquid Paraffin Emulsion, B.P.C. '49, Paste of Bismuth Subnitrate and Iodoform, B.Vet.C., (B.I.P.P.) and Intramammary Injection of Penicillin, B.Vet.C., are respective examples.

Some 'colloidal' solutions of iodine are prepared by dissolving iodine in hot liquid paraffin. These are useful externally as parasiticidal dressings.

For the removal of foreign bodies from the eye, flooding with liquid paraffin is quite efficient and usually available as an emergency home remedy.

Finally, liquid paraffin is a useful lubricant for diagnostic instruments—probangs, stomach tubes, catheters, urethral sounds, etc.

Petroleum jelly and white soft paraffin have occasionally been used in pill or bolus form as laxatives.

Bulk Purgatives. The members of this group depend for their action on an increase in volume of intestinal contents. This increase causes distension of the intestines, which induces a reflex countering contraction of musculature and an increase in power and speed of peristalsis. (This reflex reaction to distension is common to all the hollow organs.)

The methods by which this increase in volume is achieved divide bulk purgatives into two groups. Both groups utilize water, but the *simple bulk purgatives* adsorb water and themselves increase in bulk. *Saline bulk purgatives*, by virtue of the high osmotic pressures which they exert in hypertonic solutions, not only prevent the absorption of water which normally takes place but also withdraw water from the tissues into the intestines. It is therefore the bulk of the water which is the stimulating factor.

The Simple Bulk Purgatives. Probably the oldest example of this type of purgative is wheat bran. More recent and pharmaceutical compounds are Agar-Agar from seaweeds, plantain seeds or psyllium, and sodium carboxymethylcellulose.

As a group these compounds are mainly of use in small animals. They have only mild stimulant effects which are maintained throughout the whole length of the intestines, and are particularly useful when sharp foreign bodies have been swallowed—needles, sharp bones and stones. *Doses* of up to 150 grains (10·0 G.) of Agar, B.Vet.C., are recommended for dogs.

Saline Bulk Purgatives. All members of this group owe their laxative and purgative properties to their ability to draw water from the tissues into the lumen, or to retain there fluid already present. This ability is shown only when quantities large enough to create hypertonic concentrations in the intestines are given. It follows that no saline purgative should be used—nor would one be effective—in dehydrated animals where intestinal and tissue fluids are depleted. In these circumstances magnesium compounds can be very dangerous, for if purgation is not achieved the salts may be absorbed in quantities sufficient to cause nervous system depression and anæsthesia.

A minor part of the purgation is in some cases due to a slight irritant action of the drugs, either directly or because of their hypertonicity.

It is usual to administer saline purgatives in hypertonic concentrations, for it would be impracticable to administer the quantity of water necessary to achieve isotonicity relative to the doses of the salts. This delays the action (magnesium sulphate is isotonic at approximately 4 per cent.—calculation of the amount of water required to bring 1 lb. of magnesium

sulphate to isotonicity gives an interesting result) of the compounds, for time is needed for the osmotic pressure to exert its full effect and withdraw into the lumen sufficient water to distend the intestinal wall and institute, or increase, peristalsis. If sufficient water were administered orally to create isotonicity this delay would be appreciably lessened.

Saline purgatives will mainly affect the small intestine. It is obvious that volumes capable of great distension of the small intestine could be easily accommodated in the large intestines of most animals. However, the hypertonicity of the solution prevents the normal dehydration of fæces which occurs in the large intestine, and the lower colon and rectum will therefore be stimulated to some degree by the volume of fluid retained. The action will be noticed normally after three to twelve hours in simple stomached animals, but nearer to eighteen hours after dosing ruminants. Saline purgatives are less reliable in horses.

As the osmotic pressure of saline solutions is related to the number of ions present in those solutions, the strongest and most persistent purgative effect will be exerted by those compounds which are not rapidly absorbed into the tissues and yet are freely soluble and ionized. The best effect therefore is exerted by magnesium sulphate (Epsom's salts) which is freely soluble, strongly ionized and produces two ions both of which are only slowly and sparingly absorbed. Less persistent in action is sodium sulphate (Glauber's salts) which, though producing three ions in solution, loses much of its sodium by absorption. In practice, equal parts of these two sulphates are often used. By this means the initial powerful action of the triple ion sodium sulphate is added to the persistent action of the magnesium salt.

Sodium chloride, the salts of tartaric acid, and the carbonate and oxide of magnesium, are all less efficient and tend to be laxative rather than purgative.

Irritant Purgatives. This group of purgatives can be further subdivided to distinguish between those compounds which (1) do not require absorption, i.e. *direct irritant* and (2) those which do require absorption, i.e. *indirect irritant purgatives.* A further division includes a number of miscellaneous *drastic purgatives* which are no longer in general use, and which are, in the main, complex vegetable compounds: the group includes such drugs as *podophyllin, scammony, colocynth,* and *croton oil.* Barium chloride, which was once used as a smooth muscle stimulant and intestinal irritant, is an exception to this vegetable origin; 7½ gr. (0·5 G.) doses were injected intramuscularly in horses, and 30 grains are sometimes still used as a ruminal and intestinal stimulant in cattle.

Direct Irritant Purgatives. This group includes mercury compounds, sulphur, vegetable oils, and phenolphthalein, all of which affect the small intestine. Some are therefore used as adjuvants for the indirect irritants as they commence their action as soon as they arrive in the small intestine. Calomel is a typical example.

Mercury compounds which can be used are those which are largely insoluble and do not ionize to any extent. Thus, metallic mercury and calomel are the most commonly used examples. The metal itself has no purgative or laxative action unless the globules are broken up and the dispersed particles prevented from recoalescing. Chalk and liquorice are used as dispersing agents in Grey Powder and Mercury Pill, B.P.C., respectively. The increase in surface area allows the gastric juices more opportunity to attack the metal or salt, and to dissolve and ionize minute quantities which are sufficiently irritant to cause an increase in peristalsis.

Calomel, or mercurous chloride, is slightly more soluble than metallic mercury and is used in 40 gr. (2·3 G.) doses as an adjuvant to aloes for the horse, in 5–40 gr. (0·3–2·3 G.) doses for the pig, ¼–2 gr. (15·0–120·0 mg.) for the dog, and $\frac{1}{6}$–1 gr. (10·0–65·0 mg.) for the cat. Action can usually be expected within six hours in the smaller species, for irritation of the small intestine commences immediately. The whole of the alimentary tract will be affected.

The *cholagogue* action previously attributed to calomel is now largely discounted. No increase in bile secretion occurs, although an increased flow of bile into the intestines follows its administration. This is due mainly to the increased intestinal activity and the rapid passage of intestinal contents. It is an effect common to all agents which speed up the flow of the intestinal contents.

A truly soluble form of mercury is corrosive and dangerous: mercuric chloride is a deadly poison. The major uses of mercury compounds are as counter-irritants externally, in organic combinations as diuretics following injection, and as antiseptics (*q.v.*).

Sulphur has been used as an irritant laxative for many years. Until quite recently *brimstone and treacle* was widely favoured as a regularly administered laxative for children, but sulphur has never been extensively used as such in veterinary medicine. As with mercury, pure sulphur has little or no action but, when converted into sulphides and polysulphides by intestinal secretions, these sulphides exert an irritant and therefore stimulant effect on the whole length of the intestines. These sulphides are similarly responsible for the parasiticidal action of sulphur externally. Where sulphur is used internally flowers of sulphur, or sublimed sulphur, is used, but precipitated, or milk of sulphur can be used with similar effect.

Phenolphthalein is a white powder, soluble in dilute alkali and mainly used as a laboratory indicator. It possesses useful small and large intestine irritant properties. Its red colour in alkaline media provides an easy means of confirming undisclosed use: the addition of dilute ammonia solution to fæces or urine produces a marked colour reaction.

The effect on different species of animals is not constant, and the use of phenolphthalein is mainly confined to the pig, dog and cat, for which

the doses are 15–30 gr. (1·0–2·0 G.), ½–3 gr. (0·03–0·2 G.), and ¼–1 gr. (15·0–65 mg.), respectively. An alcoholic solution containing 3 gr. in 4 ml. is available for intramuscular injection in pigs.

The main advantage of phenolphthalein is the prolonged period of its action. A proportion of any dose is absorbed, and of this a considerable amount is re-excreted via the bile into the small intestine where its irritant action can be repeated. A proportion is lost by urinary excretion. More phenolphthalein is absorbed and re-excreted but each time some is lost, so that eventually fæcal and urinary excretion deplete the dose, and the intestinal concentration drops below an effective level. This cyclical action may continue for several days after an initial action within 4–6 hours, and the compound is therefore of most use in the treatment of chronic constipation.

Vegetable oils are probably the most efficient and safe of the direct irritant purgatives. As a group they act by combining in a saponification process with the alkaline bile salts of the small intestine. This process produces monobasic, dibasic and tribasic soaps. Sodium and potassium soaps are the most important ones as they are soluble and capable of exerting an irritant action on the intestinal mucosa. Glycerol is a by-product of this saponification and is useful in lubricating and breaking up the fæcal masses; it also assists defæcation by exerting a strong osmotic pressure to retain fluid within, and possibly attract fluid into, the intestinal lumen.

The soaps produced by each oil differ in their irritant properties so that we have olive oil producing the mildly irritant salts of oliveic acid, and at the other extreme castor oil giving ricinoleates and linseed oil producing linoleates and linolenates, all of which are relatively strong irritants. Small amounts of stearates and palmitates are also produced.

Oleaginous purgatives can be used in all species, but are mainly of value in non-ruminants. The oils in common use are linseed oil for the horse, 1–2 pints (0·5–1·0 litres), and castor oil 1–6 fl. oz. (30·0–180·0 ml.) for the foal, calf and pig, 60 m.–1 fl. oz. (4·0–30·0 ml.) for the dog.

The effect is seen within 4–8 hours in the smaller species, and in 12–18 hours in the horse. There is an almost complete clearance of the intestines when these oils are used, and a temporary suspension of defæcation follows until sufficient bulk reaches the small colon to restimulate the defæcation reflex. For this reason oleaginous purgatives are not indicated in chronic constipation, where the condition would be aggravated after a temporary relief. They should be followed by moist bulky food.

Both linseed and castor beans figure in plant toxicology. Linseed contains a cyanogenetic glycoside which gives prussic acid when acted upon by enzymes also present. The enzymes are activated by steeping the seed in luke warm water, and sufficient acid can be produced to kill adult cattle. Linseed tea for nursing convalescent animals should therefore always be prepared with boiling water to inactivate the enzymes.

Castor bean husks contain a toxalbumen *ricin* which is one of the most toxic substances produced by any plant. It occasionally causes trouble when cottonseed cake is contaminated with castor beans.

Indirect Irritant Purgatives. These are agents which require absorption and metabolization before substances are produced which will, on excretion into the intestine, exert an irritant action and stimulate intestinal movement. The main members of the group are aloes, cascara sagrada, senna and rhubarb—all plant derivatives. Synthetic replicas of the substances into which the active ingredients of the plant compounds are metabolized—anthraquinones—are now used more extensively. From these substances the common title of the group is derived—the *anthracene purgatives.*

Aloes, B.Vet.C.

This is the type compound and was the most widely used anthracene purgative until the introduction of synthetic anthraquinones to veterinary medicine.

The composition and activity of aloes varies with its geographical origin. The most potent and standard samples are those from the West Indies, Aloes Barbados. Other examples are from South Africa—Cape Aloes, and Socotra—Socotrine Aloes. The soluble active principle of aloes, the glycoside Aloin, B.Vet.C., is also available. Aloes and aloin should be administered in capsules or as a bolus, but should the animals chew either, the appetite may be lost for several days.

When the aloes reaches the small intestine the soluble active principle is dissolved and absorbed. At this stage the compound is inactive and relatively non-irritant. Within the body the principle circulates and is metabolized, probably in the liver, releasing into the system the active agents, or emodins, which in fact are anthraquinones. These are excreted into the large intestine which is irritated and stimulated.

Because of this excretion into the large intestine, these anthracene purgatives are of most value in those animals which suffer from impactions of the large intestine. The horse, with its numerous colon flexures and its decrease in diameter at the pelvic flexure, benefits particularly from this type of purgative. All non-ruminants respond well to anthracene purgatives.

Because of this complex cycle, purgation of the horse is delayed for at least eighteen hours. In other animals the action of aloes is more rapid, although its use in these species is now infrequent.

The *dose* of aloes for the horse varies from 120 gr.–1 oz. (8·0–30·0 G.). Aloin when used can be given in quantities of 30–120 gr. (2·0–8·0 G.).

Cascara Sagrada, B.Vet.C., (Sacred Bark) of Spanish South-American origin has been used in liquid extract and pill form for dogs and cats. The *dose* is 30–60 m. (2·0–4·0 ml.) of the extract for the dog, and 1½–8 gr. (0·1–0·5 G.) of the dry extract. *Senna*, used in the form of a fresh infusion of the seed pods, is not often used in veterinary medicine.

The final example *Rheum* (Rhubarb, B.Vet.C.), the rhizome of a Far Eastern rhubarb, contains various emodins including chrysophanic acid, a tetrahydroxy-anthraquinone. This is a dye, and may stain alkaline fæces and urine a reddish brown. It is also peculiar in that the powder and other derivatives contain a high proportion of *tannic acid*. This is a powerful intestinal astringent and will exert a constipatory action following the initial purgative effect of the anthraquinone.

These anthracene purgatives of plant origin are now superseded by those of synthetic origin, a monograph on one of which, 1:8-*dihydroxy-anthraquinone*, is included in the British Veterinary Codex. It is used mainly in the form of a dispersible powder, when a wetting agent such as the detergent sodium lauryl sulphate is included.

The advantages of synthetic compounds apply to the anthraquinones. They are of standard unvarying composition; solution and absorption rates are approximately constant under the same conditions of administration. It follows that, with the exception of idiosyncratic individuals, a forecast of the effect for a given dose can be given with assurance. Small doses will be laxative and large doses purgative. The time elapsing between dosing and action will vary according to the fullness of the intestine and the dilution of the drug. If dissolved in large quantities of water, action in the horse will follow 10–12 hours after dosing. If given in powder form to an animal with a full stomach, 24–36 hours may elapse. Young animals and race-horses are susceptible, and doses should be split and given at intervals of 8–12 hours. This is routine practice for the small species.

Dosages in the horse are approximately the same as for aloes; those for pigs are almost equal to the horse doses.

Horse and Cow:	10–30 G. (150–480 gr.)
Foals and Calves:	3·0–5·0 G. (45–75 gr.)
Sheep and Goats:	4·0–6·0 G. (60–90 gr.)
Pigs: (up to 8 weeks):	3·0–5·0 G. (45–75 gr.)
Porkers:	5·0–15·0 G. (15–25 gr.)
Adults:	10–20 G. (150–300 gr.)
Dogs:	0·15–3·0 G. (2½–45 gr.)
Cats, Rabbits etc.:	0·15–0·3 G. (2½–5 gr.)

The Neuromuscular Purgatives. This group of drugs is composed essentially of parasympathetic system stimulants. They are divided by the pharmacologist into muscarine-like and non-muscarine-like drugs.

The effect on the animal of both these groups is identical, with the exception of minor details—some have a greater effect on glandular activity, whilst others have a greater action on the heart and circulatory system.

Used as a purgative in the horse the first effect noticed is an increase in discomfort. The animal may kick at the flank, stamp, lie down and get up, and show general signs of uneasiness. It is at this time that walking the animal up and down distracts his attention and prevents him attempting

to go down and roll. This would be dangerous because of the possibility of 'twist', that is, torsion of the intestines. Salivation commences usually within five minutes of injection and is quite profuse, clear, thin and watery after the initial frothing. Patchy sweating occurs after about ten minutes. Within twenty minutes of injection soft and sloppy fæces are passed, quite often mixed with fluid; the fæces usually consist of undigested foods and are light green in colour. The effect begins to wear off in half an hour and within the hour, if there is no impaction, the animal is back to normal.

Where intestinal impaction is present most practitioners consider it unwise to use neuromuscular purgatives, owing to the danger of excessive muscular contractions resulting in rupture of the intestine. The intensification of the symptoms immediately after injection is also rather alarming to the owner, and sometimes to the veterinarian! Where death follows the veterinary surgeon may be held responsible, and it should be remembered that death is not an infrequent sequel to an attack of colic in the horse.

The *muscarine-like* drugs are those which act by stimulating the post-ganglionic fibres of the parasympathetic nervous system, thereby increasing the production of acetylcholine.

1. *Acetylcholine* itself has only a transient action because of the rapid breakdown of the substance by the cholinesterase, which is normally present at the point of secretion. Acetylcholine is therefore never used in practice.

2. *Pilocarpine*. This parasympathomimetic drug is now only used locally in the eye as a miotic in the form of a 1 per cent. aqueous solution of the nitrate. It has long been known to exert a purgative action, the main natural source being the leaves of the Jaborandi tree. Although it has an effective stimulant action on peristalsis, the potent action in slowing the heart and constricting the bronchioles has hastened its supersession by less toxic drugs.

3. *Arecoline*. Betel nut has been known for many years as a digestive stimulant and is still chewed by the natives of the East Indies and associated areas. Besides its intestinal stimulant effect areca nut is also well known for its anthelmintic properties, particularly in respect of tapeworms. The smooth muscle stimulant effect of arecoline is similar to pilocarpine, although some actions, such as the miotic effect, are not so marked.

In *horses* arecoline is used in doses of up to 2 gr. (0·14 G.) as a neuromuscular purgative, but is more popular in doses of ¼ gr. every six–twelve hours for the relief of œsophageal choke. In *cattle* its use in doses of $\frac{1}{16}$–½ gr. (4·0–33·0 mg.) as an œsophageal and ruminal stimulant was at one time widespread but, as in other species, carbamylcholine has almost entirely replaced it.

In the *dog* oral dosing only is practised. Powdered Areca, B.Vet.C., in doses of 2 gr. (30·0 mg.) per 20 lb. bodyweight, is still used by the public as a tapeworm remedy. The salt Arecoline Hydrobromide, B.Vet.C. is used in oral doses from $\frac{1}{16}$–1 gr. (4·0–65·0 mg.) at the rate of $\frac{1}{4}$ gr. (15·0 mg.) per 20 lb. bodyweight. (Approximately 1·6 mg. per kg.) Vomiting may occur following dosing and $\frac{1}{4}$ gr. (15·0 mg.) arecoline hydrobromide tablets are available incorporating 3 gr. (195·0 mg.) chlorbutol (Chloretone) to suppress the vomiting reflex.

4. *Carbachol*, B.Vet.C., is also known as carbamylcholine. A synthetic drug with parasympathomimetic actions, carbachol is now the most commonly used drug of the neuromuscular purgatives. The usual form for large animals is a subcutaneous injection containing 1·0 mg. per ml., sometimes expressed as a 1 in a 1,000 solution.

Administered subcutaneously the drug has an action similar to, but more prolonged, than other drugs of this group. The side actions on the bronchi, heart and circulatory system and the secretory system are said to be less than those of arecoline; there is relatively no action on the eye. The drug is also active following oral administration.

In *cattle* some stimulant effect is exerted on the rumen, and it is particularly used to recommence rumination when stasis has accompanied milk fever.

In dogs the 1 : 1,000 solution has the effect of causing vomition, whereas a 1 : 10,000 solution has the ordinary purgative effect.

Dosages for subcutaneous administration are:

2·0–5·0 mg. for the Horse and Cow.
0·5–1·0 mg. for the Foal.
0·5–2·0 mg. for the Pig.
0·25–0·5 mg. for Sheep.

and as an emetic in the dog 0·25–1·0 ml. of a 1 : 1,000 solution, or as a purgative 0·25–1·0 ml. of a 1 : 10,000 solution.

Non-muscarine-like drugs are represented by Physostigmine Salicylate, B.Vet.C., obtained from the Calabar, or Ordeal bean (so called because of its use by native witch doctors for trial by ordeal), and two synthetic compounds with similar actions, Neostigmine Bromide, U.S.P., and Neostigmine Methylsulphate, B.Vet. C.

These exert their action by blocking the enzyme cholinesterase, which is present in choline operated synapses and rapidly breaks down acetylcholine produced in response to stimuli at the nerve endings. The non-muscarine drugs have a great affinity for the enzyme and combine with it, so preventing the breakdown of acetylcholine; the action of normally produced acetylcholine is therefore prolonged. This gives rise to another descriptive name for the drugs—acetylcholine potentiators. Thus muscarine drugs produce acetylcholine, whereas non-muscarine drugs prolong the action of physiologically produced acetylcholine.

Physostigmine Salicylate, B.Vet.C.

This is alternatively named *eserine salicylate*. It has all the actions of a parasympathetic system stimulant, but the action on smooth muscle is greater than its secretory action so that salivation is not so profuse as with pilocarpine. Despite this fact, the parenteral injection of physostigmine is rare and the miotic action achieved by the use of the 0·125 per cent. eye ointment, or the lamellæ containing 1/1,000 gr., is the only one worth mentioning. This ocular use is valued for the antagonistic effect toward atropine and homatropine, particularly the latter. In man adhesions of the iris are prevented by the alternate use of homatropine and eserine. *Neostigmine* is sometimes preferred for this miotic action as its antagonistic action is greater. The milder stimulant effect on smooth muscle is utilized in the treatment of atony and obstruction of the urinary tract rather than for a purgative action, although some practitioners, particularly in the United States, prefer neostigmine for the treatment of ruminal stasis and impactions. In the dog and cat atony of the bladder and sometimes urethral calculi obstructions can be successfully treated with this synthetic compound. Obtainable in ampoules and multi-dose vials neostigmine is used in *doses* of 4·0–25·0 mg. in the horse and cow, and 0·25–2·5 mg. in the dog and cat.

Atropine and curare poisoning are best counteracted with neostigmine injections.

Intestinal Astringents

An astringent is a compound which precipitates protein, whether intracellular or extracellular. If intracellular precipitation occurs the process should be reversible and the cell should not be destroyed. Should the cell be destroyed, then the substance is not an astringent but a caustic. The protein precipitate is usually soluble, either in excess of protein or excess of astringent. If excess of astringent is present the re-solution may involve destruction of the cell and irritation and damage to the tissue or organ. It follows that overdosage of astringents can be dangerous and deaths are not unknown, particularly in Johne's disease in cattle (typified by chronic diarrhœa) when overdosage with ferrous sulphate and dilute sulphuric acid (McFadyean's solution) occurs.

The precipitate of protein covering the surface of a cell or tissue is relatively impermeable to the passage of fluids in either direction. It also acts as a barrier between tissue and irritant, and the underlying tissue is therefore soothed and protected from further damage, so that healing can take place. The protecting and soothing effect is enhanced by an astringent action on any exposed nerve endings so that pain is lessened; the toxins and histamine-like substances released in damaged tissues are not absorbed. Local and generalized shock are both reduced whilst the recovery rate is speeded up.

Astringents will also act as *hæmostatics*, as blood proteins are precipitated and clotting assisted. This only applies to minor venous bleeding,

for arterial pressure is usually sufficient to displace any formed clot before it has become tightly bound in the wound. However, bleeding from very small arteries can occasionally be controlled as, for example, in the docking of puppies; the caudal arteries are usually so small that Strong Solution of Ferric Chloride, B.Vet.C., is capable of stopping the bleeding, providing the wound is clean and the solution is applied directly to the end of the artery. If the hæmostatic is applied to a wound in which appreciable amounts of blood are present protein is precipitated but not at the site of bleeding, and all that is achieved is a mass of precipitate floating in fresh blood—a messy and unprofitable situation.

These principles apply to all astringents, of which there are two divisions, *external astringents*, which are mentioned in the section of drugs affecting the skin, and *intestinal astringents*.

Intestinal astringents are subdivided again into *vegetable* and *mineral astringents*. Tannic acid and catechu are commonly used examples of the first group, whilst the sulphates of iron, copper, zinc and aluminium, with one or two other compounds such as ferric chloride, are examples of metallic astringents in common use.

Vegetable Astringents. Tannic acid is found in most plants in small quantities, but in oak gall (oak apples) the concentration is very high as it is also in catechu. The tannic acid content of rhubarb has already been mentioned, and the bitter astringency of stewed tea is known to all. Gallic acid is usually present along with tannic acid, of which it is a breakdown product; its astringent properties are poor and it is not used on its own.

Tannic Acid, B.Vet.C.

Tannic acid is a light amorphous powder which is freely soluble in water and alcohol. It is used internally in doses up to 360 gr. (24·0 G.) in cattle and horses, 40 gr. (2·6 G.) for sheep and goats, up to 20 gr. (1·3 G.) for the pig, and 10 gr. (0·6 G.) for the dog. The solubility is such that the action is rapid in onset but conversion into gallic and pyrogallic acids, amongst others, is also rapid and, as these compounds are not astringent, the action quickly passes off. Continuous action, prolonged into the large intestine, is not usually achieved by tannic acid, and catechu, krameria, kino, and synthetic products of tannic acid are preferred, their lesser solubility and slow continuous release of tannic acid being more desirable. In the stomach, large tannic acid doses tend to cause irritation, nausea and sometimes emesis in the vomiting species. Precipitation of food protein which may occur in the stomach is followed by re-solution in the small intestine with the release of tannic acid. In the intestines precipitation of protein, particularly on the mucosal surface, produces a protective layer almost impervious to the passage of fluid in either direction. Stimulation of the inflamed mucosa is decreased, with a proportional decrease in peristalsis.

Precipitation of alkaloids and heavy metals by tannic acid is utilized fully in the treatment of poisoning. Insoluble tannates are usually formed and when precipitated can be removed by enemas, gastric lavage or mild purgation.

Externally, tannic acid, in the form of freshly prepared 2–20 per cent. aqueous solutions or *tannic acid jelly* (Paste of Tannic Acid, B.Vet.C.) has been used for the treatment of burns and scalds, but scar formation and contractions have led to its replacement by the other methods of treatment. Inflamed or abraded skin can be protected by precipitating a superficial layer of protein to form a pellicle; the surface cells are not destroyed but further external irritation is prevented; pain is also reduced by the effect on tissue nerve endings, and the absorption of toxins and histamine is reduced. Histamine shock is therefore reduced. A 20 per cent. ointment and 10 per cent. dusting powder are also available for this type of condition, whilst a 15 per cent. glycerin solution is available mainly as a throat and oral dressing.

Excess tannic acid redissolves the precipitate of normally insoluble protein tannate, reverses the action, and causes greater irritation. From this stems its unpopularity.

Various combinations of tannic acid with organic radicles have produced a number of synthetic compounds which release tannic acid slowly. This means that the release of acid continues throughout the whole intestine. It is in the large intestine, of course, that its action as an antidiarrhœic can be exerted with maximum effect. Methylene ditannin (Tannoform—combining tannic acid and formaldehyde), albuminates, and other compounds are available commercially.

Catechu, or gambir, is preferable to tannic acid for internal administration. It contains concentrations of catechutannic acid varying from 20–50 per cent. In veterinary practice catechu nigrum, a dark brown gritty powder, is more frequently used than the pale catechu of the B.Vet.C.

An ingredient of many astringent cattle drenches, catechu is usually combined in *doses* of 120 to 240 gr. (8·0–16·0 G.) with an equal quantity of ginger, and up to three or four ounces of a chalk and kaolin mixture. If in fluid form either chlorodyne or tincture of opium is also used, and the catechu is usually present in the form of the tincture, of which the *dose* for cattle is approximately 1 fl. oz. (30·0 ml.). Catechu is not so frequently used in other species. Dosages are in the usual proportions relating to the cattle dose. The slow release of catechutannic acid is responsible for the prolonged effect of catechu, and inflammation of the large intestine can be materially affected by the solution of catechutannic acid from the catechu which has reached the lower part of the tract in an unchanged state.

Catechu is particularly effective where dietary discrepancies are the cause of the diarrhœa, but it will often be found that, where sulphonamide therapy has apparently failed, subsequent tannic acid compound treatment

will succeed. This may be related to the fact that overdosage or prolonged oral administration of sulphonamides can result in enteritis and severe diarrhœa. Catechu and its relatives would be expected to counteract such an inflammation.

Overdosage with catechu is less likely to result in re-solution of proteinates and intestinal irritation. The incompatibilities of catechu are those of all tannic acid containing compounds: as these are all specific protein precipitants, such proteins as albumin and gelatin should not be allowed to contact the tannins, nor should they be mixed with heavy metals, particularly iron. Iron tannates are the main constituents of inks, and though these inks retain astringent properties they are not dispensed because of æsthetic disadvantages. It is important to remember this combination of tannic acid and iron compounds, for ferrous sulphate is also a widely used intestinal astringent.

Metallic Astringents. The popularity of Aluminium Hydroxide Gel, B.Vet.C., as an antacid and mild intestinal astringent is justifiably increasing in small animal medicine; it has been an accepted antidyspepsia drug in human medicine for some time. Two forms are described in the B.Vet.C., the second, a powder, being prepared from the gel by drying. The gel is a thixotropic and viscous, aqueous suspension of the hydrated oxide and carbonate of aluminium. (Thixotropism is the phenomenon shown where changes in character, related to changes in molecular shape and size, result when certain liquids or semi-liquids are agitated. Thus liquids become solid, and *vice versa*, when shaken. Many preparations of aluminium exhibit the phenomenon.)

The hydroxide gel is mainly used in the dog, in *doses* up to 120 m. (8·0 ml.), whilst the dehydrated gel is given in 10 gr. (0·6 G.) doses. It could, with advantage, be used also in calves, foals, lambs and piglets in comparable doses, e.g. up to 240 m. (15.0 ml.) or 20 gr. (1.3 G.) for the calf and foal, and for lambs and piglets in doses similar to those for the dog.

Other compounds of aluminium are more astringent and are not used internally. The hæmostatic and general astringent action of alum will be dealt with elsewhere.

Iron compounds, particularly ferrous ones, are used in veterinary medicine in Great Britain for diarrhœa (scouring), commonly in cattle but less so in other species. Combined with 120 m. (8·0 ml.) dilute sulphuric acid, ferrous sulphate in 120 gr. (8·0 G.) doses dissolved in 1 fl. oz. (30·0 ml.) water gives McFadyean's solution, which is used as a scour drench in Johne's disease of cattle. It is sometimes sufficiently effective to enable the animal to be fattened for slaughter.

The most important internal use of iron compounds is for hæmatinic purposes. (A hæmatinic is an agent assisting the build-up of pigment elements (hæmoglobin) in the blood.) The astringent action of iron is in this instance a great disadvantage as it limits, by its constipating effect,

the protracted administration necessary for full hæmatinic effect. This has led to searches for iron compounds with the minimum astringent action and the maximum hæmatinic effect; ferrous gluconate is such a compound.

Other sulphates, except copper sulphate, are not used internally mainly because of the toxicity of the metallic radicles, e.g. zinc sulphate. Copper sulphate is extensively used as a hæmatinic and anthelmintic in sheep, when its astringent properties may be of value in decreasing the absorption of other more toxic agents administered concurrently, e.g. nicotine sulphate or arsenic trioxide. Ferrous sulphate has been used in a similar manner in horses, when it has been combined with antimony and potassium tartrate and also arsenic trioxide. The copper compound is of undoubted value in this context, but the ferrous sulphate is not credited with much effect and its use in this way is obsolescent.

The astringent and hæmostatic external actions of the metallic sulphates are dealt with elsewhere.

Antidiarrhœics

Literally, these are substances which are useful in decreasing diarrhœa, but the term is more narrowly applied to those drugs which are almost inert and therefore coat and protect the intestinal mucosa. The qualification 'almost' is applied because some of the drugs have additional properties. For example, aluminium silicate in its various forms, and magnesium trisilicate are capable of adsorbing toxins; this property is extremely useful in bacterial enteritis.

The drugs involved are the inert salts of the alkaline earths and metals, calcium, magnesium, aluminium and bismuth. There are thus the carbonates of calcium and bismuth, the subnitrate and salicylate of bismuth, and the silicates of magnesium and aluminium: aluminium hydroxide, and combined bismuth and aluminium salts are also mild antidiarrhœics as well as antacids.

The salts of calcium and magnesium are considered in Chapter 11, but aluminium and bismuth salts are more easily considered here.

Bismuth Salts. Only three salts of bismuth are commonly used in veterinary practice; the salicylate, the carbonate and the subnitrate. These are tasteless and odourless, white or off-white powders which are insoluble in water, and tend to darken on exposure to light.

The *carbonate* can be used in small animals for its mild, slow antacid action in conjunction with other compounds. It also has some coating antidiarrhœic properties. Another important feature, which should be remembered when suspecting intestinal foreign bodies, is that the compound is radio-opaque and, should X-ray photographs be taken, interpretation of these must take this fact into consideration. (Owners may administer gastric sedatives containing bismuth to allay the vomiting, which is a cardinal feature of acute intestinal obstruction.) Where barium

sulphate is not available, bismuth carbonate is a useful radio-opaque substitute.

The *salicylate* splits in the small intestine to give salicylic acid salts and bismuth carbonate. The salicylic acid salt is reputed to be mildly antiseptic, its irritant action being masked by the sedative carbonate. The compound is combined in scour mixtures with other intestinal sedatives and antiseptics, the commonest being compound mixture of bismuth salicylate with brilliant green. This mixture has been widely used for the treatment of white scours in calves, but has been largely superseded by the antibiotics. The salicylate is decomposed by bicarbonates such as those of potassium and sodium, so that mixing of these together is not advisable.

The *subnitrate*, or oxynitrate, is the most active antidiarrhœic of the bismuth salts, but even so is not strongly active and its use is almost entirely confined to small animals. It is usually combined with chalk or kaolin.

Externally these three bismuth salts can be used as skin sedative dusting powders where their insolubility reduces any tendency to cake and form hard scales. The slight astringent and antiseptic properties of the small amount of ionized bismuth assist in the healing of the wounds. In the form of iodoform and liquid paraffin paste or simple paraffin pastes, bismuth subnitrate is quite useful in deep pocketing and fistulous wounds, where pus and excess granulation are common. The effect is one of mild but continuous antisepsis and astringency. These pastes are, however, very greasy and difficult to apply to wet surfaces, so that, with the decrease in horse practice and therefore of the occurrence of quittor (fistula formation in the heels of horses often associated with damaged and infected lateral cartilages), the preparations are rarely used nowadays.

Other less well known bismuth preparations are in empirical use, such as bismuth tartrate and sodium bismuth tartrate, in 1·0 ml. weekly doses for the treatment of buccal warts in dogs, and also for the treatment of arthritis. The value of this in either indication is not proved, although good results are reported from the use of sodium bismuth tartrate in buccal warts.

Aluminium Salts. The use of aluminium oxide as hydroxide gel has already been described (Antacids and Astringents). The only other aluminium compound for internal administration is kaolin, a natural aluminium silicate. In two forms, the heavy, mainly for external, and light, for internal use, kaolin is a smooth, odourless and tasteless, off-white powder. The light form is useful as an antidiarrhœic in all species and ages. Like most silicates, kaolin possesses the property of adsorbing other compounds, including bacterial toxins and vitamins. Its adsorptive properties are not so powerful as those of magnesium trisilicate. Kaolin is, however, relatively cheap when compared with the magnesium compound; it is consequently very widely used in cattle and calf scour powders and mixtures, and in most gastro-intestinal mixtures for the smaller farm

animals and household pets. Chalk, kaolin, catechu, and chlorodyne or morphine sulphate, makes a very useful gastro-intestinal sedative combination. Kaolin is also used as a vehicle for members of the vitamin B complex, particularly Aneurine Hydrochloride, B.Vet.C. and yeast.

The *dosage* of kaolin is determined more by its bulk and effect than by toxicity considerations, for kaolin is one of the least toxic of all drugs:

Horse and Cow	:	1¾–8 oz. (50·0–250·0 G.)
Calf and Foal Sheep and Goat	:	½–2 oz. (15·0–60·0 G.)
Pig	:	½–1 oz. (15·0–30·0 G.)
Dog up to	:	120 gr. (8·0 G.)

In the form of emulsion of liquid paraffin and kaolin, this silicate of aluminium is most useful in small animal dietetic and mild bacterial enteritis. The preparation has proved useful in zinc phosphide poisoning where vomition has removed the poison. *Doses* from 60 m. to 240 m. (4·0–16·0 ml.) are used.

Externally the heavy form of kaolin is used as a diluent for dusting powders and bath powders, especially the parasiticidal types where the active constituents are gamma benzene hexachloride (Gammexane), derris or similar compounds. It is non-irritant so that it can be used for skin sedative dressings but, as with talc (magnesium silicate), it should not be used where enclosure may occur, as in pocketing wounds, for it acts as a foreign body and retards healing.

As a main constituent of kaolin poultice (52–53 per cent.), with 42–43 per cent. glycerin, the heavy kaolin acts as toxin adsorbent and heat insulator, encouraging the maturation of abscesses. After the draining of an abscess-cavity the same properties encourage the speed of healing.

It should be noted that the kaolins as well as native forms of aluminium silicate (Fuller's Earth) may contain bacterial spores (especially tetanus spores) and where powders containing these components are to be used as wound dressings or on abraded skin they should first be sterilized.

Ammonium and *potassium aluminium sulphates*, collectively known as Alum, B.Vet.C., are the only other forms of aluminium in general use. The astringent actions of these compounds have more application as local styptics in human 'after shaving' preparations, but they can be used for hæmostatic effect on small wounds and oozing lesions, though they are somewhat irritant. Lotions containing 1–5 per cent. of alum, and Glycerin of Alum, B.Vet.C., (13 per cent. alum with 81 per cent. glycerin), can be used in stomatitis and pharyngitis.

Astringent dusting powders consist of a concentration of, amongst other astringent drugs, 1 in 4 or 1 in 8 alum, with kaolin and other inert compounds as diluents.

Intestinal antiseptics are a group of drugs initially believed to have an antiseptic action against infections of the intestines. The historical drugs associated with intestinal antisepsis are salol (phenyl salicylate) and

guaiacol, but although salol releases phenol when split in the intestines this is produced so slowly that little antibacterial action results. With the discovery of the antibiotics and sulphonamides the theory and practice of intestinal antisepsis have been modified and expanded. It is now routine in human intestinal surgery to destroy possible intestinal pathogens within the lumen and wall of the intestines by a rigorous campaign of antibiotic or sulphonamide medication prior to operations. The advantage of this, in all but exceptional cases, is doubtful in veterinary surgery, as many other bacteria in the intestines are destroyed, and it is upon these that a number of species rely for essential vitamin synthesis, particularly those of the vitamin B complex. However, considerable discussion and research continues in this direction, for it is considered that the growth factor responsible for increased weight gains of the young of all species when antibiotic food supplements are fed, is one of removal of subclinical infections by the antibiotics.

CHAPTER 8

ANTHELMINTICS

Introduction

THIS chapter is not intended as a treatise on intestinal parasites but sufficient parasitology will be mentioned to provide a background for discussion of the drugs and their uses.

Drugs which are grouped under the heading of anthelmintics are intended to act against parasites which inhabit the alimentary tract and its associated structures. They are thus distinguished from those drugs which act against external parasites and are called parasiticides. Those drugs which act against the parasites inhabiting the tissues and blood of animals have not yet been grouped under any one heading.

There are, of course, parasites with complicated life histories which at various stages exist in two or even three spheres. Examples are certain tapeworms which live in the tissues of one host as cystic immature stages, and in the adult worm stage inhabit the alimentary tract of those animals of which the first host is the natural prey. The horse bot fly lays eggs on the hairs of the host's coat; these hatch into larvæ which penetrate into and migrate through the tissues, reach the stomach and are finally passed in the fæces from which, in due course, are released the adult flies.

Each parasite will be mentioned, wherever possible, according to its habitat when destruction or control is attempted, e.g. tapeworms as alimentary parasites, trypanosomes and histomonas as tissue parasites, and warble larvæ as external parasites. The first will therefore be mentioned in this chapter whereas the other two will be dealt with elsewhere.

Most parasites of the intestinal tract and structures such as the bile ducts are classified under three main headings; exceptions will appear under the heading of miscellaneous.

1. *Cestodes or Tapeworms* are segmented flat worms with a complex life history involving an intermediate host which may be either warm or cold blooded. *Tænia solium* in the immature cystic form lives in the body tissues of the pig, whilst the adult worm lives in the intestine of man. In the group with cold-blooded intermediate hosts is *Dipylidium caninum* which lives in the alimentary canal of dogs and cats in the adult form, but in dog and cat fleas in the immature cyst stage. The clinical significance of these worms is related more to æsthetic considerations than to pathological potential.

2. *Trematodes or Flukes* are non-segmented, mainly flat worms with a complex life history involving snails. The adults of the important species

normally live in the bile ducts of ruminants. They are responsible for considerable losses, to the livestock industry mainly because of slow and poor development of affected animals, and to the meat industry by reason of damaged livers and poor carcases.

3. *Nematodes or Roundworms* are elongated, tubular worms which inhabit the stomach and intestines of both domestic and wild animals and birds. A small group, the 'lungworms', are found in the lung tissues and bronchi. Their life cycle involves free living forms and frequently immature forms which migrate through the host's tissues before reaching maturity in the intestines or lungs.

This group includes species which are of the greatest clinical significance.

4. The miscellaneous group includes horse 'bots', and also coccidia which can be responsible for severe gastro-intestinal disturbances and death in most species of domestic animals. Coccidiosis will be mentioned in the chapter on sulphonamides.

The Parasite/Host Relationship

The whole story of the relationship between worm parasite and host is not yet known, but is even now seen to be as complex as that between bacteria and viruses and their hosts. Indeed the picture is very similar.

The establishment of significant infection or infestation in an animal or bird is determined by a series of inter-related factors.

1. *Parasite dose.* Just as the establishment of a clinical infection by bacteria or viruses depends on the number of organisms taken in by the host within a given period, so does the number of infective eggs or larvæ taken in by the host determine whether an infestation becomes established and of clinical importance, although in some cases large doses induce the development of strong resistance by the host.

2. *Parasite virulence.* Some strains of a parasitic species are less virulent than others and the size of a dangerous dose of a particular strain will vary accordingly. This is analogous to the unequal virulence of strains of influenza, poliomyelitis, or foot and mouth disease viruses, where some strains will kill very quickly whilst others cause only mild reactions.

Some families, species, and even orders, show different levels of virulence and affinity for the different species of animals. Some orders of parasites are of less significance than others. Tapeworms, for example, are comparatively insignificant clinically when compared with the strongyles or ascarids. In general those parasites inhabiting the stomach and early part of the small intestines are the most dangerous.

3. *Parasitic competition.* Within recent years it has been found that, by removing all the species susceptible to particular anthelmintics, competition for food, vitamins and minerals is decreased and the remaining, and non-susceptible, worms increase in numbers and reach dangerous concentrations. An example of this has been seen in the case of nematodirus infestations of sheep. Prior to the routine administration of phenothiazine, clinical parasitic gastro-enteritis due to pure Nematodirus infestations was

unknown but more recently in some areas this parasite has been the one responsible for most of the clinical cases in lambs.

4. *Host resistance.* Adults are far more resistant than young stock. Considerable research is taking place into the host resistance aspect of parasitism. Resistance to parasitization can be considered as due to two related phenomena.

In the first place resistance is associated, with an antigen/antibody reaction in which the antibody may be inherited, or acquired by reaction to non-lethal doses of eggs or larvæ. Research is in progress using irradiated, and therefore "attenuated" and sterile, larvæ to create a resistance artificially.*

In the second place there would appear to be an individual resistance proportional to general health and nutrition. It is rare to find animals on a good nutritional plane succumbing to parasitic infestations. It would seem that a healthy well-fed animal exerts some influence on the parasites infesting it and controls to a certain extent the number of immature parasites which develop from the immature infective stages taken in. Also the reproductive rate of the mature parasites is affected so that the pasture and general surroundings are not so heavily contaminated with infective eggs or larvæ.

It must be realized that, though this chapter concerns the use of drugs to free animals from intestinal parasites, this is only one aspect of the treatment of intestinal parasitism. In this way therefore, anthelmintics are no exception to the rule that drugs are not the only, or even the most important, weapon in the battle against disease. Adequate diet, housing, cleanliness, exercise, pasture management etc. are some of the factors involved in the prevention and control of parasitism, as well as other forms of infection.

Finally it should be said that the mere presence of parasites within the alimentary canal is not an indication that they are causing trouble. Usually it is only when several parasites are noticed in the fæces on several occasions, or when considerable numbers of eggs are counted that concern may be felt. (It has been stated that 3,000 adult *Hæmonchus contortus* females have been found in the abomasum, and that 9,000 eggs per gramme have been counted in the fæces of apparently normal adult sheep.) It is, however, always wise to administer anthelmintics to remove parasites known to be present even if the animal is showing no signs of their effect. Where the animal is obviously ill other causes of illness should always be ruled out before anthelmintics are used, as the majority of them are poisonous. Piperazine is as yet the only exception.

For further information on the general aspects of parasitism reference should be made to the text-books by Lapage (*Veterinary Parasitology*, 1st. Edit. 1956. Edinburgh: Oliver & Boyd) and Mönnig (*Veterinary*

* The world's first vaccine produced as a result of this work was released commercially on February 25th, 1959 as an orally administered suspension of irradiated larvae with the name of Dictol.

Helminthology & Entomology, 4th Edit. 1956. London: Baillière, Tindall & Cox).

Characters of an Anthelmintic

An ideal anthelmintic should:

1. Have the widest possible therapeutic index (this is the ratio of effective dose to toxic dose, e.g. therapeutic index of 1 : 2 is very close or narrow, as one part will destroy the parasite whereas two parts will destroy the host. A therapeutic index narrower than 1 : 4 is not considered safe, and a compound with such an index is not safe to use as a therapeutic agent.) The majority of anthelmintics have narrow ratios and as a group should be used circumspectly.
2. Be effective in reasonable bulk. Some modern anthelmintics, though effective, have required such large doses that they are impracticable for routine use. Dichlorophen, B.Vet.C., indicated for the treatment of tapeworms in dogs and cats, would be of far more value were the dosage more reasonable. (At 0·2 G./kg. bodyweight the dose is equivalent to approximately six 0·5 G. tablets for a 30 lb. dog.)
3. Not require any interruption in the normal life of the animal, nor cause any check in its development.
4. Be acceptable to the animal so that administration causes no concern, and
5. Be economically acceptable.

The basic principles of curing quickly, safely, and pleasantly are again illustrated, the only addition being the modern one of cheapness.

Very few anthelmintics possess all these attributes.

The Common Helminths of British Domestic Animals and Agents Used Against Them

The helminths will be grouped in their three categories by anatomical form:

1. The flat segmented Tapeworms or Cestodes,
2. The flat, non-segmented Flukes or Trematodes.
3. The Roundworms or Nematodes which are circular in cross section. This group can be further divided into two sub-groups, the Strongyloid and the Ascaroid worms.

The Horse. Only one species of *tapeworm* occurs—Anoplocephala species in the small intestine, for the treatment of which fresh areca nut or extract of male fern are as yet the only drugs available. *Flukes* do not normally affect horses, but members of the third group, the *nematodes*, are the most important helminths of horses.

Strongyloids can cause severe symptoms; anæmia, dysentery and death may follow severe infestations. Four genera are involved,

(1) Strongylus,
(2) Triodontophorus,
(3) Trichonema,
(4) Trichostrongylus.

The first three, ('redworms'), occur in the large intestine and the fourth, which is one of the few helminths capable of passing from horse to cow, to sheep and in the reverse order, in the small intestine. A fifth genus is Dictyocaulus, a lungworm genus not of much significance in the horse.

Treatment of these strongyloids is normally by the administration of phenothiazine, but more recently it has been shown (Downing *et al.*, 1955) that piperazine will remove almost 100 per cent. Trichonema adults, 50–60 per cent. of Triodontophorus species, and a similar percentage of *Strongylus vulgaris* adults, though other Strongylus species are less affected. These figures approximate to those given by 30·0 G. doses of phenothiazine. Chenopodium, sodium glycarsamate and carbon tetrachloride are also used.

Ascaroids in the horse are of less importance. Three genera are involved:

(1) Ascaris,
(2) Oxyuris (Seatworms, whipworms or pinworms),
(3) Strongyloides.

Piperazine compounds are extremely effective against immature and mature Ascaris species, but their effect on members of the other genera has yet to be fully evaluated.

Oil of chenopodium is second choice for Ascaris species, followed by a number of other drugs such as potassium antimonyl tartrate and arsenic, both of which are frequently combined with ferrous sulphate. Until the advent of piperazine, chenopodium combined with turpentine and enemas of quassia, sodium thiosulphate or sodium chloride was the best treatment available for use against oxyurids. The efficiency of this treatment was very suspect.

Ruminants. The parasitic genera affecting cattle, goat and sheep are almost identical, and treatments, with few exceptions, consequently vary in dosage only.

Tapeworms. One genus only—Monezia, occurs in the small intestines of ruminants; —this rarely causes trouble, and then only temporarily. Treatment consists, traditionally, of copper sulphate usually with nicotine, but sometimes with arsenic. Dichlorophen has been recently used with good effect in lambs, for which the dose is reasonable in size; for cattle and adult sheep, cost and dose size prevents its general adoption. Extract of male fern and lead arsenate are also occasionally used.

Flukes. Two species, *Fasciola hepatica* and *Dicrocœlium dendriticum* are responsible for considerable extensive and severe liver disease in cattle and sheep. Fasciola is the one mainly implicated. Hexachlorethane is the drug of choice in all species, but carbon tetrachloride is widely used in sheep. Extract of male fern is now rarely used.

Roundworms. Strongyloids: As in the horse it is this group which causes the greatest trouble, and considerable losses occur annually from unthriftiness and death of stock. Species from eight strongyloid genera may be found in the stomach, small, and large intestines. The stomach worms

consist of species of Hæmonchus, Ostertagia and Trichostrongylus, all of which can, and do, cause severe losses. The small intestine worms are species of Nematodirus, Bunostomum (hookworms), and Cooperia, of which the first two are important pathogens. Some species of the genus Trichostrongylus also occur in the small intestine and can be dangerous pathogens. Two trichostrongyloids occur in the large intestine, Chabertia and Œsophagostomum (nodular worms). Both are of pathological significance.

The anthelmintic of widest application is phenothiazine, but Bunostomum and Nematodirus are resistant. Carbon tetrachloride and tetrachloroethylene are more effective against Bunostomum but neither of these drugs is considered suitable for cattle. Copper sulphate with nicotine or arsenic more efficient against Nematodirus; with these combinations toxicity is relatively high and efficiency inadequate and with these facts in mind mixtures of phenothiazine and piperazine are being tried but too few reports are yet available to assess the value of such combinations. It is probable that a new drug, given the name bephenium embonate (i.e. monohydrate), will supersede all other drugs in the treatment and prophylaxis of nematodiriasis now that initial reports (Rawes & Scarnell, 1958) are substantiated by field use. This in turn may be superseded by vaccines now under investigation.

The lungworms consist of three strongyloid genera, Dictyocaulus, Protostrongylus, and Muellerius. The first, which is the most pathogenic, is the only one of the three which occurs widely in Great Britain, causing 'husk' in cattle. No established treatment is available, but a vaccine developed by the Glasgow Veterinary School (Jarrett *et al.*, 1957) should provide adequate protection for cattle against *D. viviparus* if the investigations into commercial production methods bear fruit.* A commercially developed substance, known as cyanacethydrazide may prove useful in removing adult worms from carriers and others.

Of the *ascaroid* genera only Ascaris and Strongyloides occur, although it is doubtful whether Ascaris species are found in Great Britain.

Piperazine compounds are the anthelmintics of choice, but these also are inactive against Strongyloides species.

The treatment of all abomasal and intestinal infestations are affected by closure or non-closure of the œsophageal groove. In cattle closure of the groove is most frequently achieved by the use of approximately 60 ml. of a 10 per cent. sodium bicarbonate solution, whereas in sheep 10–20 ml. of a 5 per cent. copper sulphate solution are required.

The Pig. No *tapeworm* is normally found in the intestines of the pig in Great Britain. *Diphyllobothrium latum* is occasionally found in the small intestine but man is the definitive (usual) host for this tapeworm. Male fern extract is the compound frequently recommended, although where the worm does occur it has yet to be proved that it causes any trouble.

Flukes do not normally occur in pigs in Great Britain.

* Note: See footnote p. 102.

Roundworms of both strongyloid and ascaroid genera occur in pigs. *Strongyloids* are of three main genera:

(1) Hyostrongylus species are found in the stomach of pigs and can be quite troublesome.

(2) Œsophagostomum (nodular worm) species cause lesions in the colon which are responsible for appreciable losses of sausage skins.

(3) Metastrongylus species are the lungworms of pigs.

The treatment recommended in the past for Hyostrongylus species has been sodium fluoride. Carbon disulphide and oil of chenopodium are also used. Piperazine compounds are the most effective treatments for Œsophagostomum infestations but, as with ruminant lungworms, no established treatment is available for use against metastrongyle infestations.

The *ascaroid* species are the most important helminths of pigs. Ascaris species and Strongyloides species are the two generally involved. They normally inhabit the small intestine. Piperazine is 100 per cent. effective against adults and intestinal larvæ of *Ascaris lumbricoides*. Chenopodium and sodium fluoride were previously in wide use. Cadmium oxide and anthranilate as well as toluene have been suggested as possible drugs.

The Dog and Cat. *Tapeworms* are very common in the dog but are less frequently seen in the cat. Four genera are implicated:

Tænia species, Echinococcus, Dipylidium and Diphyllobothrium. Tænia and Dipylidium are the only two occurring normally in Great Britain. All are inhabitants of the small intestine. They are rarely more than a nuisance to the animals but are important from the Public Health aspect as household pets may act as a reservoir for the infestation of the food animals and man.

Dichlorophen would appear to be the safest cestode anthelmintic but the disintegration of the worms caused by the drug has been reputed to cause allergic reactions, and moreover owners, and veterinary surgeons too, are more satisfied if they are able to count the number of worm heads voided after treatment. Probably for these two reasons arecoline and arsenic preparations are used for cats over one year of age and dogs over three months old. Ill effects from tapeworms are not often seen and it is rarely that treatment is required under these ages.

Flukes are of no significance in the dog and cat of Great Britain. *Roundworms* are perhaps more pathogenic than tapeworms but it is mainly puppies between the ages of six weeks and six months that require treatment.

Strongyloid species occurring in the small intestine are Ancylostoma (not in Great Britain) and Uncinaria species, (hookworms), whilst Aleurostrongylus and Oslerus species occur in the respiratory tract.

The best treatment for uncinaria would appear to be piperazine but this compound is on an average only 40 per cent. effective against Ancylostoma (Sloan *et al.*, 1954). Toluene, is suggested as 100 per cent. effective

in hookworms but repeated use may cause various toxic effects and the drug is not generally adopted. Carbon tetrachloride and tetrachloroethylene are also reasonably effective but have dangerous toxicity potentials. Chenopodium is only moderately effective against hookworms.

Against the lungworms an effective treatment has yet to be discovered.

Ascaroids occurring in the dog and cat consist of species of Toxocara and Toxascaris.

Piperazine compounds again are 100 per cent. effective. Chenopodium oil is the second drug for dogs and santonin for cats. A number of other drugs are also used.

A *filaroid* species, *Dirofilaria immitis*, which does not normally occur in Great Britain, is also effectively treated by piperazine even though the adult normally lives in the heart and great vessels of the dog.

Poultry. The *tapeworms* of British poultry live in the small intestines and belong to four genera. Davainea and Raillietina species are considered of greater importance than members of the other two species, Amœbotænia and Hymenolepis.

The standard treatment is carbon tetrachloride but more recently it has been reported (Edgar, 1956) that di-n-butyl tin dilaurate and tin oxide are very efficient, though the latter was more toxic than the dilaurate. Hexachlorophene, in conjunction with phenothiazine and nicotine, is also reported as efficient (Hungerford, 1955), but dangerous to birds showing disease signs. Investigation into the action of proteolytic enzymes has indicated that further research may provide a new range of safe and efficient anthelmintics.

Flukes have been reported in ducks (Solman, 1955) but no significance is attached to these worms in poultry.

Roundworms comprise the *strongyloids* Syngamus (gapeworm) and Amidostomum (gizzard worm of geese), neither of which are easily treated. Antimony Barium Tartrate, B.Vet.C. (barium antimonyl tartrate) inhalation is reported as the best treatment available for Syngamus infestation and carbon tetrachloride for Amidostomum, though the efficiency of the chloride against the gizzard worm is suspect.

Ascaroid genera affecting poultry are those of Heterakis (cæcal worm) and Ascaridia, found in the small intestine. Phenothiazine is the drug of choice against Heterakis and piperazine against Ascaridia. Carbon tetrachloride, nicotine sulphate, and phenothiazine have also been used against Ascaridia, but with greater danger and less effect.

A genus of the order Trichinelloidea is also found in poultry in this country. This is the genus Capillaria, species of which may be found in the œsophagus, crop and small intestine of poultry. Pathogenicity is reported to be serious. Experiments on pigeons (Pouplard *et al.*, 1955) showed that fæcal counts of 4,000 eggs per gramme were invariably associated with symptoms, and that piperazine was over 90 per cent. effective against Capillaria species.

It will be apparent from examination of these lists of parasites and drugs that certain drugs have an action specifically against parasites within an order or class. Partly by chance, and partly by industry and observation, modern research has provided us with highly efficient drugs specific to both important orders of the class Nematoda as well as the class Trematoda. A truly safe and efficient specific for the eradication of members of the class Cestoda has yet to be found although some progress has been made in this direction.

With some exceptions, it will be seen that phenothiazine is highly efficient and specifically active against strongyloid species, piperazine is very efficient and active against ascaroids as well as being extremely effective against some strongyloid species, whilst hexachlorethane is very effective against the trematodes.

Classified Anthelmintics

The drugs are grouped according to the class or order of helminths against which they are active. Where overlapping of activity occurs drugs will be related to the class against which they are most commonly used.

Cestoda

Control of cestodes cannot be achieved by drug administration only, and therefore measures aimed at preventing contact between primary and intermediate hosts must also be used. Thus dogs and cats should not be fed on raw meat, while fleas and other Insecta intermediate hosts should be destroyed and suppressed wherever possible.

Organic Drugs of Natural Origin

Areca, B.Vet.C.

The use of areca and its derivatives as tapeworm anthelmintics in the dog and cat only has already been mentioned on pp. 91 and 106. Professionally the powder is now rarely used as it must be freshly ground to exert the best effect. Once ground, deterioration occurs and it is possibly this which is responsible for the many conflicting reports on the efficiency of the powder. Variations in the concentration of active principles may also be partially responsible.

Arecoline Hydrobromide, B.Vet.C., the alkaloid and main active agent of areca, is reported by Batham (1946) to be 90–100 per cent. effective against the tapeworms common in this country—Tænia and Dipylidium—as well as Echinococcus. Gordon (1939) reported success against *Diphyllobothrium latum.*

Optimum dosage is given as 1·0 mg. per kg., or approximately $\frac{1}{12}$ gr. per 12 pounds. This dosage has been used extensively in New Zealand with almost no ill effects. Administration should follow a 24 hour period of light feeding. Vomition within five minutes of dosing reduces the

effect. Should purgation not follow within 2–3 hours (commonly defæcation occurs within half an hour of dosing) a glycerin or soap enema should be given. It has been noticed that a trace of sodium hypochlorite in the enema fluid often increases the number of worms expelled, and ease of expulsion. The use of enemata when purgation does not occur is necessary to remove the worms before the paralytic effect of the arecoline wears off, for the anthelmintic action is one of paralysing the worm and at the same time increasing peristalsis. This expels the worm as it relinquishes its grip on the intestinal mucosa.

Treatment may need to be repeated two or three times at 7–10 day intervals to obtain absolute clearance of parasites, as occasionally the first dose may expel as few as 10 per cent. of the worms.

It is not usual to dose cats with this compound, though there is no scientific corroboration available for the statement that excessive bronchial secretion may be caused and result in suffocation.

Arecoline-Acetarsol, B.Vet.C. compounds are administered to dogs at the rate of 18·0 mg. per 15 lbs. (7·0 kg.) bodyweight with a maximum of 72·0 mg. (4 tablets), and to cats in doses of 9·0–18·0 mg. ($\frac{1}{2}$–1 tablet usually) according to age and size. *No dog in poor health, no puppy under three months and no cat under* 12 *months should be dosed.* For these exceptions dichlorophen would appear to be indicated.

The compounds are administered under conditions similar to those for arecoline hydrobromide. The results are variable, particularly where dieting is not strictly controlled.

Whitten (1956) says of the combination that 'It is difficult to see what advantage this compound has over arecoline hydrobromide as they both hydrolyse in the stomach and release arecoline, which is the active moiety. Acetarsol has negligible anti-cestode activity.'

Though used against poultry tapeworms the efficiency is not high.

Kamala, B.Vet.C.

This is available as a reddish-brown powder obtained from the fruits of a tree found in India and Malaya. It has been used in the dog, cat, and in poultry as an anti-cestode drug, but its efficacy in poultry has proved very low, its efficacy in cats is doubtful and the only possible indication seems to be in the treatment of Diphyllobothrium infestations in the dog. Rho (1934) reported success in treating *D. latum*, but the report is an isolated one and corroboration is not available. The powder is a strong purgative and frequently produces vomition. It should not be used when other, and better, anthelmintics are available.

Extract of Male Fern, B.Vet.C. (Ext. Filic.)

The extract is a thick dark green liquid obtained from various parts of the male fern. It contains 25 per cent. of a potent substance, filmarone, which is unstable, breaking down to give filicic acid and a substance, aspidinol.

It is still relied on as a valuable anti-cestode drug in man, mainly because it can be administered to hospitalized patients and therefore given under strict control, but also because it is effective against the majority of tapeworms which infest man.

The therapeutic index is narrow and the efficiency only mediocre, so that although active against most species of tapeworm, other drugs are preferred for the treatment of animal infestations. It is occasionally used in sheep against fluke, often combined with carbon tetrachloride.

Dosage in cattle is ½–1½ fl. oz. (15·0–45·0 ml.), sheep 60–90 m. (4·0–6·0 ml.) and in dogs 5–45 m. (0·3–3·0 ml.) It is not used in cats. Treatment is usually preceded by 24 hours' fast, and oils and fats, which aid absorption, should be excluded from the diet during the period of treatment. If purgatives are required saline types should be used.

Toxicity. Symptoms of toxicity are caused by both local alimentary irritation and remote irritation of the internal organs. Gastro-enteritis, with vomition and diarrhœa, nephritis, hepatitis, cerebral irritation with convulsions, and myocarditis may all occur. Treatment is symptomatic. (Saline purgatives to remove any drug remaining in the intestines followed, by intestinal sedatives, urinary sedatives such as hyoscyamus, glucose for the liver, nerve-sedatives such as barbiturates, and cardiac tonics such as vitamin E. and digitalis.)

Enzymes. One of the modern trends of anthelmintic investigation is in the direction of enzyme digestion of parasites, and also of interference with their enzyme systems.

Proteolytic enzyme activity was studied in 1950 by Terada and Sai-Ryo who found that an old Chinese remedy *raigan* prepared from a fungus was effective against tapeworms in man. The active agent was a non-toxic proteolytic enzyme and no purgative was required.

More recently Derbal (1955) reported that a compound containing an enzyme *papain* was effective against intestinal worms of poultry without causing any drop in egg production or lessening of growth rate.

Drezancic (1957) reports good results against *H. contortus* in sheep and points out that the pH of the gastric juices of simple stomached animals inactivates the enzyme, and that papain should therefore be administered to these species with an antacid.

A warning that enzymes will not prove a panacea for helminth infestations is given by Hohner (1955) who confirmed earlier reports that strongyloids were resistant to proteolytic enzymes.

The investigation of agents for interfering with parasite enzyme systems was prompted by the finding of Rogers (1948) that the surface layers of tapeworm proglottids are rich in alkaline phosphatase. It has recently been reported by Singh *et al.* (1956) that kamala has an inhibitory effect on the succinic dehydrogenase of *Monezia expansa*. Possibly, as more pharmacological information becomes available, we shall find that many anthelmintic drugs owe their effect to this type of action.

Organic Drugs of Synthetic Origin

Hexachlorophene and dichlorophen have both been used in recent years exclusively for the treatment of tapeworm infestations. Their use against other species gives poor results.

Dichlorophen, B.Vet.C.

This is known as Di-phenthane 70 and is available in various proprietary compounds.

It is a chlorinated derivative of phenylmethane and consists of a white powder with a phenolic odour and a combined phenolic saline taste. It is almost insoluble in water, but very soluble in alcohol and ether.

Dichlorophen is an effective bacteriostat, a fungicide and an anti-cestode agent.

As a *fungicide*, dichlorophen is widely used as a preservative for clothing, and for fabrics which are kept for long periods in damp conditions. In the 1939–45 war army canvas and webbing equipment was impregnated with this compound to good effect. Insolubility in water ensures its persistence. If finds a very wide veterinary application in the treatment of mycosis. Highly efficient against ringworm caused by species of Microsporon, it is also effective against fungi of other genera, and as a 2 per cent. alcoholic solution or ointment is of great value in the treatment of canine and cattle ringworm, where its antibacterial properties are also brought into play.

As a *tapeworm treatment* dichlorophen is used in the dog and cat against Tænia and Dipylidium, but its effect on Echinococcus is variable. Ryff *et al.* (1949, 1950) reported its excellent results against Monezia in sheep, but Enzie *et al.* (1953) could not entirely confirm these results, only partial success being achieved. Harries (1953) used the drug against heavy Monezia infestations in 550 ewes and lambs with very good effect.

Dosage:

Sheep:	0·5 G. per 6 lb. bodyweight. (Adults 5·0–15·0 G. Lambs 2·0–4·0 G.)
Dogs:	0·3 G. per kg. bodyweight. (approx. 0·5 G. per 5½ lb. bodyweight)
Cats :	0·1–0·2 G. per kg. bodyweight.

The dosages are somewhat bulky and detract from the usefulness of the drug.

The drug can be administered in tablet or suspension and is best given after overnight fasting. No purgative is needed.

It should be impressed on the client that the tapeworms are digested and passed in an unrecognizable form often 6–8 hours after dosing. This is considered by many practitioners to be undesirable as tangible results are more impressive and more easily assessed. Possible allergic reaction to the products of worm disintegration is also feared.

Should the dose be closely followed by vomition, or the results be unsatisfactory, dosing should not be repeated within 10 days.

Dichlorophen has been used in combination with other anthelmintics such as toluene, and good results for such combinations have been claimed in both dogs and cats.

Toxicity is low but the vomition and diarrhœa associated with most anthelmintics occur occasionally.

Hexachlorophene

This drug has been used in the treatment of infestations of poultry, particularly with Raillietina. Doses of 15·0–30·0 mg. per lb. bodyweight have been used effectively after overnight fasting, but drops in egg yield are reported for a week or so subsequent to dosing.

Combination with nicotine and phenothiazine has enabled comprehensive and efficient worming to be achieved by a single treatment but, where blackhead infestations are also present, high mortality rates are often reported, although normal birds are unaffected.

The preparations are usually administered in food.

Dye Compounds

The triamine dyes, particularly methyl violet, are reported as being more effective than the diamine compounds such as brilliant green when used for Dipylidium infestations of the dog, but the acridine dyes are more efficient and practical. Mepacrine Hydrochloride, B.Vet.C. in doses of 20·0–40·0 mg./kg. is effective against Dipylidium and Tænia species, but even at the rate of 50·0 mg./kg. is useless against Echinococcus. Aminacrine Hydrochloride, B.Vet.C. has been reported by Tareeva (1953) to be safe and effective in cats at the rate of 200·0 mg./kg. Further investigations into the effect of the acridine dyes are in progress.

Inorganic Drugs

Copper sulphate combined with nicotine sulphate is still widely and economically used as a combined tapeworm and roundworm remedy, but the treatment is not very efficient. As low as 50 per cent. efficiency has been reported.

Lead Arsenate, B.Vet.C. is an insoluble white powder which has been introduced in recent years almost specifically for the treatment of Monezia infestations of sheep and cattle, but it has been proved ineffective against the fringed tapeworm *Thysanosoma actinoides* which is very common in sheep in various parts of the world (Australia, America etc.).

Dosage in calves, sheep and goats is 7½–15 gr. (0·5–1·0 G.) and in adult cattle 15–30 gr. (1·0–2·0 G.). It is not safe to use in poultry but in these doses toxicity is not likely in ruminants. The dose is usually administered in a capsule and no fasting is required; it may be followed by an oleaginous purgative.

Ferric arsenate and arsenious sulphide (Trisulphide of arsenic) have also been used against Monezia infestations.

Tin compounds are being widely investigated as anthelmintics in all species. Stannous oxide and di-n-butyl tin dilaurate are in use, the dilaurate in doses of 1·0 ml., or at the rate of 0·5 ml. per kg. bodyweight, is reported as being highly efficient against tapeworms in poultry, particularly against Davainea species (Abdou, 1956). Kerr (1952) had previously reported good effect on Raillietina species at a minimum individual dose rate of 75·0 mg. per kg. bodyweight in capsules, or given in food over a 2 day period at the rate of 1 lb. in 100 lb. mash for 200 adult or 300 growing birds. It can be used with phenothiazine and nicotine and does not affect egg production.

Tin compounds have also been used in man and dogs, with good effects reported against *Tænia saginata*, *T. solium* and *Dipylidium caninum*. A dose of 0·5 G. stannous oxide daily for eight days was given to human patients by Bellon (1955).

Trematoda

It cannot be emphasized too strongly that the use of drugs is not in itself the complete answer to fascioliasis. In many cases the problem responds more completely to methods aimed at destroying the intermediate snail hosts, both by copper sulphate pasture dressings and by improving land drainage. This should be combined with periodic herd and flock dosing to gain the best results.

Organic Drugs of Natural Origin

Extract of Male Fern has been used against liver fluke in sheep and cattle, often combined with an equal amount of carbon tetrachloride and given in capsules. Capsules containing 15 m. (1·0 ml.) of each drug are still used extensively in some areas.

Organic Drugs of Synthetic Origin

Carbon Tetrachloride, B.Vet.C.

This drug is a heavy, clear and colourless volatile liquid with an odour similar to chloroform. It has a burning taste, and though non-inflammable will produce phosgene gas when ignited. The liquid is practically insoluble in water but miscible with organic solvents and oils.

Actions and Uses. The main use of carbon tetrachloride is in the treatment of *Fasciola hepatica* infestations of sheep. It is of no value against immature flukes in normal doses and is not effective against *Dicrocœlium dendriticum*. Hexachlorethane has displaced it as a treatment for 'fluke' in cattle.

Carbon tetrachloride is absorbed slowly but the presence of animal or vegetable fats and oils will increase the absorption rate. Once absorbed and circulating, the drug is excreted at various points—the lungs, the kidneys, but mainly through the liver. The biliary system extracts the tetrachloride

and returns it to the intestines, and in so doing the mature and nearly mature adult flukes in the bile ducts are destroyed. The immature flukes in the liver tissue are unaffected and consequently monthly dosing is required where heavy infestations occur.

The use of the drug against Ascaridia in poultry and hookworms and ascarids of dogs, has given place to piperazine treatment although tetrachlorethylene is still used. Gizzard worm in geese is also treated with carbon tetrachloride but the effects are not very satisfactory.

Carbon tetrachloride has been developed in France and England as an injection for the treatment of parasitic bronchitis (husk), mainly in cattle. Reports indicate it to be of some value though the safety margin is low.

Dosage: Cattle: 1·0–5·0 ml. (15–75 m.)
Sheep: 1·0–3·0 ml. (15–45 m.)
Dog: 1·0–5·0 ml. (15–75 m.) at the rate of 0·1–0·2 ml./kg. (0·5–0·1 ml./lb. approx.)
Poultry: 1·0–5·0 ml. (15–75 m.)

In cattle, administration is as a drench mixed in ½–1 pint liquid paraffin, but capsules are a more suitable form of administration in other species. Care should be exercised that capsules should not be broken in the mouth, for the tetrachloride has similar anæsthetic properties to chloroform. No fasting or purgatives are necessary but dosing is usually carried out before morning feeds, and can be followed 2–3 hours later by a saline purgative. It is advisable, before flock or herd dosing with carbon tetrachloride and similar chlorinated hydrocarbons, to withhold concentrate foods for a week or so prior to dosing, and to try the effect on a few of the worst affected individuals in the group. Cattle show frequent individual susceptibility, and flock susceptibility is responsible for frequent losses in sheep where dosing with carbon tetrachloride is not adequately controlled. Pigs, horses, and cats are not suitable species for dosing with this drug.

Toxicity is typical of the group of the carbon and chlorine compounds and is due to the considerable damage which can be caused to the liver. Death is usually due to liver failure following extensive fatty changes, but earlier symptoms are hyperæsthesia and convulsions, followed by coma. Hypocalcæmia and low liver glycogen content are predisposing causes and treatment of toxicity should consist of intravenous calcium borogluconate and dextrose injections, whilst the detoxicating activities of the liver should be reduced by cutting the protein intake.

Hexachlorethane, B.Vet.C. (C_2Cl_6)

This white or off-white crystalline powder has an odour faintly resembling that of camphor. It is almost tasteless, insoluble in water, slightly soluble in alcohol but soluble in most other organic solvents. Up to 5 per cent. wetting or dispersing agent is usually included to aid administration.

Actions and Uses. Absorption of hexachlorethane is fairly rapid and its metabolism follows a similar course to carbon tetrachloride except that the majority is excreted via the liver. Although it was claimed that hexachlorethane attacked immature flukes, more recent trials show that immature flukes, and particularly those in the liver tissue, are unaffected. All Fasciola species are affected but a claim by Kaplan *et al.* (1947) that Dicrocœlium in sheep were successfully eliminated has yet to be confirmed. Hexachlorethane is also effective against Hæmonchus and *Trichostrongylus axei* in the stomach of ruminants but not against intestinal parasites.

Dosage and Administration:

Cattle: 15·0–100·0 G. ($\frac{1}{2}$–3$\frac{1}{2}$ oz.) at the rate of 10·0 G. per 100 lb. bodyweight.

Sheep and Goats: 8·0–15·0 G. ($\frac{1}{4}$–$\frac{1}{2}$ oz.)

Administration is by drench or stomach tube and the precautions adopted to prevent toxic symptoms with carbon tetrachloride should be observed. No advantage over the tetrachloride is shown except by near toxic doses in sheep, and the extra cost does not seem to be warranted. In cattle, however, the drug is the best available and is relatively efficient.

Dosing should continue at monthly intervals where repeated infestation may occur.

Toxicity is relatively low but herd and flock susceptibility does occur. Treatment is the same as for all chlorinated hydrocarbons.

Inorganic Drugs

There are no drugs of an inorganic nature available for treating trematode infestations.

Nematoda

The control of this class of parasite follows the pattern of other classes. Mere administration of drugs is valueless without husbandry methods aimed at reducing food and water contamination, whether it be in the stable or byre, or at pasture. In some cases, as for example in strongyle infestations of the horse, practitioners are relying more and more on small repeated doses of a drug to depress egg laying by the female worms and at the same time reduce hatchability: by this means pasture infestation can be kept at a minimum. Correct grazing husbandry related to adequate but not overstocking, mixed species grazing and periodic harrowing to break up and expose to light and air the fæcal droppings of the animals will assist in maintaining a safe level of pasture contamination.

A. Anthelmintics Affecting Strongyles

Organic Drugs of Natural Origin

Nicotine Sulphate

This alkaloidal salt is rarely used in pure form. *Solution of Nicotine Sulphate, B.Vet.C.* is the most widely used compound containing nicotine

and consists of a 40 per cent. aqueous solution of the sulphates of the mixed alkaloids extracted from tobacco. It is a brown liquid with a characteristic odour and burning taste.

Actions and Uses. Internally, solution of nicotine sulphate can be used alone against tapeworms and trichostrongyles in sheep and cattle, and Ascaridia in poultry, but it is most commonly used combined with copper sulphate, both being present in concentrations of 1 per cent. This combination is very effective and is frequently used in sheep and lambs against roundworms and tapeworms. Its use in Ascaridia of poultry is outmoded by piperazine compounds.

Externally, the solution is used to paint poultry house perches and walls as a treatment for red mite, lice, etc. The structures are painted in the evening and the heat generated by the birds in the closed up house during the night volatilizes the alkaloidal sulphate which destroys the parasites. Sheep dips containing nicotine sulphate are also available.

Dosage and Administration: Solution of Nicotine Sulphate, B.Vet.C.

Cattle: 60–90 m. (4·0–6·0 ml.)
Sheep: 15–20 m. (1·0–1·3 ml.)

One per cent. nicotine sulphate solution combined with one per cent. copper sulphate is given to sheep at the rate of 1 fl. oz. (28·0 ml.) per 35 lb. bodyweight, to a maximum of 5 fl. oz. For cattle the maximum dose is 10 fl. oz. of the 1 per cent. solutions. The solutions are administered by continuous feed injectors in sheep, and by drenching in cattle.

Toxicity. Nicotine sulphate solutions are frequently used as plant sprays, and so toxic is this alkaloid that poisoning from grazing contaminated herbage is possible. The alkaloid is also used as a poison bait for pigeons and similar crop ravagers, and though access by domestic animals should not be possible poisoning may be seen, particularly if birds, falling and dying, are eaten by dogs or cats, The immediately fatal oral dose of nicotine for a dog is two drops of the alkaloid, and for a man about 64.0 mg. (1 gr.). It equals hydrocyanic (prussic) acid in rapidity of action.

Toxic symptoms are related to the pharmacological effect of the alkaloid on the nervous system.

The effect of nicotine on the central nervous system, and also the peripheral system, is one of initial stimulation followed by paralysis. The medullary centres such as the respiratory, vagus, vomiting and vasomotor centres are strongly stimulated, as well as the motor cells of the spinal cord. This stimulation produces convulsions, with emesis, defæcation and urination. The initial, and usually brief, stimulation is followed by depression and paralysis. Peripheral action consists mainly of a ganglion blocking or curare-like effect. Death is due to respiratory paralysis and asphyxia, mainly because of the curare-like paralysis of the diaphragm and chest muscles.

Symptoms in poisoning not immediately fatal will therefore be salivation followed by emesis, diarrhœa, urination and parasympathetic sweating. These symptoms are followed by muscular weakness and collapse, often with convulsions.

Treatment consists of neutralizing unabsorbed nicotine by administration of, or gastric lavage with, tannic acid or potassium permanganate, combating heart failure with adrenaline injections and, above all, of continuous artificial respiration.

Organic Drugs of Synthetic Origin

Antimony Barium Tartrate, B.Vet.C.

This is a white or creamy white powder which is odourless, tasteless and practically insoluble in water. It is very irritant to mucous membranes. The only action of any veterinary interest is its effect on *Syngamus trachea*, the gapeworm of poultry. Treatment consists of confining the birds in a small enclosed space (50 birds in about 8 cu. ft.) and dispensing the drug in a fine powder which must of necessity be inhaled by the birds. They themselves further disperse the powder by flapping their wings.

Toxicity is said to be rare when this treatment is adopted, but attendants should beware of inhaling or getting the drug in their eyes, for the irritation is quite severe even though it is short lived.

Phenothiazine, B.Vet.C.

This most important anthelmintic is a green amorphous powder which darkens on exposure to light. It is insoluble in, and is not wetted by, water, but is reasonably soluble in alcohol and acetone. As the compound is not 'wetted' by water it is used mainly in the form of a dispersible powder formed by the addition of approximately 5 per cent. of a detergent. When dispersed in water a uniform suspension is formed which settles slowly but is easily redispersed by stirring.

It has been reported recently that the particle size of the drug has an effect on the drug activity (Douglas J. R. *et al.*, 1956; Gordon, 1956; Whitten, 1956). The smaller the particle—under 10 microns—the more active is the compound. This has yet to be fully substantiated.

Actions and Uses. The pharmacology of phenothiazine is still debated, but the accepted theory agrees with a large proportion of the known facts. There appear to be variations between the species, and the greater toxicity amongst some species is probably related to these differences. In general, there remains within the intestines about 50 per cent. of any dose and it is this unabsorbed proportion which is responsible for the anthelmintic effect. It has been shown that phenothiazine is ingested by the parasite and, by using a labelled sulphur (S^{35}) isotope, absorption through the cuticle of some parasites has been proved. It also appears that *Ascaridia galli* at any rate shows a selective absorption of the drug, for the phenothiazine was

absorbed more rapidly and in greater quantity by the parasite than by the surrounding mucosa (Lazarus *et al.*, 1950). Approximately five times more drug is taken in by the parasite than is absorbed by an equivalent weight of mucosa. This drug becomes fixed in the parasite tissues. The precise way in which the lethal effect is exerted is not known, but it is not related to the quantity absorbed, for some parasites unaffected by the drug will take into their tissues an amount lethal to susceptible worms, and yet show no signs of toxicity.

Mature parasites only are destroyed, which necessitates repeated dosing to destroy the parasites that were immature at the time of the previous dosing.

What happens to the drug during the time it remains in the intestines is debated, some workers saying that there is a change into phenothiazone, others that phenothiazine sulphoxide is formed, and still others who say that there is little change. Following absorption, quantities of the oxidation product phenothiazine sulphoxide occur in the portal circulation and further oxidation occurs in the liver, with the production of leucophenothiazine and other substances which are excreted mainly in the urine and bile. The two compounds leucophenothiazine and leucothionol are colourless when excreted but are oxidized in the atmosphere to the brown-red dyes phenothiazone and thionol. These are fast dyes and indelibly stain wool. It is therefore important, as these compounds appear in the urine within 30 minutes of oral dosing, to disperse flocks immediately after administration, otherwise staining and ruining of many fleeces can occur. Staining will also occur if phenothiazine suspensions are spilt on the fleece during administration. Discolouration of milk may also occur, but æsthetic considerations are the only ones of any consequence. It is interesting that milk containing these phenothiazine excretory products is reported to keep fresh far longer than normal milk; this is no doubt due to the bacteriostatic effect of the dye compounds. Clients should always be warned, if using the drug for the first time, that excretions and secretions will be coloured.

Phenothiazine is used against strongyle parasites in ruminants, horses and related species, poultry and in some laboratory animals such as rabbits. There are no indications for its use in the dog and cat, and the dog in particular is very susceptible to poisoning. The drug is not used in human medicine because of a similar susceptibility. There is rarely, and since piperazine has proved effective against nodular worms (Œsophagostomum) it might almost be said never, any indication for its use in pigs, which as a species are susceptible to toxic effects.

In the *horse* phenothiazine is effective against the redworms—Strongylus, Triodontophorus and Trichonema species. Against *Trichostrongylus axei* phenothiazine is not consistent, nor is it satisfactory against Oxyurids and must be combined with chenopodium and other drugs.

In *ruminants* the genera of strongyles most affected are Hæmonchus, Ostertagia and Œsophagostomum; the effect on trichostrongyles is

variable probably because of the variation in particle size in the different batches of commercial phenothiazine, but they respond to the higher doses as do Cooperia species. Nematodirus species do not respond satisfactorily to phenothiazine treatment. Some Bunostomum species respond and some workers report activity against Chabertia species, but no effect is exerted on tapeworms or flukes. Phenothiazine is unusual in that it affects both immature and mature forms of *Hæmonchus contortus*.

Dosage and Administration:

Single dose treatment:

Horse:	10·0–30·0 G. (150 gr.–1 oz.) at 3·0 G./100 lb.
Cattle:	20·0–60·0 G. (300 gr.–2 oz.) at 10·0 G./100 lb.
Sheep and Goat:	5·0–40·0 G. (75 gr.–1½ oz.)
Poultry:	0·25–1·0 G. (4–15 gr.)

Repeated doses:

Horse:	2·0–5·0 G. (30–75 gr.)
Foals:	1·0–2·0 G. (15–30 gr.)
Cattle:	0·5–5·0 G. (7½–75 gr.) at 0·5 G./100 lb.
Sheep:	0·25–0·5 G. (4–7½ gr.)

Young foals, calves under three months, lambs under one month, and heavily pregnant females should not be dosed. Doses for sick or debilitated animals should be calculated with care. No purgation is required.

Phenothiazine may be administered in the food, as a drench or by stomach tube, in tablet form or as salt licks.

In *horses*, it is preferable to administer the compound in food wherever possible, but, though described as a tasteless and odourless powder, some horses will refuse medicated mashes even after starvation. In these cases electuaries or administration by stomach tube are the methods most commonly used, although rigid gelatin capsules are often a very useful means of giving the powder.

As blood horses are susceptible to phenothiazine poisoning practitioners are very chary of administering full doses and prefer to give half doses on each of two successive days. Debilitated animals, even when this course is adopted, may show signs of toxicity, for complete excretion does not take place before the second dose is given so that a cumulative effect is exerted.

Arising from this, prophylactic doses of up to 5·0 gramme in the food daily have become very popular, and reports of such doses administered continuously for 5–10 years indicate that no toxic effects occur in the host and no phenothiazine resistance is developed by the parasites. This method of treatment is valuable in that (a) egg production by adult females in the intestines is reduced, (b) hatchability of eggs passed in the fæces is considerably reduced, and (c) that, of the infective larvæ which are taken in by the horses, relatively few reach maturity. It also means that pastures

carry a relatively minor parasite load and that the danger to foals running with adults is considerably reduced.

In *sheep*, drenching guns with a continuous feed from canisters on the backs of the operators and with œsophageal nozzles, are being used for flock dosing with phenothiazine dispersible powders. This means that doses are injected directly into the œsophagus and staining of the fleece during administration is minimal. Another popular way of giving phenothiazine to sheep is in the form of tablets—an elongated tablet weighing about 5·0 gramme is the usual one—which are administered by balling gun, forceps or by hand. Sheep unfortunately soon learn to hold the tablet and cough them out when released back into the flock. This means that tablets are discovered when the flock is dispersed and the offenders impossible to identify.

Repeated daily administration of 0·5 gramme doses has been shown to be as effective as in horses but individual dosing is impracticable, and in Great Britain the salt lick requirements of sheep are insufficient to provide adequate dosage levels of phenothiazine. In America the use of 1 part phenothiazine to 9 or 10 parts mineral or plain salt has been given up to 11 year trials and proved satisfactory. Where salt licks have proved unsuccessful, mineral and phenothiazine food supplements in the ratio of 1 part phenothiazine to 18 or 20 parts mineral supplement have proved of use.

Where intermittent dosing operates, administration should take place at approximately monthly intervals with emphasis on late winter and spring dosing, when a seasonal increase of infective larvæ on pasture occurs. Where low level dosing is used it is advisable to give therapeutic doses once in spring and once in the autumn in order to irradicate or lessen the adult parasite burden.

In *cattle*, the story follows much the same pattern as in sheep, but on the whole larger doses—up to 0·2 gramme per lb. bodyweight—are required against parasite species other than Hæmonchus and Œsophagostomum. The usual method of dosing cattle with phenothiazine is in the form of a drench. Salt licks containing the drug have yet to be proved of value and low level dosing is not yet generally adopted.

The low toxicity of phenothiazine for *poultry* makes it a useful anthelmintic for birds. Individual dosing with 0·5 G. pills or tablets for fowls, and 1·0 G. for turkeys, is the safest and most accurate method of administration but medication of dry or wet mash feed is the most practical way of treating birds. The food is medicated once a month.

Toxicity. Phenothiazine is toxic in two ways. The first is by causing a hæmolytic anæmia which affects all species except sheep and goats, but is of most importance in horses and, to a lesser extent, cattle. The cause of the hæmolysis is not known but it has been suggested that in horses the phenothiazine and its derivatives are no more than activators of an enzyme lysolecithin which is normally found in horse blood. This enzyme

has been shown to lyse red blood cells *in vitro*. Signs and symptoms are those typical of a hæmolytic anæmia—dullness, lack of appetite (anorexia), weakness, enlargement of the heart and vital organs such as liver and kidneys, frequent and weak pulse, some œdema and jaundice. Severe enteritis also occurs. All tissues deteriorate rapidly following post mortem.

Treatment is symptomatic only, with extensive use of whole blood transfusions where practicable. No antidote is known.

The second type of toxicity results in the occurrence of photosensitization. It occurs most frequently in calves but lambs have also shown lesions on exposed lightly pigmented skin areas such as the muzzle, ears and eyes, and particularly the cornea. The cause of the photosensitization is reputed to be due to the saturation of the liver conversion processes and the passage of phenothiazine sulphoxide into the general circulation. When exposed to bright sunlight within 24–48 hours of dosing, irradiation of the affected and exposed tissues results in a process similar to severe sunburn and all non-pigmented skin areas become inflamed and frequently slough: corneal opacity and ulceration is a manifestation of the same phenomenon.

Treatment, where exposure has occurred, consists of antihistamine applications with local and general sedatives, in conjunction with protection from further exposure to direct sunlight.

Inorganic Drugs

Arsenic and Its Compounds

Four compounds of arsenic are used as anthelmintics, *Arsenic Trioxide, B.Vet.C.* (white arsenic), *Lead Arsenate, B.Vet.C., sodium arsenite* and *Sodium Glycarsamate, B.Vet.C.* The last of these is of comparatively recent origin and is stated to be safe and effective against strongyles in the horse, for which it is mainly used. Lead arsenate had already been mentioned, p. 112, as an effective tapeworm remedy for ruminants, but the other two are now rarely used in Great Britain as anthelmintics.

Arsenic Trioxide, B.Vet.C. is a white, tasteless, odourless, powder which is slowly soluble in water to the extent of 1 in 60 parts. The addition of dilute acids or alkalis greatly increases solubility.

Actions and Uses. Arsenic is available for general purposes in various compounds, amongst which *Arsenical Solution, B.Vet.C.* (Fowler's solution), containing 1 per cent. w/v arsenic trioxide, Tablets of Ferrous Carbonate and Arsenic, B.P.C. (Blaud & arsenic tablets), which contain 1/100 grain of arsenic, and tablets containing 1/100th and 1/50th grain of arsenic with magnesium sulphate, are common examples. The organic compounds such as the trivalent *Arsphenamine* and *Neoarsphenamine, B.Vet.C.* and the pentavalent *Acetarsol, B.Vet.C.* have also been widely used but are now superseded in almost every direction by more efficient and less toxic drugs. Before absorption, arsenic and its compounds have

been used for anthelmintic purposes. For horses, against roundworms, it has been used in 5 gr. (0·3 G.) doses combined with 60 gr. of ferrous sulphate, administered daily for 6 days and followed by a strong purge on the seventh day. This method is similar to one using potassium antimony tartrate instead of arsenic, but neither combination is very efficient and they are not in wide use to-day.

In *sheep*, a combination of copper sulphate 4 parts and sodium arsenite 1 part was originated as the 'Government Wireworm Remedy' in South Africa and used throughout the world in *doses* of 0·2 G. for 2–4 month old lambs, up to 0·625 G. for four tooth adults. The toxic dose is close to the effective dose and any factor which increases the absorption rate can cause death. It is therefore essential that water should be withheld for 7 hours before and 7 hours after dosing. Its efficiency against worms other than Hæmonchus species is not very great and the copper sulphate-nicotine sulphate mixture is preferred even though Ostertagia species are resistant.

Sodium Glycarsamate, B.Vet.C. is a pentavalent organic compound and is a white powder, soluble in six parts of water, developed mainly for oral administration in horses. It is administered in food, preferably in a mash followed and preceded by two non-medicated mash feeds. It should be repeated in 7–10 days.

As with arsenic trioxide and other organic arsenicals, sodium glycarsamate is also used as a general and skin tonic.

No arsenical compound should be administered orally in cases with gastro-enteritis nor should they be used where liver or kidney function is disturbed.

Absorption of arsenic trioxide is irregular and slow but is faster where inflammation of the small intestine is present; the arsenites and arsenates are more rapidly absorbed. This is an important factor in sheep dip poisoning when arsenite and arsenates, usually of potassium, contaminate streams. The pentavalent compounds acetarsol and sodium glycarsamate are also rapidly absorbed, but the trivalent arsphenamines are not usually administered orally as they are less stable.

After absorption the inorganic arsenicals are removed relatively slowly from the blood, the pentavalent compounds more rapidly and the trivalent compounds very rapidly following injection. The inorganic and trivalent compounds are absorbed to a large extent by the tissues but a large part of pentavalent compounds is rapidly excreted. Storage is mainly in the liver and kidneys, particularly the latter, but small amounts can be found in most tissues following arsenic treatment.

Within the body most of the actions of arsenic can be attributed to its effect on the capillaries. It would appear that the oxidation processes within the endothelioid cells are slowed, with a consequent relaxation and dilation of the capillaries; an increase in vessel permeability also occurs. These processes result in the slowing down of capillary circulation, which allows greater deoxygenation and removal of nutrients from the blood concurrently with an increased uptake of metabolites.

The general tonic action is ascribed to an increase in splanchnic circulation, for this area is amongst the first to be affected. Increased food, minerals, and vitamin absorption results, with consequent benefit to the animal.

The skin tonic action is similar, for increased nutriment is carried to the skin and increased removal of waste products also occurs. Arsenic is widely used as a skin tonic.

It is also possible that tissue oxidation processes in general are depressed and energy requirements decreased, so that fat depot reserves will increase.

Other internal actions have been ascribed to arsenic but they are now largely discounted. Amongst these actions are the reputed reticulocyte stimulation, and an effect on tumour tissue. It is maintained by some that arsenic has a particular affinity for pathological tissue and has a depressant effect on tumour cell division; leukæmia has been treated with arsenic because of its reputed specific toxicity for abnormal white blood cells.

External actions and uses include its use as:

1. A *parasiticide* in the form of sheep dips, popularly in combination with sulphur. A common prescription contained 20 lb. each of white arsenic, potassium carbonate, and sublimed sulphur, dissolved in 10 gal. soft boiling water with 4 lb. soft soap, and the whole diluted to 1,000 gal. This was initially effective against lice, ticks, keds and mange but some species of tick became immune to arsenic, and it has been superseded by benzene hexachloride, dicophane and similar products. The concentration of arsenic is approximately 0·2 per cent. and consequently it is not advisable, when arsenic dips are used, to dip animals with open wounds, nor to dip on hot days or immediately after driving sheep. Absorption can take place through open skin glands and is increased when the skin vessels are dilated by the heat. If the sheep are having difficulty in breathing in hot weather or from exertion, they are liable to swallow quantities of dip when totally immersed.

2. A *caustic*. If applied to unbroken skin for long periods reddening, followed by vesication, and finally necrosis and sloughing, occur. It has been effectively used as a paste applied to mallenders and sallenders, which are chronic, excessively granulating ulcers in the angles of the knee and hock joints, respectively, of horses. The effect is achieved by the same basic action as internally, namely dilation of capillaries, but carried to the stage of paralysis. This is followed by blood stasis, clotting and death of the tissue, which consequently sloughs out leaving clean fresh tissue below. No damage is done directly to cell protoplasm, for corneal avascular tissue is unaffected by arsenic applications.

A restriction of oxidation processes is probably responsible for the remarkable preservation of bodies following death from arsenic poisoning, and following the use of arsenical embalming fluids.

The *excretion* of arsenic compounds is slow with the exception of the pentavalent ones, which are mainly excreted through the kidneys. The trivalent organic compounds are excreted almost equally via the bile and

the urine. Small quantities of inorganic arsenic are lost in all secretions and excretions such as sweat and skin scales, tears, saliva, nail and hoof parings, hair and milk. Following a single dose, excretion may continue for 7–10 days, but following a course of treatment secretions and excretions may still contain arsenic ten weeks or more after administration of the last dose. Arsenic is one of the best examples of a *cumulative* drug, for the excretion rate of most arsenic compounds is so much slower than the absorption rate that even very small therapeutic doses, if administered over a long enough period, can result in chronic toxicity due to the build-up of tissue concentrations.

Tolerance towards arsenic by the oral route can be achieved by administering gradually increasing doses over a long period. A point of conditioning can be reached where individuals can, with impunity, take doses which would cause acute arsenical poisoning in an unconditioned animal. This tolerance is ascribed by some to a mucosal resistance to the absorption of arsenic from the intestines. In these cases, of course, the individuals are still susceptible to poisoning by injections of arsenic.

Dosage and Administration:

Arsenic Trioxide, B.Vet.C.

Horse and Cow:	3–10 gr. (0·2–0·7 G.)
Sheep and Pig:	¼–¾ gr. (16·0–48·0 mg.)
Dog and Cat:	1/100–1/10 gr. (0·65–6·5 mg.)

Arsenical Solution, B.Vet.C.

Horse and Cow:	½–2 fl. oz. (15·0–60·0 ml.)
Sheep and Pig:	10–75 m. (0·6–5·0 ml.)
Dog and Cat:	1–8 m. (0·06–0·5 ml.)

Sodium Glycarsamate, B.Vet.C.

Foal:	60–120 gr, (4·0–8·0 G.)
Adult Horse:	120–360 gr. (8·0–24·0 G.)

Commercially, doses at least four times greater than these have been recommended.

Acetarsol, B.Vet.C.

Dog and Turkey:	2–8 gr. (0·12–0·5 G.)
Cat:	1–2 gr. (0·06–0·12 G.)
Fowl:	4 gr. (0·25 G.)

Neoarsphenamine, B.Vet.C.

Horse and Cow:	45–90 gr. (3·0–6·0 G.)
Sheep and Goat:	4–12 gr. (0·25–0·8 G.)
Dog:	3–7½ gr. (0·2–0·5 G.)
Turkey:	½–1¼ gr. (20·0–75·0 mg.)
Fowl:	1½–2¼ gr. (0·1–0·15 G.)

All doses are for oral administration except those for neoarsphenamine which are for intravenous injection only, as any perivascular leakage may cause sloughing, and oral administration is attended by destruction of the compound.

Oral dosing of small animals may result in emesis, particularly when arsenical solution is given, and this, to a certain extent, prevents overdosage.

Most animals will accept arsenic and its compounds in food as they are almost tasteless.

Toxicity. Chronic arsenical poisoning is not so frequent now in either animals or man. (In Elizabethan days 'Leicester's cold' was a common name for chronic arsenic poisoning, so named because people disliked by the Earl of Leicester frequently suffered from 'colds' from which they just as frequently died!). Occasional cases occur in animals grazing on pasture contaminated by arsenical dust and fumes from industrial plant. Signs of poisoning are not very distinctive, but unthriftiness, indigestion, oculo-nasal discharges, œdema, and infected mucous membranes, with a normal temperature and weak irregular pulse, coinciding with the possibility of pasture contamination, should be accepted as grounds for strong suspicion.

Acute toxicity is rare in dogs and cats, but is also less common generally in Britain than hitherto, as farmers are more aware of the dangers of pasture and water contamination with horticultural sprays and sheep dips. The signs are fairly typical, shock, severe gastro-enteritis with frequent emesis in the vomiting species, and rapid collapse. These signs in farm animals are usually associated with a history of crop spraying, of fresh grazing and access to new drinking water, although where sheep dips contaminate streams the grazing history may direct the search away from a mineral poisoning diagnosis. Acute ergot poisoning has been known to simulate arsenic poisoning.

Post-mortem examination shows poor diagnostic features in chronic poisoning, but in acute poisoning extremely severe gastro-enteritis occurs with the intestinal wall thickened to an inch or more in places by diphtheritic green and black tissue. The liver and kidneys will be congested, slightly enlarged and friable. Analysis of kidney tissue, which usually contains the highest concentrations, gives positive proof.

Treatment of chronic poisoning consists mainly of removing the source of poisoning, but the treatment of the acute poisoning, though necessitating removal of the source, requires the administration of sodium thiosulphate both orally and intravenously as a 10 per cent. solution. Dimercaprol, B.P.C. (B.A.L.—British Anti-Lewisite) has been suggested as a possible treatment, in doses up to 2·0 mg. per lb. daily for three or four days. Oral administration of freshly precipitated ferric hydroxide is also given with the aim of precipitating any arsenic still remaining in the intestines.

B. Anthelmintics Affecting Ascarids

Organic Drugs of Natural Origin

Chenopodium Oil, B.Vet.C.

Also known as Oil of American Wormseed, this drug was, until the discovery of phenothiazine and piperazine, the most useful roundworm treatment for all simple stomached animals. Its use in ruminants is not recommended. It is a steam-distilled, pale yellow volatile oil with a characteristic, unpleasant odour and a bitter burning taste. It contains 65 per cent. or more of an active principle *ascaridole* which is available commercially in a purified form.

Actions and Uses. Chenopodium acts by paralysing the worms which release any hold they may have on the mucosa and can be evacuated by peristalsis. A purgative is required to speed up the expulsion of paralysed worms and to remove any excess chenopodium oil. An oleaginous purgative is usually preferred, but salines may also be used.

In the *horse* the drug is moderately effective against both strongyles and ascarids. It has also been recommended in maximum doses after 36 hours starving, for the treatment of oxyuriasis, but 240 m. (15·0 ml.) per 1,000 lbs. followed by 1¾ pints (1·0 litre) of linseed oil under these conditions is somewhat rigorous. Phenothiazine has replaced it as a treatment for strongyle infestations, and, for ascarid and oxyurid infestations, piperazine is superior in all respects even though only 50–60 per cent. effective against the Oxyuris species.

In the *pig* chenopodium oil, usually mixed in castor oil in the 1 in 20 parts required by the British Veterinary Codex for making *Solution of Chenopodium*, B.Vet.C., has been very widely used. The danger of pneumonia involved with drenching, and the necessity for individual dosing, makes the drug unsuitable for mass dosing and sodium fluoride food medication had largely replaced chenopodium before piperazine became available. Chenopodium oil is reported as being 60–70 per cent. effective against *Ascaris lumbricoides* in the pig.

For the *dog* chenopodium oil was very effective and, if used with discretion, moderately safe against *Toxascaris leonina* and *Toxocara canis*. It is useful in hookworm infestation but is not so effective as either carbon tetrachloride or tetrachlorethylene. A combination of 2 parts tetrachloride and 1 part chenopodium oil, given to children at the rate of 7 drops for each year of age, was reported to give 98 per cent. efficiency by Odriosola (1955) in a survey and report on hookworm therapeutics. Uncinaria is the only hookworm reported in Great Britain and is of relatively slight significance, but where difficulty has been experienced with other treatments this combination might be considered. Normally, puppies of six weeks and under should not be wormed, but should clinical considerations make it necessary, chenopodium oil ¼ m. (0·016 m.) in 60 m. (4·0 ml.) of

castor oil may be administered to fox terrier, Scottish terrier or similar sized puppies of four weeks.

Chenopodium oil is not recommended for *ruminants or cats.*

Dosage and Administration:

Horse:	60–240 m. (4·0–15·0 ml.)
Pig:	2½ m. (0·16 ml.) per week of age, or 6 m. (0·4 ml.) per lb. bodyweight with a 60 m. (4·0 ml.) maximum.
Dog:	½–10 m. (0·3–0·7 ml.)

Chenopodium oil should *always* be accompanied, or followed immediately, by a purgative. Castor oil is the best in the pig and dog, and linseed oil for the horse. *Liquid paraffin should not be used on any account*, as the slow, laxative effect predisposes to absorption of the chenopodium oil and to toxic effects. This is especially important where clinical signs of ascariasis are evident. The oil may either be mixed in the purgative oil or may be given in a capsule prior to administration of the purgative.

Toxicity. It is quite common in newly weaned puppies to meet symptoms of gastro-intestinal irritation with emesis, diarrhœa, and convulsions following doses of 'patent medicine' worming mixtures containing chenopodium oil. Death is due to exhaustion and respiratory failure. The usual cause of the poisoning is the inclusion of liquid paraffin as the purgative vehicle which has resulted in non-evacuation of the chenopodium oil and hence its absorption. Normal doses may also cause toxic effects in very debilitated patients. Treatment consists of mild saline purgation followed by warmth, glucose-saline injections and a high carbohydrate diet as soon as the appetite returns.

Santonin, B.Vet.C.

This drug is obtained from the flower buds of Artemisia species, the Levant wormseed. It is a white crystalline powder which yellows on exposure to light and has a slightly bitter taste after an initial delay. It is insoluble in water but soluble to the extent of 2 per cent. in alcohol and 57 per cent. in chloroform.

Actions and Uses. Santonin affects the parasites by irritation and a muscular stimulant action, but in therapeutic doses has no effect on vertebrate muscle. This action is related to its lactone structure. Roundworms only are affected, the chief species being the ascarids of the horse, pig, dog and cat. The drug is expensive and economics have restricted its use mainly to dogs and cats, and occasionally pigs.

The efficiency is not very great though authoritative proof is not available. Shillinger (1927) reported 10 per cent. efficiency at best in dogs, even with adequate dosage and correct administration.

Nevertheless, when combined with calomel in equal quantities, santonin has been a useful drug for administration in the treatment of ascariasis in cats, small doses being administered on two or more successive days.

The drug must not be used on animals under 8 weeks of age and like many used in the treatment of ascariasis, it is obsolescent.

Dosage and Administration:

Pig:	2–10 gr. (0·13 G.–0·6 G.)
Dog:	½–3 gr. (30·0 mg.–0·2 G.)
Cat:	¼–1 gr. (15·0–65·0 mg.)

It is best administered to pigs in the form of electuary, and to dogs and cats as pills. Calomel is the usual purgative but saline ones may be used. Administration should take place after overnight fasting, preferably after a small meal of bread and milk.

Clients should be warned that some of the drug will be absorbed and will be excreted in the urine, which it colours yellow if acid, and pink to purple if alkaline.

Toxicity. Santonin is readily absorbed, and that is why a purgative which begins its action immediately following administration, and is reasonably active, should always be given. This purgative, by rapid expulsion, prevents undue absorption of the santonin as well as expelling the live but paralysed worms.

Symptoms of poisoning are those of gastro-intestinal irritation initially, followed by intense nervous and muscular stimulation. Thus there is emesis and diarrhœa, followed by muscular twitchings of the head and neck, and convulsions. Death, as in strychnine poisoning, is due to asphyxia during a spasm.

Treatment consists of a saline purgative and pentobarbitone sodium injections to control the convulsions. Warmth and glucose saline injections are of assistance.

Quassia, B.Vet.C., is traditionally used in the form of a fresh infusion as an enema in the treatment of Oxyuris infestations in the horse. The infusion is prepared by macerating 1 oz. of quassia wood chips in a pint of distilled water, and the liquid obtained is then injected into the rectum after removal of fæces. The process should be repeated weekly. *Sodium thiosulphate* and strong *salt* solutions are as good if not better, and are more easily prepared. The drug has also been used as a bitter.

Turpentine Oil, B.Vet.C., has already been mentioned (p. 74) as a carminative and antizymotic. It has also been used, in combination with chenopodium oil at the rate of 1 fl. oz. (30·0 ml.) turpentine with 120 m. (8·0 ml.) chenopodium in 1 pint (600 ml.) linseed oil, as a treatment for strongyles and oxyurids in the horse. It was used in cattle against roundworms and is still used in intratracheal injections for parasitic

bronchitis (husk or hoose) in cattle and sheep. It is, in all these cases, of debatable value.

Organic Drugs of Synthetic Origin

Butyl Chloride, B.Vet.C.

This anthelmintic is a clear, colourless, inflammable, volatile liquid with a characteristic ethereal odour and sweetish taste. Soluble in ether and dehydrated alcohol, and miscible with fixed oils, butyl chloride is almost insoluble in water.

Actions and Uses. Butyl chloride is widely used in some parts of the world as an effective treatment for Ascaris infestations in dogs. It has been reported as being 98·7 per cent. efficient against Toxocara and Toxascaris species, 84·3 per cent. against Ancylostoma and Uncinaria (the hookworms of dogs), and from 18–50 per cent. efficiency against Trichuris, the true whipworm, which is not found in Great Britain. Much larger doses are required to remove whipworms.

It is also effective against ascarids and strongyles in the horse but is rarely used, mainly for economic reasons.

Butyl chloride is not satisfactory for ruminants or pigs.

Dosage and Administration:

Horse: ½–3 fl. oz. (15·0–90·0 ml.)
Dog: 15–75 m. (1·0–5·0 ml.) for ascarids.
75–360 m. (3·0–24·0 ml.) for whipworms.

The doses for the dog against ascarids are estimated at the rate of approximately 15 m. (1·0 ml.) per 8 lb. body weight, to the maximum which applies for animals of 40 lb. body weight and over. Approximately 75 m. (5·0 ml.) for each 8 lb. body weight to the maximum for over 40 lb. is necessary against whipworms.

The drug is best administered by soft gelatin capsule, but it can be given by stomach tube in the horse or in a suitable purgative oil. Activity is said to be reduced if the butyl chloride is dissolved in the oil owing to the reduced dispersal of the chloride and therefore reduced contact with the parasites.

Administration should be preceded by a 12–24 hour fast, and followed 30–60 minutes after dosing by a purgative which may be castor oil for the dog, linseed oil for the horse, or a saline in either species.

Toxicity is said to be very low and it is widely preferred in the United States in place of the more toxic carbon tetrachloride and tetrachlorethylene.

Carbon Disulphide, B.Vet.C.

This drug is a highly volatile, clear, colourless or pale straw coloured liquid with an offensive odour. It is highly inflammable, forms explosive

mixtures with air and has volatile anæsthetic properties. The liquid is slightly soluble in water but very soluble in the organic solvents and both fixed and volatile oils.

Actions and Uses. Carbon disulphide is effective against gastric myiasis (bot infestation in the stomach) in the horse and also against ascarid infestation in the horse and sometimes in the pig. Its use is now restricted almost entirely to the treatment of bots but recently a combination of piperazine and carbon disulphide has produced an active and reasonably safe combined bot therapeutic anti-ascarid agent. Bots will appear in the fæces for several days after dosing, reaching a peak about the third day.

Dosage and Administration:

Foals:	60–120 m. (4·0–8·0 ml.)
Adult Horses:	120–240 m. (8·0–16·0 ml.)

No purgative is required and administration in an oily solution, besides encouraging absorption, also restricts and reduces its activity in the same way as with butyl chloride. Soft gelatin capsules or stomach tube administration are the best means of giving the drug.

Food and water should be withheld for 12–24 hours before dosing and for four hours after dosing. If capsules are used, care should be taken to make sure they are not broken in the mouth, or laryngeal spasm and general anæsthesia may follow in addition to severe irritation of the oral mucosa.

Toxicity is quite high and severely debilitated and pregnant animals should not be dosed. The drug is strongly irritant and will cause damage to the alimentary mucosa, so that should a capsule be broken in the mouth irrigation with liquid paraffin is indicated. Following absorption the main tissue affected is nervous tissue. Symptoms are initially of excitement followed by depression, coma and death from respiratory failure. Treatment is symptomatic.

Hexylresorcinol, B.Vet.C.

This is a white or yellowish crystalline powder which is soluble in alcohol, glycerin and ether, and in fixed vegetable oils. The odour is pungent and is characteristic; the taste is sharp and astringent.

Actions and Uses. This drug is not widely used as an anthelmintic but has come back into fashion as a bactericide. It is effective against Gram positive bacteria, particularly streptococci and staphylococci, and, as it acts in both alkaline and acid pH, it is occasionally used as a urinary antiseptic. It is relatively inactive against Gram negative bacteria and spores.

Hexylresorcinol is only moderately effective in ascarid and hookworm infestations of the dog and ascarids in the pig, but some practitioners use

the compound because of its relative lack of toxicity. This means that providing the irritant action in the mouth is overcome and gastro-enteritis cases are avoided, the drug can be used with safety. It is indicated therefore in debilitated cases in which more effective but more toxic drugs should not be given. Piperazine has made the drug obsolescent as an anthelmintic.

Dosage and Administration:

Pig: 30–60 gr. (2·0–4·0 G.)
Dog: 3–15 gr. (0·2–1·0 G.)

Fasting for 12 hours before and after administration is recommended, and a purgative should follow 24 hours after dosing. The drug can be given in capsules, or dissolved in olive oil or similar fixed oils. Both these methods avoid the irritant oral effect. Dosing should not be repeated for 3 or 4 days.

Toxicity. The drug is not recommended for cats and, because of its mucosal irritant effect, hexylresorcinol should not be used in cases with gastro-enteritis, which rules out a large number of parasitized animals.

Piperazine Hydrate, B.P.C.

This drug has been known for many years as a treatment (of doubtful value) for gout. In 1954 the first veterinary publications began to appear indicating that a drug had been identified which would be a considerable advance over all others for the treatment of ascariasis. These early indications have been fully substantiated.

The hexahydrate is physically unstable, being very deliquescent, and consequently the drug is used in the form of the more stable salts: the adipate (from adipic acid), the citrate, the phosphate, sulphate and hydrochloride are all satisfactory. A further compound with carbodithioic acid is also available commercially. All are white crystalline powders, very soluble in water, with a saline taste and no odour.

Actions and Uses. All the piperazine compounds have similar effects, with slight variations. Their action is one of narcosis of the parasite which can then be removed from the intestines by normal peristalsis, possibly augmented by a laxative or purgative, which should preferably be of a saline nature. Should the parasite not be removed and the piperazine be entirely eliminated the parasite will recover from the narcosis and return to normal activity. This can be demonstrated by washing a paralysed worm in normal saline and observing the subsequent recovery which takes place in an hour or two.

The parasites affected are mainly ascarids and nodular worms of all species of domestic animals; they respond with almost 100 per cent. efficiency. There is a variable effect on hookworms and strongyles, but no effect on whipworms (e.g. Trichuris species), or tapeworms.

In the *horse* it has been reported (Downing *et al.*, 1955) that piperazine adipate removes almost 100 per cent. of mature and immature *Parascaris*

equorum and adult Trichonema species, over 80 per cent. of adult Oxyuris species, and up to 60 per cent. of Triodontophorus species and of *Strongylus vulgaris*. They reported there was no effect on other Strongylus species, Habronema species or tapeworms. Against the strongyles they indicated that these results were similar to those achieved by maximum doses of phenothiazine. Poynter (1956) reported equivalent effect with the normal dose of the adipate, citrate, phosphate and carbodithioic acid compounds when tested in horses, whilst the carbodithioic acid compound was equally effective against the small strongyles and the ascarids at about half the normal dose.

Similarly, reports have shown that piperazine is equally effective in exotic equine species such as zebras.

In *cattle* and *sheep* piperazine has been used but is only indicated for ascarids and nodular worms—*Ascaris vitulorum* and Œsophagostomum species; the former does not occur in Great Britain.

In *pigs* piperazine compounds are extremely efficient against *Ascaris lumbricoides* and Œsophagostomum but the action on Hyostrongylus is not so good.

In *dogs* and *cats* the action is 100 per cent. efficient against Toxocara and Toxascaris species, up to 75 per cent. against hookworms and has practically no effect on whipworms (Trichuris species) or tapeworms. The heartworm, *Dirofilaria immitis* responds very well. Its effect on zoo canine and feline species is equally good at doses proportional to their weight. In *poultry Ascaridia galli* responds extremely well but *Heterakis gallinæ* is not quite so susceptible.

This drug is the drug of choice for the treatment of ascariasis in all species.

Dosage and Administration:

Horse and Cow:	0·1 G. per lb. bodyweight. Maximum 80·0 G. (Foals 1 oz. (30·0 G.), yearlings 2 oz. (60·0 G.)).
Sheep and Goat:	4·0–8·0 G.
Pig:	1·0 G. per 20 lb. live weight in each of three successive feeds or 3·0 G. per score if dosed individually.
Dog and Cat:	0·05 G. per lb. bodyweight (0·11 G. per kg.) (Puppies under 5 lb., cats and kittens, 0.25 G. maximum.)
Poultry:	0·3 G. approximately, for each adult bird. (about 75·0 mg. per lb. bodyweight) given in each of two successive feeds or in drinking water for two days.

No fasting is required but the drug should preferably be administered to hungry animals. A purgative is not essential but laxatives assist in expelling the paralysed worms which otherwise will appear in the fæces

after about 24 hours and continue to be excreted for several days. This continued excretion is particularly seen where doses are divided and administered over a period.

The drug is administered either in the food or drinking water. Most *horses* will accept the drug in bran mashes but, if necessary, aqueous solutions may be administered by stomach tube or the drug may be given as an electuary. In *pigs* the usual method for mass dosing is to divide the calculated dose into equal parts and administer them in two successive, either wet or dry, feeds. For individuals, single doses may be given. Medications of the drinking water for several days has also given good results. *Dogs* and *cats* are usually dosed with tablets. *Poultry* are normally dosed by medication of the drinking water on each of two successive days; no other drinking water should be available.

In all cases separate worming pens should be used, for the eggs within voided parasites are viable and reinfection can occur if regular pens are contaminated.

Toxicity. The toxicity of piperazine compounds is normally very low. Occasional neurotoxic symptoms and emesis occur in small animals but these are usually of a transient nature. The drug can be administered to pregnant animals and also to those animals suffering from gastro-enteritis, which makes the anthelmintic almost unique.

Tetrachloroethylene, B.Vet.C.

This is a liquid similar in most respects to carbon tetrachloride.

Actions and Uses. Tetrachloroethylene is most active against the ascarids of horses, pigs, dogs and cats, but its main value lies in its effect on hookworms. An appreciable effect on horse bots is also reported. It is effective against many strongyles of sheep and cattle, particularly Hæmonchus species, but there are numbers of reports of severe toxicity in cattle and as it has few advantages over phenothiazine its use is not recommended for these animals. It is used extensively in sheep in various parts of the world.

Dosage and Administration:

Horse and Cow:	½–1 fl. oz. (15·0–30·0 ml.) at the rate of 0·05 ml./lb. bodyweight.
Sheep:	Up to 9 months 40–75 m. (2·5–5·0 ml.) Adults up to 115 m. (7·5 ml.)
Pig:	40–160 m. (2·5–10·0 ml.)
Dog:	15–75 m. (1·0–5·0 ml.)

The administration details are similar to those for carbon tetrachloride. Capsules are used and mineral or vegetable oil mixtures are also used, although fats and oils are not recommended as they increase the absorption rate, which is normally low. A saline purgative an hour or so after administration is useful in dogs, but it is said that omission of a purgative is followed by better results, even though absorption is greater.

Toxicity is similar to that of carbon tetrachloride but to a lesser degree. Tetrachlorethylene should not be used in animals debilitated for any reason, nor should it be given to pregnant animals. Cases of toxicity in the dog are relatively common, mainly from overdosage. Should a capsule break in the mouth during administration the danger of anæsthesia is far less than with carbon tetrachloride.

Treatment consists of the lowering of protein and fat diets and the increase of carbohydrate foods. Choline chloride orally or injected can also be used, and calcium, injected as borogluconate, should be given in addition to a high calcium level in the diet before and after dosing.

Toluene $C_6H_5 : CH_3$ is a light, clear, almost colourless and highly inflammable liquid with a benzene-like odour.

Actions and Uses. Toluene, also known as toluol, is from 87–100 per cent. effective against ascarids and hookworms, and 75 per cent. effective against whipworms in the dog and cat (Enigk *et al.*, 1955). Several reports have indicated a good effect on ascarids, including immature forms, and on *Gasterophilus intestinalis* (horse bot fly larvæ) in the horse. It is safer than carbon disulphide and is therefore to be preferred. The drug has yet to be fully evaluated.

Dosage and Administration:

Horse:	0·2 ml. per lb. bodyweight.
Dog and Cat:	0·1 ml. per lb. bodyweight.

In the *dog* and *cat* toluene is best given in capsules, but solution in fixed oils is permissible. It should be given fasting to obtain the best results. It can be combined with dichlorophen to give comprehensive treatment.

In the *horse* the drug should be given by stomach tube and fasting is not essential. In the United States it is administered to foals as young as 12 weeks and repeated at 6 months, and then periodically during the yearling period (Smith, 1955).

Toxicity. Toluene is relatively non-toxic when used in the recommended doses. Smith (*ibid.*) reported only one mild case out of 454 horses dosed. Most reports on small animal toxicity indicate a similar tolerance.

Inorganic Drugs

Antimony preparations are not popular for *internal* administration now, except for trypanosome and schistosome treatment by injection. These diseases occur in tropical and sub-tropical areas and have been the target of antimony preparations since Erhlich first expounded his chemotherapy postulations and produced his organic antimony and arsenic preparations. *Antimony sodium tartrate* is a cheap, widely used form, but for safe mass therapy more complex organic preparations such as Stibophen, U.S.P., have been devised.

In this country *antimony and potassium tartrate* has been used in 30–60 gr.

(2·0–4·0 G.) doses with 60 gr. (4·0 G.) doses of ferrous sulphate, preferably exciccated, in the treatment of roundworm infestation of horses. It was usual to include these drugs in the morning feed on six successive days and follow them on the seventh day by a laxative or purgative. It was not a very effective treatment and has been superseded. This 'tartar emetic' is also used in small doses as an expectorant and in larger doses as an emetic; its emetic effect is drastic and dangerous, and it should not be used for this purpose.

Externally, *antimony trichloride* is used as a caustic in many proprietary disbudding collodia (erroneously known as dehorning collodia.) It is combined usually with salicylic acid and must be vigorously applied to the horn buds after defatting the area with ether or benzene. Any grease will prevent adherence of the collodia and give poor results. Surrounding skin should be protected with soft paraffin.

Cadmium in the form of the oxide and the anthranilate has been developed in the United States. Both are for the treatment of ascariasis in the pig and are given in the food over a period of three days. Approximately 90 per cent. efficiency is reported (Burch *et al.*, 1955; Guthrie, 1954) against ascarids.

The oxide is fed at a concentration 0·015 per cent. in dry feed and the anthranilate at 0·044–0·066 per cent. The medicated food is readily accepted and weight gains are not appreciably affected.

The *toxicity* is reported to be relatively low and its use in pregnant sows and in debilitated animals is effective and safe; it is stated that any overdosage is counteracted by vomiting. From the human health point of view it is reported that the tissue concentration following dosage (approximately 1·0 mg./100·0 G.) was less than in some humans with no history of cadmium dosing. The excretion rate of cadmium is very slow.

It was concluded (Turk *et al.*, 1956) that sodium fluoride, though more effective as an anthelmintic, results in refusal of food and weight losses, and in view of this and the higher toxicity the cadmium compounds were preferred.

Sodium Fluoride, *B.Vet.C.* is a white or off white powder with a saline taste. It is soluble in water.

Actions and Uses. This drug is used therapeutically as an anthelmintic for pigs. It is over 90 per cent. effective against ascarids and satisfactory against the stomach worm *Hyostrongylus rubidus*. Its action against other worms is negligible.

Sodium fluoride is used as an enzyme poison to preserve blood samples collected for phosphate analysis: it prevents enzyme breakdown of organic phosphates within the erythrocytes and therefore prevents the diffusion of these phosphates into the plasma where they would falsify any plasma or whole blood estimations.

Dosage and Administration. The drug is given at the rate of 0·15 G. per lb. bodyweight. It should be given in dry food at a concentration of 1 per

cent., or 1 oz. fluoride to 7 lbs. feed. In the United States, where mass dosing is more commonly practised, a dry mash medicated to a 1 per cent. concentration is fed for one day. Treatment should not be repeated.

Toxicity. The dry feeding acts as a deterrent to over-eating but should an excessive dose be taken gastric irritation causes vomiting. If, however, wet mashes and swill are medicated the protective emetic action does not operate and the fluoride will be absorbed. Severe gastro-enteritis, hepatitis and nephritis occur, followed by collapse and death. Bain (1953) attributed fatal hæmorrhages in 27 out of 28 pigs castrated one week after dosing to the anticoagulant properties of the fluoride. Other unwormed pigs in the control group were castrated without any fatalities.

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CHAPTER 9

THE RESPIRATORY SYSTEM

THE circumstances in which drugs may be used to influence the respiratory system are firstly, where there is inflammation of the lungs and the airways leading to the lungs, and secondly, where there is interference with the mechanics of respiration. Inflammatory conditions include pneumonia, bronchitis, tracheitis and laryngitis, caused by bacteria, viruses and worm parasites. Interference with the respiratory rate and depth is usually related to depression or stimulation of the medullary centres, the former occurring most commonly during general anæsthesia whilst stimulation may occur physiologically in fevers and diseases which interfere with oxygenation of the blood.

The early stages of inflammation of the lungs and air passages are usually accompanied by an increase in viscidity, and a decrease in volume of mucus. This results in a dry, inflamed, and painful mucosa which is irritated at each successive inhalation and results in a harsh, dry, painful and entirely useless cough—frequently referred to as an 'unproductive' cough. In the treatment of this condition the aim is to cause an increase in mucous secretion to protect the mucosa and at the same time reduce the frequency of the damaging cough, partly by preventing stimulation of the mucosa by coating it with mucus and partly by centrally depressing the cough reflex. This can be achieved by the combined use of expectorants such as ipecacuanha, ammonium chloride and potassium iodide, with either codeine or opium. In the recovery stages of respiratory tract inflammations there is usually an excess of mucus and tissue débris in the airways, which prevents free passage of air and stimulates coughing with each respiratory movement. The aim of therapy in these circumstances is to increase the fluidity of the mucus, stimulate the activity of the cilia of the mucosa so that all the debris may be expelled by coughing and ciliary movement. Ipecacuanha, squill, ammonium chloride, and potassium iodide, may be given orally for this purpose. At this stage coughing should be reduced only if it is continuous and preventing the animal and its owner from resting and sleeping.

Expectorants will increase the fluidity and volume of respiratory secretions, and in the early stages of inflammations will relieve pain and tend to reduce slightly the incidence of coughing. Chronic inflammatory conditions will also benefit.

Cough sedatives reduce the incidence of coughing usually by central depression of the cough centre. They should not be used when respiratory

secretions are copious unless coughing is excessive and causing exhaustion—this state is uncommon in animals.

By destroying the infecting agents in the respiratory system, chemotherapeutics which are effective against bacterial and helminth parasites will assist in respiratory sedation but are not considered as cough sedatives in normal classifications. The agents which are used against helminth parasites will be mentioned in this chapter under 'Anthelmintics' but the antibacterial agents are considered elsewhere (see Part III, Chemotherapeutics.)

In respiratory depression during anæsthesia *analeptics*, which cause convulsions if administered to normal animals, will stimulate the respiratory centre in the medulla, increasing rate and depth of respiratory excursions. Analeptics are detailed along with other stimulants in Chapter 16 (3) Nervous System Stimulants. Various other compounds such as ammonia, carbon dioxide and prussic acid may be used as respiratory stimulants during anæsthetic depression.

Expectorants

The expectorants may be classified according to their route of administration and their site of action.

1. Local expectorants: These act directly on the mucosa of the respiratory airways and may be applied:

(a) By inhalation, e.g. steam, terebene, eucalyptus, benzoin, iodine vapour, etc.

(b) By excretion via the mucosal cells: volatile oils, potassium iodide.

2. Reflex expectorants which act by irritation of the œsophagus and stomach causing irritation, nausea and a concurrent increase in the rate of production and the volume of bronchial secretions. Ipecacuanha, squill, antimony and potassium tartrate are widely used examples of the so-called emetic expectorants, whilst ammonia compounds and many volatile oils also cause reflex effects.

Inhalants. This group of drugs is not frequently used in veterinary medicine, mainly because animals resent the strong odours of inhalants, but also because the steam is usually generated from water in a bowl or bucket and the animal, at any rate initially, has to be restrained in order to keep its head in the vapour. Steam kettles are rarely used because of the difficulty of restricting the area and maintaining the animals living quarters at a high enough temperature.

By far the best method of vaporizing inhalants is to fill a bucket (for large animals) or a bowl (for small animals) with steaming hot water and pour a few drops of the inhalant onto the water. The heat vaporizes the inhalant with the steam, and when the animals head is held in the steam both this and the vapour must be inhaled. In large animals the bucket may be put in a sack and the animals head introduced into the sack. This is frequently resented, and is an unsafe method because of the danger of

upsetting the steaming water. An alternative is to heat a building brick, put it in a bucket and the bucket in a sack; the inhalant is then placed on the brick and the animals head held in the sack.

In small animals the steam method is quite practicable and safe. Dogs in particular will soon learn that relief can be gained by holding their noses over the steaming bowl and will co-operate actively.

Inhalants are of most value for clearing nasal and laryngeal exudates but tracheal and bronchial exudates are also affected. In large animals, equine influenza is probably the condition for which inhalants are most indicated, but strangles cases and similar conditions would also benefit. In small animals the distemper complex of dogs and feline influenza benefit most.

Benzoin, B.Vet.C.

This balsamic resin is obtained by incising the bark of a tree native to the East Indies and Siam. The crude substance occurs as resinous masses of a greyish or reddish brown colour with whitish 'tears' embedded in it. Benzoin is used in the form of Compound Tincture of Benzoin, B.Vet.C. (Friars' Balsam), or Inhalation of Benzoin, B.Vet.C., which are very similar, the first containing balsam of tolu and aloes, as well as the benzoin, storax and alcohol of the inhalation. Two per cent. Siam benzoin is used as a preservative in Benzoinated Lard, B.P.C.

Actions and Uses. Externally the compound tincture has been used as an antiseptic dressing for small cuts, but this is now obsolete. When given by mouth benzoin is reputed to cause a reflex expectorant action but this effect is uncertain. Following absorption, excretion occurs mainly via the kidneys, which are slightly stimulated by irritation: at the same time a slight urinary antiseptic effect is exerted. When administered by inhalation, loosening of mucus and débris occurs mainly in the nasopharyngeal and laryngeal regions, but some action occurs lower in the respiratory tract. The steam mixed with the vapour is possibly the major therapeutic agent. One to two teaspoonfuls of either inhalant per pint of water is sufficient.

Eucalyptus Oil, B.Vet.C.

In the fresh, pure state, oil of eucalyptus is colourless but, as with all volatile oils, it turns yellow with age and oxidation. It has a characteristic pungent, penetrating odour and taste. The solubilities are typical of volatile oils—very slightly soluble in water but soluble and miscible with organic solvents.

Actions and Uses. Eucalyptus oil is frequently incorporated in ointments and oils for the treatment of catarrh in humans by application around the nostrils. This can be used in animals but is usually resented; occasionally applications to the muzzle will cause blistering and this mode of administration should not be encouraged amongst owners. In small animals, if this type of application must be used, rubbing on the fore legs is preferable

to muzzle applications: volatilization and inhalation is usually just as good. Steam inhalation is superior in effect though more troublesome in application. Eucalyptus has also been included as a fly repellant in skin dressings and sprays: it is also included for antiseptic and deodorant properties in skin and wound dressings. These uses are obsolescent.

Terebene, B.Vet.C.

This compound is a mixture of hydrocarbons obtained by distillation of turpentine which has been treated with sulphuric acid. It is a colourless or pale yellow liquid, with an odour and taste resembling those of turpentine. It is almost insoluble in water but soluble in organic solvents.

Actions and Uses. Terebene can be used in place of turpentine (see Chapter VII. Alimentary System), but its main indication is as an irritant expectorant, administered by inhalation or by mouth. If given by mouth it has the carminative and antispasmodic action of turpentine before absorption; after absorption, excretion is via the kidneys, when it has the irritant diuretic and urinary antiseptic action of volatile oils, and also via the lungs, when it has an irritant expectorant action. It has been included in intratracheal injections for 'husk' in cattle.

Dosage.

Horse:	1–2 fl. oz. (30·0–60·0 ml.)
Cow:	1–4 fl. oz. (30·0–120·0 ml.)
Sheep and Goat:	60–180 m. (4·0–12·0 ml.)
Pig:	30–120 m. (2·0–8·0 ml.)
Dog:	4–15 m. (0·25–1·0 ml.)

Non-Inhalant Local Expectorants. These expectorants are administered orally and excreted in small amounts by the lungs. The group includes potassium and sodium iodides, potassium citrate, and creosote.

Potassium Iodide, B.Vet.C., is the most important member of the group. After oral administration the iodide ion can be detected in the bronchial secretions within 30 minutes. The increase of secretions, which has been reported, is in dispute, but the liquefaction which occurs is most beneficial in chronic bronchitis. Irritation makes it contra-indicated in acute inflammatory conditions.

Reflex Expectorants. The reflex expectorants are a group of compounds which promote an increase in volume and fluidity of respiratory secretions and an increase in ciliate activity by stimulation of nerve endings in the pharyngeal, œsophageal, and gastric mucosa. This stimulation initiates reflexes which result in stimulation of the respiratory mucosal cells.

Ammonia in the form of carbonate or chloride is frequently used as a reflex expectorant in both the human and veterinary fields. It has been shown (Perry and Boyd, 1941) that in rabbits large doses (0·5 G./kg.

of the carbonate and 0·4 G./kg. of the chloride) will cause profuse respiratory secretion by stimulation of the vagal nerve endings in the stomach. The viscosity and pH are reduced, whilst the volume of secretion and activity of the cilia of the mucosa are increased. While these doses are far greater than those used clinically, the long and widespread use of ammonium salts indicate some clinical benefit.

These compounds are indicated in both acute and chronic bronchitis, especially where the respiratory mucosa is dry and secretions sparse.

Emetic Expectorants. Ipecacuanha, squill, balsam of tolu, and antimony and potassium tartrate are all emetic expectorants. Their action is one of irritation of the oral, pharyngeal and gastric mucosa to the extent of causing nausea, one of the physiological results of which is an increase in all body secretions, including sweat, saliva and respiratory secretions. They are therefore useful expectorants for all types of respiratory system inflammations.

Ipecacuanha, B.Vet.C.

The South American Indians used ipecacuanha long before the European invasion and the name they gave to the plant may be translated as 'the little wayside plant which causes vomiting'. The root is the source of all the pharmaceutical forms, of which the liquid extract, the tincture, and the prepared powder are official in the Veterinary Codex, and are standardized in terms of emetine, one of the constituent alkaloids. Apart from these compounds, ipecacuanha is also a constituent of Dover's Powder (Ipecacuanha and Opium Powder, B.Vet.C.) and of Aspirin with Dover's Powder which is also official in tablet form.

There are three main constituent alkaloids: *emetine*, *cephaëline* and *psychotrine*, the first of which has emetic and expectorant properties, the second is mainly emetic, whilst the psychotrine and other subsidiary alkaloids have very little significant action.

Actions and Uses. In small doses ipecacuanha is a reflex expectorant with an action extending over a period of several hours. Some diaphoretic or sweating action is also exerted in man, but this has not been confirmed in animals. Small doses are also reputed to stimulate gastro-intestinal activity but this action is of little therapeutic significance.

In large doses the drug causes emesis in the vomiting species, but the drug is rarely used for this purpose: this emetic action is mainly a local one although some central stimulation also will occur.

The powder is very irritant and will cause severe pain if it contacts mucous membranes, especially the eye; in this respect it is very similar to digitalis.

In man, ipecacuanha and the alkaloid emetine are effective in treating amœbic dysentery, and it has been used in cattle against coccidiosis, though other compounds such as the sulphonamides are preferred.

Dosage. Prepared Ipecacuanha, B.Vet.C.

Horse:		30–90 gr. (2·0–6·0 G.)
Pig:	(emetic)	30–45 gr. (2·0–3·0 G.)
	(expect.)	1½–5 gr. (0·1–0·3 G.)
Dog:	(emetic)	15–30 gr. (1·0–2·0 G.)
	(expect.)	⅙–2 gr. (10·0–120·0 mg.)
Cat:	(emetic)	4–12 gr. (0·25–0·75 G.)
	(expect.)	⅙–1 gr. (10·0–60·0 mg.)

Liquid Extract of Ipecacuanha, B.Vet.C.

Horse:		30–90 m. (2·0–6·0 ml.)
Pig:	(emetic)	30–45 m. (2·0–3·0 ml.)
	(expect.)	1½–5 m. (0·1–0·3 ml.)
Dog:	(emetic)	15–30 m. (1·0–2·0 ml.)
	(expect.)	½–3 m. (0·03–0·2 ml.)
Cat:	(emetic)	4–12 m. (0·25–0·75 ml.)
	(expect.)	¼–1 m. (0·016–0·06 ml.)

Tincture of Ipecacuanha, B.Vet.C.

Horse:	120 m.–1 fl. oz. (8·0–30·0 ml.)
Dog:	5–60 m. (0·3–4·0 ml.)
Cat:	5–15 m. (0·3–1·0 ml.)

Powder of Ipecacuanha and Opium, B.Vet.C.

Horse: ½–1 oz. (15·0–30·0 G.)
Dog: 1½–10 gr. (0·1–0·6 G.) This may be administered in tablet form, either alone or with aspirin. The latter official formula contains only 2½ grains of Dover's Powder and the dose of ½–4 tablets is therefore twice that of the Dover's Tablet (5 gr.)

Tincture of Squill, B.Vet.C., or *Syrup of Squill*, B.P.C., are common constituents of cough mixtures and are included for their emetic expectorant action.

Dosage.

Horse and Cow:	¼–1 fl. oz. (7·5–30·0 ml.)
Pig:	10–15 m. (0·6–1·0 ml.)
Dog:	2–15 m. (0·13–1·0 ml.)

The syrup is less than half the strength of the tincture.

The compounds of squill are also used for the heart action which they possess by virtue of their cardiac glycoside content.

Balsam of tolu in the form of syrup (Syrup of Tolu, B.P.) is also a frequent ingredient of cough mixtures for dogs because of its slight reflex expectorant action. The *dose* is from 10–30 m. (0·6–2·0 ml.) for dogs.

Antimony Potassium Tartrate, B.Vet.C.

This compound is not of vegetable extraction. It is a white crystalline powder which is soluble 1 : 17 in water, soluble in glycerin, but insoluble in alcohol. The sodium salt is more soluble (1 : 1·5) in water and is frequently preferred because of this, for it is identical in its therapeutic effect.

Actions and Uses. In small doses antimony potassium tartrate (tartar emetic) is a reflex emetic expectorant. In large oral doses it is an emetic in the vomiting species but is dangerous because emesis may be almost continuous, and death from exhaustion has occurred: it is no longer used as an emetic. By intravenous injection antimony potassium tartrate has been used as a treatment for blood parasitism by Leishmania, Schistosoma and Trypanosoma species. It is now being superseded in most directions by more modern and safer therapeutics.

Dosage. Intravenously:

Horse and Cow:	$2\frac{1}{2}$–$4\frac{1}{6}$ gr. per cwt. (0·15–0·25 G. per 50·0 kg.)
Dog and Cat:	$\frac{1}{120}$ – $\frac{1}{40}$ gr. per lb. (1–3 mg. per kg.)

Orally (Expectorant):

Horse:	5–30 gr. (0·3–2·0 G.)
Cow:	15–75 gr. (1·0–5·0 G.)
Sheep, Goat, Pig:	$1\frac{1}{2}$–$7\frac{1}{2}$ gr. (0·1–0·5 G.)
Dog:	$1\frac{1}{2}$–5 gr. (3·0–15·0 mg.)

Orally (Anthelmintic):

Horse:	60–120 gr. (4·0–8·0 G.)

For trypanosomiasis, horses and cattle have been given 1·0–1·5 G. in 20·0–30·0 ml. water once daily for four days, by intravenous injection.

Toxicity results in liver damage if sublethal doses are given over a period, but acute oral poisoning is typical of antimony and arsenic in that severe gastro-enteritis is caused. Treatment is symptomatic.

Respiratory Stimulants

When respiration is depressed, particularly in anæsthetic depression, or when animals are suffering from anoxæmia as in coal gas poisoning, respiratory stimulants may be useful. These stimulants may be local irritants causing reflex stimulation (ammonia), they may be analeptics given intravenously (picrotoxin, etc.), or they may be 'natural' stimulants in the form of oxygen plus 5 per cent. carbon dioxide administered by inhalation.

Local Irritants. These are applied by inhalation. Ammonia gas evolved from the stopper of a bottle of Strong Solution of Ammonia, B.Vet.C. or from a sample of carbonate of ammonia, is the irritant usually given. This causes reflex stimulation of the respiratory centre as well as the vasomotor centre: both respiratory and circulatory improvement follows. Once breathing has stopped ammonia is not very effective clinically, but whilst breathing and cardiac action continues improvement in respiratory rate and depth can be achieved with ammonia.

The Analeptics. These medullary stimulant and convulsant drugs are detailed in Chapter 16. They are administered intravenously or intramuscularly and cause a stimulation of the respiratory and vasomotor centres in the medulla. They are far more effective than is the inhalation of ammonia.

The 'Physiological' Stimulants. These consist of hydrocyanic acid and mixtures of Oxygen, B.Vet.C., and Carbon Dioxide, B.Vet.C.

Stronger Solution of Hydrocyanic Acid, B.Vet.C., acts as a respiratory stimulant if one drop is applied to the back of the tongue of the animal in which respiratory collapse is threatened. The acid is rapidly absorbed and causes a marked increase in rate and depth of respiration, with a rise in blood pressure. These effects are due to reflexes initiated by stimulation of the carotid body. The effect is transient (10–15 seconds). Large doses will cause poisoning of the oxidase enzymes, and death due to anoxia follows rapidly on administration. Death is painful (this is disputed by some authorities) and it is inhumane to destroy animals using prussic acid without prior anæsthesia: such a practice cannot be too strongly condemned.

Oxygen–Carbon Dioxide

Oxygen is normally stored compressed in cylinders which are painted black over the lower two-thirds and white over the upper third. It is an odourless and tasteless gas.

Actions and Uses. Oxygen is the first essential of all life and no animal can survive for longer than a few minutes with its source of oxygen cut off. During anæsthetic respiratory depression, in coal gas poisoning, in drowning, during severe pneumonia, or cardiac decompensation with venous congestion and stagnation, amongst other conditions, oxygenation of the blood and tissues is decreased. Unless this anoxia is counteracted rapidly there is great danger, firstly of irreversible damage to brain tissue, and secondly, if anoxia is continued longer, of death from asphyxia.

Anoxia of tissues and anoxæmia may be counteracted in one of two ways. The first consists of stimulating the medullary centres with drugs; this causes an increase in the respiratory intake of air, and speeds the circulation of blood through the lungs and into the body after oxygenation. The analeptic drugs, also ammonia and hydrocyanic acid, will do this,

animal independent of hæmoglobin due to the oxygen dissolving in the plasma. It follows from this that in *carbon monoxide* (*coal gas*) *poisoning*, where the hæmoglobin carrying capacity is reduced by the formation of carboxyhæmoglobin, the administration of oxygen at a pressure greater than one atmosphere would be of considerable benefit. In practice this is not feasible and the administration of oxygen with 5 per cent. carbon dioxide for approximately one hour using a mask and artificial respiration is the best that can be done, unless blood transfusion is possible. Neither oxygen administration nor transfusions should be continued for beyond one hour, for respiration even in fresh air for one hour is sufficient to reduce blood concentrations of carbon monoxide to below the danger level, and three hours sees the elimination of almost all the carbon monoxide. Personal experience indicates that if the animal is still breathing when rescued, free breathing in the open air brings about recovery of consciousness within 15–20 minutes. Animals should be kept warm and allowed to rest for 24 hours, after which further trouble is unlikely.

Asphyxia by drowning is more complicated, for water must first be expelled from the lungs before oxygen can be administered satisfactorily Injection of oxygen intravenously or subcutaneously at the rate of 500 ml. per hour has given immediate relief from cyanosis and dyspnœa in man but care is required to guard against gas emboli.

The use of high concentrations of oxygen alone in threatened respiratory collapse, pulmonary œdema, bronchopneumonia, etc. is not advisable if administration is prolonged, but for the short periods for which oxygen may be used in animals, no serious side actions should be anticipated. It is, however, advisable in all cases to include carbon dioxide at a concentration of 5 per cent. This causes greater pulmonary ventilation by its physiological stimulation of the respiratory centre: a secondary result is that pulmonary secretions are more easily expelled because of the increase in volume, and decrease in viscosity, of these secretions which follows the hyperæmia induced by the carbon dioxide: the increased pulmonary ventilation also provides increased propulsion of these secretions through the respiratory airways.

Dosage and Administration. A concentration of 40–60 per cent. oxygen (normal air concentration 20 per cent.) is the optimum for practical purposes if administration is by an intratracheal tube or oxygen tent, but concentrations higher than this can be achieved by use of a mask. A flow

of 5–8·0 litres a minute will supply the necessary concentrations when the tube or tent are used. All oxygen administered should be warmed and humidified by passing through warm water.

Where *carbon dioxide* is used it is preferably administered from a combined cylinder which contains oxygen 95 per cent., carbon dioxide 5 per cent. The cylinder is painted black in the lower two-thirds, and the upper third is in alternate quadrants of grey and white.

Pure carbon dioxide gas is contained in cylinders painted completely grey. It may be used to supply the carbon dioxide in mixed gases, but there is a danger of over- or under-dosing which is avoided by using the gases already mixed. Besides its use as a respiratory stimulant, carbon dioxide may also act as caustic for destroying warts: it is not advisable to use it as a local anæsthetic spray although it has been occasionally used for this purpose.

Cough Depressants

Cough sedatives are used to reduce the frequency of coughing when it is causing pain and exhaustion. This depression may be achieved by (1) *local action* using *demulcents*, such as glycerin, honey etc., *expectorants* such as ammonium chloride which produces profuse and thin respiratory secretions to coat and soothe the membranes when dry and inflamed. Atropine, hyoscine and belladonna can be used to reduce profuse secretions but they are rarely indicated in respiratory inflammations: they are useful mainly as bronchial relaxants in pulmonary emphysema or 'broken-wind' in horses, and occasionally in cattle. (2) *central action* using the opium derivatives such as codeine, diacetylmorphine (heroin), dihydrocodeinone and Pholcodine, B.P.C.

Codeine

This alkaloid of opium is not controlled under the Dangerous Drugs Acts, for though addiction can develop, it does so only very slowly: withdrawal is not accompanied by the degree of disturbance that occurs with stronger addiction drugs, nor are the clinical results of addiction so disastrous.

The alkaloid is most commonly used as Codeine Phosphate, B.Vet.C., which is a white crystalline powder with a bitter taste, no odour and a solubility of 1 : 4 in water: it is far less soluble in organic solvents. Aqueous solutions are acid to litmus.

Actions and Uses. Codeine exerts its effects centrally having a sedative and, in large doses, a hypnotic effect. It has relatively little depressant effect on the respiratory centre and on respiratory secretions, but the cough centre is selectively depressed and the analgesic effect is appreciable. It has far less constipatory effect than the other alkaloids of opium.

Codeine phosphate is used most commonly in the dog, either as the syrup alone, in cough mixtures, or in the form of tablets in combination

with aspirin and phenacetin (A.P.C., Compound Tablets of Codeine, B.Vet.C.).

It is used far less frequently in large animals.

Dosage. Codeine Phosphate, B.Vet.C.:

Horse and Cow:	3–30 gr. (0·2–2·0 G.)
Pig and Dog:	¼–1 gr. (15·0–60·0 mg.)

Compound Tablets of Codeine, B.Vet.C.:

Dog:	1–2 tablets.

These tablets contain 4 grains each of aspirin and phenacetin and ⅛ gr. codeine phosphate.

Syrup of Codeine Phosphate, B.Vet.C.:

Horse and Cow:	¼–3 fl. oz. (8·0–90·0 ml.)
Pig and Dog:	12–45 m. (0·75–3·0 ml.)

This syrup contains codeine phosphate, approximately ¼ gr. in 60 m. (5·0 mg. per ml.).

Doses may be repeated every four hours if necessary.

Dihydrocodeinone Bitartrate, N.F., is more active than codeine when equal weights of base are compared. No reports of its use in animals are recorded.

Diamorphine hydrochloride or heroin is controlled in all proportions by the Dangerous Drugs Acts. Because of its severe addiction effects, world organizations are endeavouring to stop all manufacture and usage. In veterinary medicine heroin has no advantages over other cough sedatives and is now rarely used.

Pholcodine, B.P.C. (1957 Supplement), which is a morpholinœthyl ether of morphine, is not controlled by the Dangerous Drugs Acts. It has been introduced recently as a human cough sedative in doses of $\frac{1}{12}$–¼ gr. (5·0–15·0 mg.) in the form of a linctus or cough syrup. Veterinary use is not reported, but would follow that of codeine.

Respiratory System Anthelmintics

The lungworms of cattle, sheep and pigs are responsible for considerable economic losses annually. For many years *intratracheal injections* in cattle and sheep have been used in conjunction with changes in management methods but, though these injections have been claimed to give a very good cure rate in some areas, the general opinion is that they are of very little use: it is probable that the spontaneous recovery which frequently occurs, associated with the changes in husbandry, have been responsible for improvements which have been attributed to the injections.

A frequent sequel to intratracheal injections is the development of abscesses or necrosis affecting mucosa, tracheal cartilagenous rings, and inter-ring tissue. In some cases inflammatory reaction is so great that stricture occurs with a progressive increase of dyspnœa which necessitates

slaughter. This may be related to two causes, the first being mechanical damage by insertion of the needle through a tracheal ring instead of between two rings; portions of cartilage become isolated and cause foreign body reactions: the second, and most frequent cause of damage, is the infiltration of some of the injection through the aperture caused by the needle, or leakage during withdrawal of the needle. These injections frequently contain turpentine and phenol, amongst other compounds, both of which are highly irritant. Occasionally, at post mortem, two areas on opposite sides of the trachea may be seen: these two are related, one to the site of entrance of the needle into the trachea, and the other to where the needle point has been pushed across the diameter of the trachea and into the mucosa on the other side. It cannot be emphasized too strongly that intratracheal injections can be fraught with considerable dangers, and great care should be taken when carrying out this type of treatment.

A typical formula is quoted below.

℞	Liquefied Phenol, B.Vet.C.	240 m. (16·0 ml.)
	Turpentine Oil, B.Vet.C.	10 fl. oz. (284·0 ml.)
	Potassium Carbonate, B.Vet.C.	1½ oz. (42·0 G.)
	Olive Oil, B.Vet.C.	5 fl. oz. (142·0 ml.)
	Water	to 1 pint (568·0 ml.)

A single dose of this for a yearling would be ½ fl. oz. (16·0 ml.). Three injections of this dose on three successive days have been recommended, but the damage that could be done to the lungs by even one dose can be imagined, containing as it does 120 m. (8·0 ml.) turpentine and 6 m. (0·4 ml.) liquefied phenol.

Recently, both in France and Great Britain parenteral injections of *carbon tetrachloride* have been used and remarkable recoveries have been claimed. The dangers of toxicity from liver damage and anæsthesia have been responsible for considerable doubt in the minds of practitioners and the injections are not popular. Controlled trials in N. Ireland (Baxter, 1957) have failed to substantiate initial claims of good effect.

Even more recently cyanacethydrazide in forms suitable for oral and subcutaneous administration have been marketed commercially for cattle, sheep and pigs under the names Helmox and Dictycide. They have created great interest. However, Baxter (1957) has pointed out various shortcomings in the accounts of the initial trials (Walley, 1957) and reports little evidence of benefit, controls in his trials showing a recovery rate as rapid as that of treated cattle. Practitioners are divided in opinion, some claiming remarkable recoveries, whilst others report to the contrary. In view of these conflicting opinions judgment on the efficacy of these compounds must await longer and wider experience.

It is probable that more permanent results will be obtained by the research now proceeding into the active immunization of animals by serological methods, using live vaccines prepared by X-ray sterilization of lungworm larvæ (Jarrett *et al.*, *loc. cit.*). *Note:* See footnote p. 102.

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CHAPTER 10

THE HEART AND CIRCULATORY SYSTEM

(i) HEART AND PERIPHERAL VASCULAR SYSTEM

ALTHOUGH this system has been arbitrarily divided into three sections (1) heart, (2) peripheral vascular system, and (3) blood, it is rarely possible to influence one part of the cardiovascular system without affecting the remainder in some way. For example, if the potassium content of the blood is abnormally increased, as may happen in the potassium chloride treatment for acetonæmia suggested by Carlstrom (1950), there is an action on the heart resembling that of vagal stimulation in which the contractions decrease in power, lose their rhythm and eventually cease altogether. Likewise, if the peripheral vessels are dilated as in shock, the heart rate will increase in an endeavour to maintain the blood pressure and to keep the blood moving through the vessels; at the same time the dilated vessels allow the passage of fluid from the blood into the tissue spaces, and a decrease in circulatory volume occurs with an increase in the proportion of cells (hæmoconcentration). This integration of the whole system cannot be overstressed, for too frequently are practitioners surprised when an animal dies of heart failure during or shortly after an intravenous injection—often of calcium or magnesium preparations. (Calcium ions have the opposite effect on the heart to potassium and cause an increase in the power and speed of contraction, but in excess produce a permanent contraction with stoppage of the heart in systole. Magnesium is similar in effect to potassium and causes inco-ordination, sudden dilation, and then arrest of the heart). In recognizing this integration it should be noted that many of the drugs which affect the heart also act on the vascular system directly.

Drugs Affecting the Heart

The agents which affect the heart have been subdivided into (1) *heart stimulants*, (2) *heart tonics* and (3) *heart depressants*. Members of the first group exert mainly rapid but transient stimulant effects on the heart whereas those of the second group have an augmenting action which is slow in onset but prolonged in duration. The last group, though still used occasionally has at the moment no justifiable place in veterinary medicine: when diagnostic and surgical techniques are developed to the stage which allows us to practise cardiac and cranial surgery this statement may need modifying.

Heart Stimulants

A heart stimulant has been defined as an agent which increases the heart rate and the contractile power of heart muscle. This may be achieved by the use of:

(1) *Sympathomimetic amines* which include adrenaline, noradrenaline, ephedrine and amphetamine. (2) *Parasympatholytics* such as atropine, hyoscine and synthetic chemicals with similar actions. (3) *Cardiac muscle stimulants* of the purine or xanthine series such as caffeine and theophylline. (4) *Reflex stimulants* which act by local irritation. In this group are classed the so-called 'diffusible stimulants' such as ammoniacal and alcoholic preparations, and also the irritant injections of camphor and ether, although these injections are of doubtful value.

Analeptics such as picrotoxin, nikethamide or leptazol have a slight stimulant action on the heart although it is an indirect effect, partly attributable to respiratory effects and partly to the vasomotor stimulant action possessed by some of the group (e.g. leptazol).

The Sympathomimetic Amines. Of the sympathomimetic amines only adrenaline is used occasionally as a heart stimulant, for administration of noradrenaline does not produce an increase in cardiac output but, on the contrary, results in a steady rise in intracardiac blood pressure and a slowing of the heart rate. The other amines are of more significance as peripheral vasoconstrictors and have little clinical value as heart stimulants.

Adrenaline is mainly of use in acute heart failure associated with anæsthesia although its use in light chloroform and cyclopropane anæsthesia is contra-indicated. Administration may be by the intravenous route or by direct intracardiac injection: doses for the *dog*: 0·1–0·3 ml., and for the *horse* and *cow*: 2·0–4·0 ml. of a 1 : 1000 solution of adrenaline (Injection of Adrenaline, B.Vet.C.). The injection should be combined with cardiac massage through the chest wall and artificial respiration.

Adrenaline is of little use as a cardiac stimulant in other circumstances for its action is very short lived. Other uses are mentioned in the section on the sympathomimetic amine effects on the peripheral circulation.

The Parasympatholytics. Atropine and hyoscine produce an increase in heart rate equivalent to the degree of vagal depression of the heart. However, the side actions are so numerous and the action so prolonged that the parasympatholytics find no place in veterinary medicine as heart stimulants.

The Xanthine Derivatives. The xanthine derivatives caffeine, theophylline and theobromine have a direct action on the heart muscle as well as some central stimulation of the vasomotor and vagal centres so that the total effect is unpredictable. In general, the increased muscular power which results from the direct action on the heart muscle causes an increase in ventricular output even though the heart rate may not increase appreciably. There is also some 'heart tonic' action, for the coronary artery is dilated, allowing an increased blood supply to the heart itself.

Theophylline is the most active and caffeine the least active of the group when cardiovascular effects are compared. Theophylline is now rarely used in human medicine, for it has been replaced by aminophylline which has a greater solubility but similar effects. Aminophylline has been recommended for pulmonary emphysema (broken wind) in horses and also for pulmonary congestion (cardiac asthma) in the dog when this is due to cardiac insufficiency: *doses* used for the horse have been 30–75 gr. (2·0–5·0 G.) in food or by capsule daily for two or three weeks: in the dog ¾–1½ gr. (50·0–100·0 mg.) by mouth three or four times daily have been suggested.

Although these drugs may be injected, the peripheral vasodilatation which occurs makes them unsatisfactory for use in heart failure and in other cases where such vasodilatation is detrimental.

Reflex Stimulants. The value of camphor and ether injections has been strongly debated but such injections are still used. They are reputed to have a cardiac stimulant action by virtue of their local irritant effect which, it is suggested, causes reflex cardiac and respiratory stimulation. Doses are detailed on page 315.

Also classified in this group are the 'diffusible stimulants' which, when they reach the stomach, 'diffuse' through the wall causing irritation of nerve endings and initiating impulses which cause reflex stimulation of the heart. These gastric reflexes augment those initiated by irritation of the mouth and nasopharynx during administration. It is probable that those reflexes originating in the nose, mouth and pharynx are more powerful than those originating in the stomach.

The diffusible stimulants consist mainly of volatile, mildly irritant fluids and gases: ammonia, acetic acid, and alcohol are perhaps the most frequently used compounds. Administration may be by inhalation of ammonia—or by oral administration of such compounds as Aromatic Spirit of Ammonia, B.Vet.C., or Spirit of Nitrous Ether, B.Vet.C., the doses of which are approximately the same. (Horse and Cow: 1–4 fl. oz. (30·0–120·0 ml.) Sheep and Pig: 60–240 m. (4·0–16·0 ml.) Dog: 10–60 m. (0·6–4·0 ml.).) Dogs and cats usually object to the volatile irritants.

These reflex stimulants are of no value in anæsthetic cardiac emergencies with perhaps the exception of ammonia which is frequently used although the effect is not satisfactorily assessed. The group is of far more value in debilitating conditions such as equine influenza, pneumonias and pleurisy.

Cardiac emergencies should, logically, be treated by the administration of heart stimulants, but it will be seen from the preceding comments on the various groups that there is no stimulant which is suitable for this purpose. In human surgery the emergency treatment for 'ventricular' standstill is 'artificial respiration and manual squeezing of the heart' (Woolmer, 1953). The value of adrenaline is debated because of the danger of causing ventricular fibrillation, but calcium chloride in doses of

2·0–4·0 ml. of a 10 per cent. solution is suggested as a possible means of restarting a heart, even when all other methods fail. Ventricular fibrillation carries a grave prognosis, for electric shock therapy or procaine (several ml. of a 2 per cent. solution) injected into the left ventricle are only rarely effective. In veterinary surgery, positive pressure apparatus is rarely available and artificial respiration and cardiac massage are then limited to external pressure: where mechanical means of maintaining respiration are available direct manual massage of the heart through an incision in the diaphragm or chest wall may be tried. Procaine injections may assist in many cases. It is probable that most cases of cardiac arrest during veterinary anæsthesia are due to ventricular fibrillation which is indistinguishable from cardiac standstill except by electrocardiography or direct visual observation. The prognosis is far worse than in human cardiac arrest even should direct heart massage be possible.

Heart Tonics

The term 'heart-tonic' has been applied to those drugs which improve the nutrition and tonicity of the cardiac muscle. The cardiac tonics are slow in taking effect but the duration of action is prolonged, an attribute which is conducive to cumulation. The only heart tonics of veterinary significance are the *cardiac glycosides* derived from three plants—species of digitalis, strophanthus and squill. The digitalis glycosides are the most active and important.

Digitalis and Its Glycosides

Two species of the plant genus Digitalis provide a series of glycosides, the action of which cannot be paralleled by any synthetic compound: their mode of action is still unknown despite a known history of 180 years and intensive study over the last 20 years or more.

The main source of the digitalis glycosides is the purple foxglove *Digitalis purpurea:* a second species *D. lanata*, the woolly foxglove, is of lesser importance as a general source of cardiac glycosides, though one glycoside, digoxin, is usually obtained from it. The leaves and seeds are the plant structures normally used for processing.

From the seeds of *D. purpurea* is obtained a mixture of glycosides which when standardized is known pharmaceutically as Digitalin, B.Vet.C. The glycosides contained are *digitalinum verum* and a number of water soluble glycosides of unknown constitution.

The leaves of *D. purpurea* contain a number of glycosides, only three of which, digitoxin, gitoxin and gitalin have been prepared in crystalline form: the others are amorphous but are more soluble than the crystallizable glycosides.

The seeds and leaves of *D. purpurea* also contain several saponins including digitonin, gitonin and tigonin which, though they have no heart tonic action themselves, probably increase the activity of the glycosides by affecting solubilities, absorption rates and similar factors.

The leaves of *D. lanata* produce glycosides, known as lanatosides A, B and C, from which, by hydrolysis, are obtained digitoxin, gitoxin and digoxin, respectively. Lanatosides A and B are acetyl derivatives of the natural purpurea glycosides A and B of *D. purpurea* which also release digitoxin and gitoxin respectively during extraction.

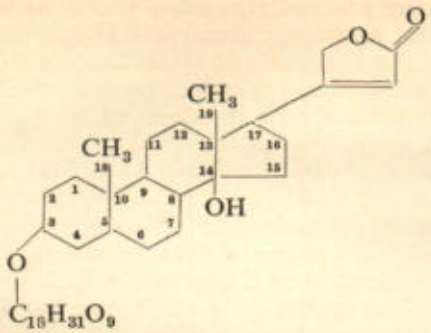
Digitalis Glycosides. A glycoside, as already defined in Chapter 5, consists essentially of a sugar and another compound which exerts the activity characteristic of the glycoside and is known as a *genin* or *aglycone*. Although the aglycone has this characteristic action and the sugar has no specific action their combination as a glycoside is far more active than the aglycone, indicating the synergistic action of the two. It is probable that the sugar increases the solubility of the aglycone and its ability to enter cells; the absorption and utilization of the aglycone are therefore improved. The sugars and genins produced by hydrolysis of the digitalis glycosides are set out in the Table 1 along with the saponins and their products of hydrolysis.

Table 1

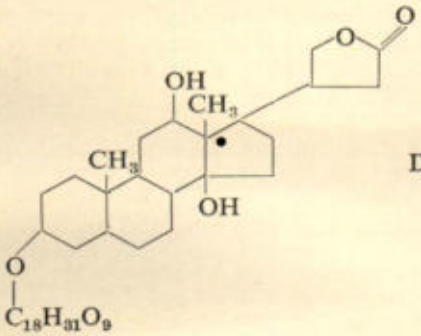
Glycoside or Saponin	Genin	Sugar(s)
Digitoxin	Digitoxigenin	3 molecules Digitoxose, $C_6H_{12}O_4$.
Gitoxin	Gitoxigenin	
Gitalin	Gitaligenin	2 molecules Digitoxose.
Digoxin	Digoxigenin	3 molecules Digitoxose.
Digitalin	Gitoxigenin or Digitaligenin	1 molecule each digitalose $C_{17}H_{14}O_5$ and glucose $C_6H_{12}O_6$.
Digitonin	Digitogenin	4 molecules galactose and 1 molecule xylose.
Gitonin	Gitogenin	3 molecules galactose and 1 molecule pentose.
Tigonin	Tigogenin	2 molecules each glucose and galactose with some rhamnose.

Structurally, the digitalis glycosides have a steroid form with a lactone ring attached at carbon 17 (see sex steroids and corticosteroids p. 344 *et seq.* and p. 643) *et seq.* and the sugars attached through an oxygen atom at carbon 3. The formulæ of digitoxin (i) and digoxin (ii) illustrate these points.

These glycosides are white or yellowish powders which are odourless but have an intensely bitter taste. Digitalin is very soluble in water and alcohol but only very slightly soluble in other solvents. Digitoxin and digoxin are almost insoluble in water but both are soluble in alcohol, whilst the former is soluble in chloroform but not in ether and the latter is insoluble in chloroform. Prepared Digitalis, B.Vet.C., which has a standard

(i) 

Digitoxin

(ii) 

Digoxin.

digitalis activity, is a green powder with a slight odour, a bitter taste and a markedly irritant effect on all mucous membranes. The presence of saponins is indicated by frothing when shaken with water.

Assay. The glycosides digitoxin and gitoxin are available in pure form and estimation by weight is therefore possible, but normally the potencies of all digitalis preparations and derivatives are estimated biologically using one of the methods mentioned in Chapter 5 in the section on 'Assay Methods'.

Actions. The actions of all the digitalis glycosides are qualitatively the same but individual variations in potency exist. Although the potency ratios vary according to the type of assay (cat, frog, pigeon, etc.), it is generally accepted that digitoxin is the most powerful of the cardiac glycosides but is closely followed by digoxin: digitalin is far less powerful than either. Digitoxin provides full effects within six to eight hours of either oral or parenteral dosing and can be detected in the urine for as long as fifty days after a single dose: it is therefore a strongly cumulative drug. Digoxin exerts some cardiac action within one hour of an oral dose and maximum effect follows within six hours: intravenous administration

gives some immediate effect and reaches a maximum in about two hours: the majority is excreted within two days and the drug is therefore far less cumulative than digitoxin.

Digitalin, B.Vet.C. which is readily soluble in water, is not so predictable in its effect and is rapidly excreted so that its cumulative effect is relatively slight.

Digitoxin is less inclined than the other glycosides to cause nausea and vomiting; it is very efficient whether administered orally or by injection (dose ratio 1 : 1) and is therefore normally given by mouth. Digoxin causes vomiting far more frequently than digitoxin and has a less efficient route dose ratio (1·5 oral to 1·0 intravenous) indicating a lower alimentary absorption: digoxin is therefore of most use for achieving digitalization (maximum digitalis action) rapidly by the intravenous route in cases requiring immediate relief from the effects of cardiac insufficiency.

The *pharmacological actions* of the digitalis group affect the cardiovascular system: the effects result partly from central stimulation of the vagal centre of the medulla and partly by a direct action on the heart muscle and nervous control mechanisms.

The effect of digitalis glycosides is primarily exerted on the muscle fibres of the heart, for heart muscle has a great affinity for cardiac glycosides and as much as 37 times more of any glycoside is concentrated on or in heart muscle than in any other body tissue. The glycosides are adsorbed onto the heart muscle and are probably assisted in entering the muscle cells by the sugar component: it is probable that the aglycone separates from the sugar within the cell, but its further metabolism is unknown and amazement is constantly expressed at the tremendous effect these aglycones exert on the muscle fibres. The effect on the muscle fibres is indicated by an increased tonus during diastole due to a slight shortening of each individual fibre, and a strong and sustained systole due to a prolonged and greater shortening of the fibres during systole. This increased effort is followed by an increased refractory period with an increased conduction time in the bundle of His, but a more powerful impulse. During the prolonged diastole which provides a long resting time, there is an increased coronary circulation and therefore an improved nutrition of the cardiac muscle. All these factors favour an improved heart action and a greater throughput of blood with an increase in blood pressure.

These effects are thought to promote a reflex vagal response (in addition to some direct stimulant action on the medullary centres) in which impulses transmitted by the vagus centre in the medulla attempt to neutralize the local action on the heart by weakening the conduction of nerve impulses, muscle tone, and irritability, and by shortening the refractory period. However, the vagal stimulation which occurs serves only to augment the local direct action on the heart muscle, for all but the weakening of conduction are ineffective and this weakened auriculoventricular conduction coincides with and intensifies the increased conduction time created by the local action on the bundle of His. The central

and local actions therefore combine to give a less frequent heart contraction, a stronger systolic phase, and a prolonged diastole with an increased ventricular filling time which in turn brings into play Starling's law of the heart whereby increased filling promotes increased muscular reaction in systole: venous pressure is reduced, arterial blood pressure is increased and cardiac throughput is also increased.

A subsidiary effect is exerted on the peripheral vessels which are differentially constricted, the arteriolar constriction being greatest in the intestines and spleen, weakest in the skin and brain, and intermediate in the kidneys. This action serves to augment the blood pressure.

An effect which is secondary to and consequent upon the cardiac effect, is a diuretic action in animals suffering from œdema due to cardiac insufficiency. There is no such action in normal animals. This diuretic effect is due to the resorption of transudates following the decrease in venous pressure; the increased blood volume allied with the rise in arterial blood pressure causes an increased renal throughput of blood, an increased filtration, and therefore greater urine production. The diuretic effect is therefore incidental and not, as was originally thought, a primary action of digitalis.

Uses. Diseases and malfunctions of the heart in domestic animals have received little attention mainly because, with the development of cardiac lesions and of venous congestion, the animal becomes a liability and is usually destroyed. It sometimes happens, however, that aged horses, especially at stud, are treated and usually some attempt is made to maintain the health of dogs affected with valvular discrepancies. The main value of digitalis is in the treatment of cardiac œdema and venous congestion consequent on cardiac decompensation: the so-called 'cardiac asthma' in old dogs is due mainly to congestion of the lungs and is not a true asthma. Digitalis is rarely used in cats because of the danger of inducing emesis by central stimulation of the vomiting centre, although digoxin by injection is less likely to cause emesis and has been used occasionally.

Dosage. All crude preparations of digitalis, that is Prepared Digitalis, B.Vet.C., and Tincture of Digitalis, B.Vet.C., will cause local irritation and vomiting in those species capable of emesis—pig, dog: in these species the glycosides should be used. In ruminants the glycosides are largely destroyed in the rumen and parenteral administration is obligatory. The intravenous route is preferred for all parenteral dosing although subcutaneous and intramuscular administration has been recommended (British Veterinary Codex): abscess formation is not an uncommon sequel to administration by these last two routes due to the irritant effect of the glycosides.

Prepared Digitalis, B.Vet.C.	Horse:	15–60 gr. (1·0–4·0 G.) orally.
Tincture of Digitalis, B.Vet.C.	Horse:	120–240 m. (8·0–16·0 ml.)
	Pig:	10–30 m. (0·6–2·0 ml.)
	Dog:	5–15 m. (0·3–1·0 ml.)

If used in the pig and dog the tincture should be adequately diluted with a demulcent vehicle.

Digitalin, B.Vet.C.	Horse:	$\frac{1}{4}$–1 gr. (15·0–60·0 mg.)
	Dog:	$\frac{1}{60}$–$\frac{1}{6}$ gr. (1·0–10·0 mg.)

The officially recommended routes of administration are the subcutaneous and intramuscular injection routes, but this compound is most frequently administered orally in the dog in tablets containing $\frac{1}{100}$–$\frac{1}{30}$ gr. (approx. 0·5–1·0 mg.), the dose being repeated three times daily.

Digitoxin, B.Vet.C.	Dog:	$\frac{1}{600}$–$\frac{1}{60}$ gr. (0·1–1·0 mg.) orally or intramuscularly.
Digoxin, B.Vet.C.	Dog:	$\frac{1}{240}$–$\frac{1}{100}$ gr. (0·25–0·6 mg.) orally or intravenously.

The official doses recommended for oral or parenteral administration are:

Initial dose:	Dog: 0·05–1·0 mg.	Cat: 0·05 mg.
Maintenance dose:	Dog: 0·025 mg.	Cat: 0·01 mg.

The methods of administration adopted in the United States are based on a dose calculated to achieve maximum safe effect (digitalization), a working average for Digitoxin, U.S.P., (contains not less than 90 per cent. pure glycoside $C_{41}H_{64}O_{13}$) being taken as 0·14–0·28 mg. per 10 lb. bodyweight (U.S.D. 25th Edit., 1955, p. 1974). In the 'intensive' method half the calculated dose is given immediately, followed by a quarter of the dose six hours later and by one eighth every four to six hours thereafter until signs of toxicity occur (vomiting, diarrhœa, depression, and cardiac irregularities). A second method, known as the 'rapid' method, consists of one seventh of the calculated digitalization dose given every six hours, while the 'slow' method provides for one tenth of the calculated dose administered every eight hours until toxic symptoms are noticed. Once the animal is saturated, the daily dose is assessed according to individual response and with due regard for the cumulative action of the glycosides used. The dose which will maintain a level just short of toxicity should be aimed at: it usually falls between the limits of one quarter and one tenth of the quantity required for digitalization.

Toxicity. Digitalis toxicity is mainly the result of cumulation and is associated most commonly with digitoxin. The symptoms consist of anorexia, vomiting, diarrhœa, mental confusion and depression, a slowing of the heart rate (bradycardia), and prolonged systole with a short diastole. If the toxicity is not recognized, fibrillation and heart failure in the systolic phase occur. *Treatment* consists of stopping further dosing, removal of any unabsorbed drug with emetics, or preferably, a purgative such as castor oil, and the administration of atropine to limit vagal stimulation.

Strophanthus

The seeds of a tropical East African climbing plant *Strophanthus kombé* are the source of a standardized mixture of glycosides officially recognized as *Strophanthin K*. A powder and a tincture are also prepared from the seeds.

Strophanthus has actions qualitatively similar to those of digitalis but there is less tendency to cause local irritation; absorption and excretion are more rapid so that the danger of cumulation is less; and a stronger diuretic effect is exerted.

Tincture of strophanthus is occasionally used but the glycosides are irregularly absorbed by the oral route and Strophanthin K, B.Vet.C., administered either intramuscularly or intravenously is preferred.

Dosage:

Horse and Cow:	$\frac{1}{60}$–$\frac{1}{8}$ gr. (1·0–12·0 mg.)
Dog:	$\frac{1}{240}$–$\frac{1}{60}$ gr. (0·25–1·0 mg.)

Squill

The bulb of white squill or *Urginea maritima*, a native of the Mediterranean area, contains two cardiac glycosides with relatively weak heart tonic actions. The powder and tincture are therefore rarely used for their effect on the heart but are frequently administered as emetic-expectorants in cough mixtures: the emetic-expectorant action is due to local irritation of the stomach which stimulates reflexly a bronchiolar secretion. The *dose* of the tincture is 120 m.–1 fl. oz. (8·0–30·0 ml.) in horses and cattle, and 5–15 m. (0·3–1·0 ml.) in dogs.

A red variety of squill is used in the manufacture of certain rat poisons because of a toxic glycoside known as scilliroside contained in the bulb. Red squill rat poison is reputed to be non-lethal to domestic animals because its irritant action precipitates vomiting before any harm can be caused—rats are unable to vomit. In practice the theory is not invariably accurate and poisoning of household pets may occur.

Drugs Affecting the Peripheral Circulation

The drugs of clinical importance are those which will produce vasoconstriction and an increase in blood pressure. In human medicine and surgery, *hypotensive* agents are of great importance in the treatment of permanent high blood pressure (hypertension), and in the creation of hypotension as a means of keeping an operation site clear of blood in areas where tourniquets cannot be used. So far, neither of these uses of hypotensive drugs has been applied in normal clinical veterinary practice but the creation of vascular hypotension is being developed as an anæsthetic technique in the veterinary schools.

There are several methods of increasing blood pressure.

1. The first is purely mechanical and consists of intravenous injections of plasma extenders (expanders) such as saline-dextran solutions, polyvinyl

pyrrolidone, and blood products including whole blood, plasma, and serum, and various plasma and serum fractions. These will be referred to in the section on Blood.

2. The second group are the vasomotor stimulants normally referred to as analeptics. Of these, nikethamide probably has the greatest effect on the peripheral vascular system. The analeptics are referred to in Chapter 16 (Nervous System Stimulants).

3. The third group comprises the vasoconstrictors including the alkaloids of ergot and the pressor factor of the posterior pituitary gland (see Chapter 18, Reproductive System), but mainly the sympathomimetic amines.

4. The fourth group consists of antihistaminics which antagonize the hypotensive effect and other actions of histamine.

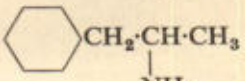
The sympathomimetic amines and the antihistaminics are dealt with in this section.

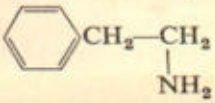
Sympathomimetic Amines

This is the term applied to a group of compounds with basic attributes which, when administered to an animal, produce effects similar to those which follow the stimulation of the sympathetic nervous system.

Chemically, the group is described as consisting of three sections, one of which contains alkyl amines (iii) with from four to eight carbon atoms:

(iii) Alkyl amines. $CH_3 \cdot (CH_2)_{1-5} - CH(NH_2) - CH_3$

(iv) Cyclo-alkyl amines. 

(v) Aryl alkyl amines. 

a second which contains cyclo-alkyl amines represented by the general formula as in (iv), and the third section which consists of aryl alkyl amines represented by (v).

It is the third group (v) with which the clinician is mainly concerned, for most of the drugs used clinically occur in this group, including adrenaline, noradrenaline, ephedrine and the amphetamines. The group has been classified firstly by the character of the aromatic nucleus, e.g. phenyl, monohydroxyphenyl or dihydroxyphenyl, alkyl amines: variations in the alkyl side chain provide a further means of subdividing these subgroups and there are thus ethylamines and isopropyl amines—primary and secondary amines are the most important.

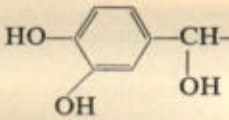
The sympathomimetic amines of veterinary significance fall into two groups, the phenyl- and dihydroxyphenyl- groups. In the *phenyl group*

are amphetamine and ephedrine, which in general have low pressor activity ($\frac{1}{100}$th of adrenaline) but are absorbed unharmed from the gastro-intestinal tract and have a relatively prolonged action. They are β phenyl-α methylethylamines (or β phenyl-isopropylamines). In the *dihydroxyphenyl group* occur adrenaline and noradrenaline which are the most potent but the least stable of these amines.

Adrenaline, B.Vet.C.

This compound, known in the United States as epinephrine, is one of the active principles of the adrenal gland from which it may be extracted, though the adrenaline used commercially may also be prepared synthetically. It is a white or creamy white powder which is only slightly soluble in water and insoluble in organic solvents. With acids, adrenaline forms salts which are water soluble: the bitartrate or acid tartrate is the one now most frequently used, for it is more stable than the hydrochloride formerly used. The powder is unstable in air and light, while neutral and alkaline solutions darken and deteriorate under the same conditions: acid solutions protected by sodium metabisulphite will withstand autoclaving at 115°C for thirty minutes, but are destroyed in the absence of the antioxidant.

Chemically, adrenaline is (—),1,(3 : 4 dihydroxyphenyl),2,methyl aminoethanol, represented graphically as in (vi). It is probably synthesized in the adrenal medulla from the amino-acid tyrosine, with arterenol (*l*-noradrenaline) as an intermediate stage.

(vi)  Adrenaline.

Actions. Adrenaline has almost all the actions produced by stimulation of the sympathetic nervous system. The adrenaline stimulates the organs directly, and is either destroyed by enzyme oxidation (amine-oxidase) or excreted in conjugated form.

Externally, adrenaline has no effect on intact skin but will cause vasoconstriction when applied to inflamed mucosæ, abraded skin and wounds, and therefore has a local hæmostatic effect. When applied to the eye in concentrations of 2 per cent., mydriasis (dilatation of the pupil) occurs, but this is of little veterinary significance.

Internally, the actions depend on the route of administration. Adrenaline is destroyed in the gastro-intestinal tract and oral dosing is therefore of little value. Subcutaneous and intramuscular injections cause local vasoconstriction which slows absorption, and marked systemic effects should not be expected. The full systemic effects follow intravenous injection, but persist for only a few minutes due to rapid dispersal and oxidation of the adrenaline unless continuous infusion is carried out, when the effects will persist for as long as the infusion continues.

The systemic effects of adrenaline have been described as those involved in 'fear, fright and flight', so that all mechanisms involved in exertion are improved whereas other unnecessary functions are reduced to a minimum. Thus, following the intravenous injection or the natural release of adrenaline by fear, the following reactions occur:

1. Passive dilatation of the vessels of the brain, lungs, and also of the coronary system, occurs as the increased blood pressure overcomes the resistance of what few constrictor fibres exist in these vessels. This is accompanied by an active dilatation of the vessels to the skeletal muscles.
2. A reduced blood supply to the skin, gastro-intestinal canal and kidneys follows powerful vasoconstriction of arteries, capillaries and veins.
3. An increased heart rate is followed by a slower rate but a more powerful contraction as the aortic and carotid reflexes impose vagal slowing on the heart, initially accelerated by adrenaline stimulation of the accelerator centre in the medulla.
4. The spleen contracts to increase the number of circulating blood cells.
5. The bronchi relax making aeration of the lungs easier and, in the horse, hyperpnœa accompanies the rise in blood pressure, whilst in other species apnœa may occur.
6. The glycogen of the liver is depleted with the formation of glucose, necessary for the supply of energy required during the increased exertion. Muscle glycogen is converted into lactic acid.
7. The activity of the stomach and intestines is reduced; relaxation of the main musculature with constriction of the sphincters is the usual response.

Other actions are variable or of slight clinical significance.

Uses. The actions of adrenaline are utilized clinically in three directions:

1. *Hæmostasis* may be achieved in capillary hæmorrhage by local application. It should be remembered that a temporary overdilatation occurs as the effects of the adrenaline wear off and secondary bleeding may result unless coagulation is achieved while the affects of adrenaline last. In epistaxis—nose bleeding—, which is not uncommon in high spirited thoroughbreds before races and may occur as a result of accidents in all species, adrenaline can be instilled or sprayed into the nostrils in concentrations of 1 : 5000 (1 part Solution of Adrenaline, B.Vet.C., plus four parts sterile water). Concentrations of 1 in 1,000 may be used in severe hæmorrhages, but the intense ischæmia caused may lead to local necrosis and retard the healing of damaged tissue. If adrenaline is used to arrest capillary hæmorrhage in operation fields, dilutions of 1 in 30,000 to 1 in 100,000 are suitable. Adrenaline solutions may be applied by swabbing or spraying.

To minimize the incidence of secondary hæmorrhage, about 1 per cent. of ephedrine hydrochloride may be incorporated with the adrenaline solution: the effect may be prolonged for several hours and no secondary dilatation follows recovery.

2. When incorporated in local anæsthetic solutions, adrenaline hydrochloride causes local vasoconstriction and slows absorption of the anæsthetic, thereby prolonging its action. Strengths of 1 in 10,000 to 1 in 50,000 are normal. Although the vasoconstriction also keeps the operation field free of blood, secondary dilatation may result in post-operative capillary bleeding.

3. The use of adrenaline in threatened and actual *cardiac collapse* has been mentioned earlier in the chapter: intravenous or direct intracardiac injection of 1 in 1000 solutions in doses of 0·25 ml. in the dog, and up to 4·0 ml. in the horse, have been used but are definitely contra-indicated during collapse associated with chloroform, cyclopropane and chloral hydrate (Detweiler, 1952) because of the probability of causing irreversible cardiac fibrillation. This danger is always present if adrenaline is used in anæsthetic collapse and the drug is therefore best ignored in favour of artificial respiration with cardiac massage.

4. Adrenaline has been used in the treatment of allergic conditions in all species. Serum allergy in all species, blue nose, purpura hæmorrhagica and laminitis in horses have all been treated with adrenaline: subcutaneous injection of up to 4·0 ml. of 1 in 1000 solutions three or four times daily have been used in blue nose and purpura; in laminitis 2·0 ml. of 1 in 2000 solutions injected subcutaneously on either side of the fetlock and repeated 24 hours later have been suggested.

In all such cases antihistaminics have superseded adrenaline.

Dosage. Injection of Adrenaline, B.Vet.C.:

Intravenously:	Horse and Cow:	2·0–4·0 ml.
	Dog:	0·1–0·3 ml.
Subcutaneously:	Horse and Cow:	2·0–8·0 ml.
	Dog:	0·1–0·5 ml.

This injection contains sufficient Adrenaline Acid Tartrate, B.Vet.C., to provide a concentration of 1 in 1,000 (0·1 per cent.) adrenaline. Solution of Adrenaline Hydrochloride, B.Vet.C., also contains 0·1 per cent. adrenaline and may be used for external application in place of the official injection.

Toxicity. Adrenaline is non-irritant but if injected subcutaneously in high concentrations an ischæmia may result which is sufficiently prolonged to cause necrosis or at least an area in which the coat colour is permanently bleached. Massage may help to avoid these effects.

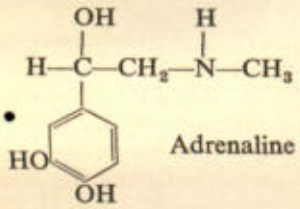
The fibrillation which may follow the use of adrenaline in cardiac collapse during anæsthesia has been mentioned previously. Adrenaline administration in hypotension associated with the phenothiazine pre-anæsthetic sedatives is ineffective if not actually contra-indicated and *l*-noradrenaline should be used.

Adrenaline should not be used by parenteral injection, in the treatment of internal hæmorrhage, for though some temporary control of bleeding may be achieved in the splanchnic area and skin, the rise in blood pressure will overcome this capillary resistance and more severe bleeding will then occur.

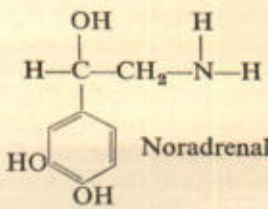
Noradrenaline

The adrenal medulla contains about 10 per cent. of arterenol or noradrenaline, which is probably a stage in the conversion of the amino-acid tyrosine into adrenaline: it is also released at the nerve endings of post-ganglionic sympathetic nerve fibres. Chemically, the hormone differs from adrenaline in having no methyl group attached to the nitrogen of the amine group and may therefore be represented as in (vii).

(vii)



Adrenaline



Noradrenaline.

Racemic noradrenaline consists of equal parts of the relatively inactive dextro- and the active lævo-isomers, and is therefore only half as active as *l*-noradrenaline. The acid tartrate is the usual salt from which injections are prepared: this salt is a colourless or cream crystalline substance which is odourless and has a solubility in water of about 1 in 5 (U.S.P. 1 in 2·5) Solutions are unstable and darken on exposure to light and air: sodium metabisulphite assists in maintaining acidity and in preventing oxidation.

Actions. Following administration, *l*-noradrenaline is converted into adrenaline and is therefore inactivated and excreted in a similar manner.

The action of noradrenaline is mainly one of peripheral vasoconstriction which differs from that caused by adrenaline in that the vasoconstriction is general and occurs in the vessels supplying skeletal muscle. As a result of this, there is a progressive rise in arterial and venous blood pressure which causes a reflex slowing of the heart: there is little increase in cardiac output. Noradrenaline is less active than adrenaline in causing bronchodilatation and gastro-intestinal stasis: it has little effect on the blood supply to the brain but reduces that to the kidney and thus decreases filtration.

Uses. In human medicine and surgery, noradrenaline is becoming increasingly accepted as an agent for countering hypotension in cases of surgical and non-surgical shock. Harthoorn (1953) has suggested intravenous injections of 1·0–2·0 microgrammes per kg. (0·5–1·0 μg. per lb.) bodyweight *l*-noradrenaline for the treatment of shock (acute vascular

hypotension) and collapse during the administration of anæsthesia to cats and dogs. In surgical and traumatic shock, up to 10·0 μg. per kg. (5·0 μg. per lb.) can be given intramuscularly. Where intravenous drips are in use, surgical shock may be treated by adding noradrenaline to the infusion in doses of up to 50·0 μg. per kg. (22·7 μg. per lb.) body weight. In man, the infusion rate is normally 6·0–8·0 μg. per minute initially, followed by a maintenance dose of 2·0–4·0 μg. per minute.

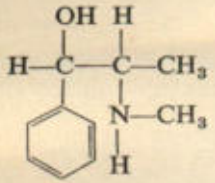
Clinical use in the veterinary field is not reported.

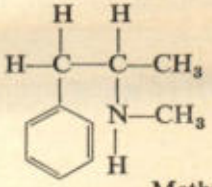
Ampoules are available: each ml. of solution contains the equivalent of 1·0 mg. *l*-noradrenaline. (2·0 mg. of the tartrate are equivalent to 1·0 mg. base.)

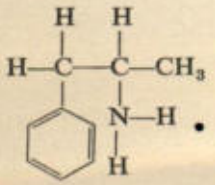
Ephedrine

One of the β phenylalkylamines, ephedrine is derived from various species of *Ephedra* shrubs which are mainly native to China and Japan, though other species are found throughout the world. The alkaloid is now widely prepared by synthetic processes.

Chemically, the compound is the hemihydrate ($\frac{1}{2}$ H_2O) of (—)-2-methyl amino-1-phenylpropanol and may be graphically represented as in (viii). Reduction of ephedrine results in the replacement of the hydroxyl group by a hydrogen atom and produces desoxyephedrine or methylamphetamine (ix).

(viii)  Ephedrine

(ix)  Methyl-amphetamine

(x)  Amphetamine.

The alkaloid itself is a white crystalline substance with no odour when fresh and a bitter taste: it is slightly soluble in water (1 : 35), soluble in alcohol, ether and chloroform, but less soluble in oil (1 : 25). The hydrochloride is also a bitter tasting crystalline solid but is soluble in water and alcohol (1 in 5), and insoluble in oils, as would be expected of an alkaloidal salt.

Actions. Ephedrine is active whatever the route, but effects are delayed for up to one hour after oral administration: although ephedrine is less

powerful in its effects than adrenaline the action is prolonged and effects may be present as long as four or five hours after oral administration. Part of the action of ephedrine is related to its inhibition of the amine-oxidase destruction of adrenaline. This potentiation of the effects of adrenaline is not the whole effect, for adrenaline has very little central nervous system effects whereas ephedrine has: this action is directly related to the absence of hydroxyl groups from the benzene ring nucleus. The compound is excreted by the kidneys unchanged: this lack of metabolization no doubt has a strong bearing on the prolonged action of the compound.

Ephedrine has little effect on the heart in therapeutic doses beyond perhaps a slight increase in rate and a dilatation of the coronary vessels, but its effect on the blood pressure is different from that of adrenaline in that the rise in systolic and diastolic pressure following oral administration is sustained for as long as five hours. Following intravenous injection of small doses, the pressure rises quite strongly, is maintained at the elevated levels for 10–15 minutes and subsequently returns to normal: there is no overdilatation of vessels similar to that which occurs with adrenaline, and there is therefore no subnormal pressure immediately following the increase. Ventricular fibrillation does not follow the use of ephedrine during chloroform anæsthesia.

In other respects the results of ephedrine administration are qualitatively similar to those following the use of adrenaline.

Uses. Ephedrine is not used commonly in veterinary medicine, and with the advent of amphetamine and methylamphetamine it is unlikely to gain popularity.

It has been suggested as a treatment for urticarial conditions, as an antidote to morphine and barbiturate overdosage, and as a mydriatic (pupil dilatator), when the effects are likely to develop in about 30 minutes and persist for as long as 12 hours following instillation of a few drops of solutions containing up to 5 per cent. of the hydrochloride or base.

Dosage. Oral or parenteral: $\frac{1}{4}$–$\frac{1}{2}$ gr. (15·0–30·0 mg.) If the drug is to be injected, the hydrochloride should be used and any subcutaneous injections should be carefully dispersed by massage. Oral dosing is preferable and effects may be maintained for up to three days by repeating the dose every four to eight hours.

Amphetamine, B.P.

This racemic compound is also a β phenyl-alkylamine with a close relationship to ephedrine (see (viii) and (x)). It is a slowly volatile liquid with a characteristic odour and acrid taste. The salts are white crystalline substances. Both the base and its salts (phosphate and sulphate) have the solubilities normally associated with alkaloids and their salts.

Amphetamine is racemic but the dextrorotatory form, which is approximately twice as active as the racemic form though qualitatively identical, is known as Dexamphetamine, B.P.C.

Actions. The actions of amphetamine are similar to those of adrenaline and ephedrine in type but there are marked quantitative differences. Amphetamine is active when administered by mouth, the base is locally active when the vapour is inhaled, and the salts may be given by intravenous or intramuscular injection. Following oral administration, effects commence within about five minutes and reach a maximum in about 30 minutes: cardio-respiratory effects have lasted for as long as seven hours. About 50 per cent. is excreted within 48 hours of dosing, whilst the remainder is slowly metabolized. The actions of amphetamine are significant in four directions: (1) cardio-respiratory stimulation; (2) central nervous system stimulation, (3) antispasmodic action; and (4) metabolic stimulation with a decrease in appetite.

The peripheral vasoconstriction caused by amphetamine results in a slow but considerable rise in blood pressure which may persist for several hours. It also has a respiratory stimulant effect due to central stimulation.

The cerebral and medullary stimulant effect of amphetamine is most marked: it is stated to be greater than that of all other sympathomimetic amines and superior to ephedrine, nikethamide, leptazol and caffeine in antagonizing the respiratory depressant effect of morphine.

The antispasmodic action is not so marked as are the previous two actions but the delayed emptying of the stomach no doubt has a bearing on the appetite reducing effect, which is exerted on dogs as well as humans. The metabolic rate is increased at the same time and the combined effect assists in reducing bodyweight. The dextro-isomer is more effective for this purpose.

Dosage. As an analeptic, the following doses may be taken as a guide only, for the safely tolerated dose will vary according to the degree of depression in each individual case:

Horse and Cow:	0·1–0·3 G. subcutaneously or intramuscularly.
Dog:	0·5 to 2·0 mg. per lb. (1·1 to 4·4 mg. per kg.) bodyweight by any parenteral route.

For stimulant and weight reducing purposes, the dose for small animals is 2·5–10·0 mg. repeated according to response. For the first purpose dosing is by the parenteral routes but for the latter use oral dosage is usual.

Note. The minimum lethal dose per kg. in sheep is 15·0 mg., in dogs and rabbits 20·0 mg. and in monkeys 20·0–25·0 mg. The doses relate to subcutaneous administration in all but dogs, in which the dose was estimated for oral administration.

Methylamphetamine, B.P.C., and its hydrochloride have actions similar to those of the amphetamine compounds but their analeptic effects are

superior. The lævorotatory isomer is said to be more active than the dextrorotatory form. The dosage in man is 2·5 to 10·0 mg. orally once or twice daily: as a parenteral analeptic 10·0–15·0 mg. are given by slow intravenous injection and the dose repeated in 15–20 minutes if necessary: intramuscular doses are slightly higher (up to 30·0 mg.). The compound has not so far been widely used for veterinary purposes.

Overdosage, indicated by hyperexcitability and cardiac irregularities, may be countered by the administration of short acting barbiturates.

Histamine and the Antihistaminics

The importance of histamine as a factor in the causation of certain pathological conditions was first suggested in 1910 by Dale and Laidlaw, who pointed out a possible relationship between histamine and the ætiology of anaphylaxis and allergy: since that time it has been established with reasonable certainty that histamine release is a major factor in the development of these two phenomena. It has also been suggested that wherever tissue is damaged there is a production of histamine which causes either local or general shock: this postulation is debated, but there is no doubt that histamine administration is followed in most species by a train of reactions very similar to those seen during the development of traumatic and surgical shock. There is also no doubt that other factors besides histamine release are involved.

Histamine. This occurs in an inactive form in all tissues, but especially in the lungs, skin, intestinal and muscular tissues. It is formed from the amino-acid histidine by decarboxylation mediated by an enzyme *histidine decarboxylase*: bacterial decomposition of proteins also produces histamine and fairly high concentrations exist in septic foci where tissue destruction is in progress. Histamine is slowly destroyed by enzyme action, the effective enzyme being *histaminase* which is concentrated mainly in the intestinal mucosa, liver and kidneys, but occurs elsewhere in lower concentrations.

The mode of action and physiological purpose of histamine are unknown: even its effects have not been identified in all species although enough is known to indicate that species variations occur. In general, man, monkey, dog, cat and fowl respond in a similar manner, showing a marked fall in blood pressure, whereas rabbits and guinea pigs show a rise, probably due to arteriolar constriction. The effects in the larger domestic animals have not been satisfactorily investigated.

The main actions of histamine, and those against which antihistaminics are of most use, are a marked fall in blood pressure, an increase in capillary permeability, and spasm of all smooth muscle including that of the bronchi, intestines, and uterus. An action against which antihistamines are of no value, is the marked increase in gastric secretion: this secretion has a high acidity and low pepsin content.

The fall in arterial blood pressure is mainly caused by a dilatation of arterioles and capillaries, excluding the pulmonary vessels which contract

in concert with the bronchial muscles, but including, in the dog, the coronary vessels. An increased heart rate with weakened muscle power accompanies the fall in blood pressure.

The clinical effects consist of salivation, vomiting in those species capable of this function, abdominal pain (colic) and diarrhœa, dilatation of skin capillaries and increased heat loss, a rapid weak pulse, a decreased circulating blood volume with loss of fluid and possibly protein into the tissues, and an increased respiratory rate with acute dyspnœa.

The effects of histamine may be antagonized by:

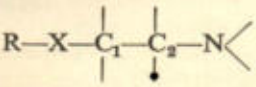
1. Physiological antagonists. These consist mainly of the sympathomimetic amines, adrenaline, noradrenaline, ephedrine, amphetamine and others. These drugs are still used quite frequently to counter the cardiovascular effects of allergic reactions.
2. Destructive antagonists. Histaminase has already been mentioned as the enzyme which destroys histamine produced naturally in the body. It has been used clinically but is too slow in acting to be of much value.
3. Pharmacological competitors or antimetabolites. A series of compounds has been developed in recent years which antagonize the action of histamine, according to the most widely held theory, by competing for tissue receptors and thus preventing the access of histamine to the cells. They therefore have some structural similarity to histamine. Members of this group are known as *antihistaminics.*

The Antihistaminics. Interest in antihistaminics was stimulated by a report, in 1937 by Bovet and Staub of the Pasteur Institute in Paris, on two compounds designated 929F and 157F by their discoverer Fourneau, an eminent French organic chemist. These two compounds were shown to have antihistaminic activity but proved too toxic for clinical use. Since then many compounds with antihistaminic activity have been developed and marketed.

The antihistaminics show some chemical resemblance to each other and the relationship of chemical structure and clinical activity is now becoming clearer, although in both these respects exceptions exist.

The majority of the antihistaminics (U.S.D. 25th Edit. 1955, p. 1575) conform to a formula (xi), to which several generalizations can be applied.

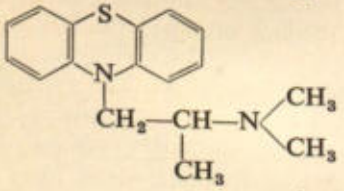
(xi)



1. In this formula R is often known as the nucleus whilst the rest is referred to as the side chain, but in many cases the atom X is often incorporated in the ring structure which comprises the nucleus (see Promethazine, xii). The nucleus is usually composed of two or more cyclic groups which may be aromatic or heterocyclic or both, and in many cases the activity has been enhanced by attachment of a halogen,

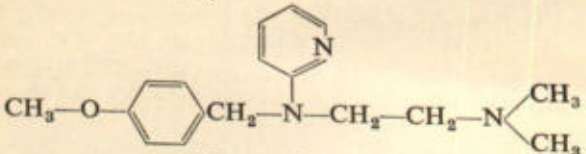
or a small alkyl or alkoxy group, in the para position of the ring of a benzyl or phenyl group (see Mepyramine xiii).

(xii)



Promethazine.
(N-(2-dimethylamino-2-methyl) ethyl phenothiazine)

(xiii)

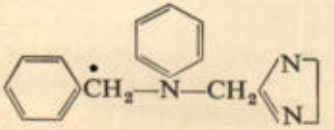


Mepyramine.
(2-[(2-dimethylaminoethyl) (p-methoxybenzyl)amino]pyridine)

2. The place of 'X' in the general formula may be taken by one of three atoms, nitrogen, oxygen or carbon. Antihistaminics representative of these three types are, respectively, tripelennamine (or mepyramine), diphenhydramine (also dimenhydrinate), and prophenpyridamine. These chemical differences are of considerable clinical significance, for compounds containing nitrogen at 'X' are usually far more powerful than those containing either oxygen or carbon atoms in this position; those containing carbon, though they have a decreased activity also possess fewer side actions and a lower toxicity, whilst those compounds with oxygen in place of 'X' have sedative side effects, though such effects are not by any means confined to oxygen-containing compounds as reference to chlorpromazine will show. (Chlorpromazine may be looked upon as an antihistaminic in which the sedative side effects are developed almost to the exclusion of the antihistaminic action.)

3. The structure of the remainder of the side chain also has a marked effect on the antihistaminic action for maximum effect is achieved when this chain consists of two carbon atoms and a dimethylated nitrogen atom. The carbon atom valencies are normally completed by hydrogen atoms although attachment of a methyl group to carbon 2 of the side chain as in promethazine appears to increase antihistaminic activity, whilst similar substitution of one of the hydrogen atoms on carbon 1 reduces activity. Increase of the carbon atoms in the side chain in any other manner reduces activity. Antazoline (xiv) constitutes a partial exception to this

(xiv)



Antazoline.

side chain theory for the dimethyl-aminoethyl side chain is replaced by a methyl-iminazoline group. Nevertheless, in support of the theory the potency of the compound is less than that of more orthodox preparations and the side actions are also weaker, the lack of local irritation being of clinical significance.

The physical characters are very similar. All are white or creamy white crystalline powders which are either odourless or have only a slight odour, most have a bitter taste and may cause a local numbing of the tongue due to local anæsthetic effects. All are basic compounds which form salts, the solubilites of which in water, alcohol, and chloroform, vary from less than 1 : 1 up to 1 : 6, with the exception of antazoline which is soluble only to the extent of 1 : 50 in water, 1 : 65 in alcohol and is only slightly soluble in other solvents. Many of the salts are unstable and darken on exposure to air and light.

Actions. Antihistaminics are satisfactorily absorbed from the gastro-intestinal tract of simple-stomached animals but not of ruminants. Although satisfactory, absorption following oral administration in small animals is relatively slow and a delay of up to 30 minutes can be expected before any effects become apparent. The delay is shorter following intramuscular administration, while immediate effects follow administration by the intravenous route which, however, is not a satisfactory route for the administration of antihistaminics because of the danger of causing cardiovascular disturbances. The duration of effect varies from as little as three hours for diphenhydydramine hydrochloride up to 24 hours or more with promethazine hydrochloride; this duration of action is proportional to, and is an indication of, the rate of destruction.

External application is suitable only for the treatment of skin lesions in which the surface is broken or congestion and inflammation are present. Little absorption takes place through intact skin.

The method by which the antihistaminics counter the action of histamine is not known, but the general accepted theory suggests that, because of structural similarities, the antihistaminics act as antimetabolites and compete with histamine for the specific 'receptors' in the tissue cells, thereby blocking the entry of histamine into the cells. This means that the antihistaminics must be available to the cells in greater quantity than the histamine and must have a greater affinity for the cell receptors. The action is therefore analogous to those of the sulphonamides and antibiotics, which block the access of essential metabolites to bacterial cells; in the case of antihistaminics, however, the role is protective and not destructive.

The antihistaminics counter the actions of histamine in varying degrees. The most easily countered effects are the contractions of the smooth muscle in the bronchi, intestines and uterus. The vascular effects are less easily countered but the action of the antihistaminics in this respect is of greatest clinical importance for they prevent capillary dilatation and

permeability, —the effects of histamine which cause marked falls in blood pressure and œdema of the tissues, especially the subcutaneous plaques and swellings so typical of serum reactions.

Significant side actions occur but the nature and intensity of these vary with each individual drug and patient. The side effects of most importance are:

(1) Central nervous system depression (*cf.* chlorpromazine), which results in drowsiness and lethargy during treatment.

(2) Local anæsthetic effects, which may be three or four times as great as those of procaine and are of value in external therapy, although irritant effects on tissues prevent their specific use as local anæsthetics.

(3) Gastro-intestinal disturbances in simple-stomached animals when oral administration is prolonged.

(4) Intravenous administration may cause prolonged periods of excitement which may necessitate barbiturate sedation.

(5) Marked interference with the allergic diagnostic tests, particularly the tuberculin test. Antihistaminics must be avoided while such tests are in progress.

Uses. It must be emphasized that antihistaminics have no effect on the causal factors of any of the conditions mentioned below and administration must therefore be continued until the causes have been removed either by concurrent therapy or by the natural body processes. Should the ætiological factors not be removed then symptoms will recur following withdrawal of antihistaminic treatment. Antihistamine therapy is thus symptomatic treatment only.

If allergies are acute and severe, antihistamine compounds are usually too slow in action to be of immediate use unless given by slow intravenous injection. As administration by this route is attended by some danger of causing hyperexcitability, it is advisable to give adrenaline initially, followed by oral or intramuscular dosing with an antihistaminic. In all cases, systemic therapy should be continued for about three days unless dramatic recovery follows within 24 hours of dosing. Oral dosing in small animals should be carried out either at meal times or shortly after feeding; gastric irritation is thereby decreased and absorption time prolonged.

The conditions in which antihistamines are of most value are those associated with allergic congestion, œdema, pruritis, and any condition usually associated with traumatic histamine release.

In the first group occur all types of urticaria, serum allergies and allergic dermatitis cases, whilst in the second group may be placed moist eczema in dogs, especially when associated with otitis, 'sweet itch' or 'summer itch' in horses, plant photosensitization cases, insect bites, burns and scalds.

A number of conditions commonly believed to be allergic in origin have also been treated with antihistamines although the character of these conditions makes assessment of results difficult. Purpura, lymphangitis, 'blue nose', and pulmonary emphysema (heaves or broken wind) in

horses respond to varying degrees. Some cases of bloat in ruminants (those due to histamine atony of the rumen following over-eating), have been treated with antihistaminics and good results have been claimed.

In addition, conditions associated with gross tissue destruction are reported to benefit from antihistamine treatment. The rationale for this use of antihistaminics is that in the process of protein destruction large amounts of histamine are produced and absorbed to the detriment of the sick animal: neutralization of this histamine confers benefit proportional to the amount present. Acute septic and gangrenous mastitis, septic metritis and retained placentæ, myoglobinuria and azoturia, as well as acetonæmia, in which protein conversion to sugar involves protein breakdown, have all responded to varying degrees.

An illicit use of antihistaminics has been discovered in recent years; this is the use of their sedative effects for the doping of greyhounds.

The use of antihistamines to combat surgical shock has given disappointing results, although clinical assessment of any benefit is extremely difficult. As the cost of corticosteroids decreases it is probable that they will supersede the antihistaminics as anti-inflammatory and anti-œdema therapeutics.

Toxicity. The main symptoms of toxicity are the hyperexcitability and possibly convulsions which result from overdosage. Treatment is symptomatic and usually consists of the injection of sedative doses of short acting barbiturates.

Antazoline Hydrochloride, B.P.C.

Better known as Antistin (commercial name), antazoline is less active than many of the other antihistaminics but has the advantage of causing less residual irritation, which makes it more acceptable for local application. Parenteral administration is accompanied by fewer untoward reactions. It may be used as a 0·5 per cent. ophthalmic solution, as a 2 per cent. cream for topical use, and as ampoules or tablets containing 100·0 mg. for parenteral and oral administration respectively. Applications need to be repeated every six to eight hours to achieve maximum success. *Dosage:* The drug has not been used extensively for systemic action, but the dose for small animals would be about 100·0 mg. given three or four times daily.

Diphenhydramine Hydrochloride, B.P.C.

This compound is widely known as Benadryl. It is one of the less active antihistaminics and is more toxic than other commonly used members of the group. Onset of effects is fairly rapid but the duration is short, three hours being the limit for reliable control of symptoms. The strong local anæsthetic effect makes the compound very useful for local application in urticarial pruritis and other skin conditions. It has been used orally in capsule form or as a solution for the treatment of travel

sickness and for urticaria in small animals. It may be given parenterally and is also applied externally as a 1 per cent. lotion or 2 per cent. cream.

Dosage. Dosage for large animals is from 0·2–0·3 G. for the adult horse and cow repeated in 12–24 hours if necessary, but in the dog the dosage rate is about 1·0 mg. per lb. (2·2 mg. per kg.) bodyweight by mouth every twelve hours and 0·6–1·0 mg. per lb. (1·32–2·2 mg. per kg.) bodyweight parenterally.

Mepyramine Maleate, B.Vet.C.

Known in America as pyrilamine maleate, this medium duration antihistaminic was the first of the group available in Great Britain and is known widely as Anthisan. The effects of mepyramine maleate persist from six to eight hours. The compound is a good general antihistaminic which is fairly well tolerated and may be given by oral or intramuscular administration for systemic action; it can also be applied topically for local effect. Because of the irritant action following parenteral use it is advisable to use 5 per cent. solutions only in large animals: the 2·5 per cent. solutions are suitable for small animal treatment. Intramuscular *dosage* of the 5 per cent. solution is 10·0–30·0 ml. in cattle and horses, 5·0–10·0 ml. in sheep and pigs; 1·0–5·0 ml. of the 2·5 per cent. solution is satisfactory for dogs. Oral doses in dogs vary from 50·0–100·0 mg. Doses should be repeated every eight to twelve hours. Topical applications of a 2 per cent. cream should be applied twice daily.

Promethazine Hydrochloride, B.Vet.C.

This compound, the second antihistaminic to be introduced into veterinary practice in Great Britain, is known commercially as Phenergan. Promethazine is one of the most active of the group but its side actions are also more pronounced including anticholinergic and hypnotic activity. Its duration of effect is in excess of 24 hours, which reduces the need for repeated injections—single daily doses are sufficient. Intramuscular and oral administration follow the same pattern as with other antihistaminics. Local applications usually contain 2 per cent. of promethazine hydrochloride and require application once or twice daily.

Dosage. Large animals are injected intramuscularly with a 5 per cent. solution at the rate of 5·0–20·0 ml. for cattle and horses, 2·5–10·0 ml. for sheep and pigs: small animals (dogs) require from 1·0–5·0 ml. of a 2·5 per cent. solution. Single daily injections should be given on three occasions.

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CHAPTER 11

THE HEART AND CIRCULATORY SYSTEM

(ii) THE BLOOD

The blood is probably the most important 'tissue' in the animal body. Its functions are wide and varied and any change in the blood is soon reflected in tissue function just as changes in tissue metabolism are rapidly followed by changes in the blood. The diversity of the responsibilities of the blood are indicated by the more important functions listed below:

1. The transport of oxygen from the lungs to the tissues is the most vital function performed by any body tissue.
2. Nutritional substances are transported from the intestines to the tissues and nutritional products synthesized in the body are distributed from their points of manufacture to their sites of utilization.
3. Metabolites produced by the various tissues are carried to the excretory organs.
4. Changes in the fluid balance between cells, extracellular fluid, and the blood are neutralized by the blood in conjunction with the organs of excretion.
5. The pH of the tissues and tissue fluids is maintained constant by means of the electrolyte and buffer mechanisms of the blood.
6. Body heat is regulated by the take up and release of heat by the blood.
7. The hormones which are essential for the control and co-ordination of the body functions are all distributed by the blood.
8. Antibody fractions and macrophages in the blood are important factors in the defence of the body against the attack of pathogenic organisms.

The variety and importance of these functions and the ubiquitous distribution of blood and the tissue fluids with which it is in constant equilibrium make the blood an ideal means of circulating soluble therapeutic agents to all cells of the body, but it must be remembered that any damage to the blood will be immediately projected into the tissues. The rapidity with which cyanides, non-volatile anæsthetics, or strychnine cause generalized effects bears striking witness to this statement.

In carrying out intravenous injections, therefore, although the blood is capable of accommodating prodigious amounts of abnormal substances without any material change in its physical characters, this accommodation should be imposed upon as little as possible. In order to aid accommodation assistance may take the form of making solutions isotonic, neutral in reaction, equal in temperature to that of the body, or failing these, of

giving the injections so slowly that the blood can dilute and accommodate the fluid as it is injected.

Oxygen Transport

The blood of domestic animals carries between 15·0–20·0 ml. of oxygen per 100·0 ml. of arterial blood. Of this, only a small proportion is in physical solution in the plasma, the remainder being combined with hæmoglobin within the red blood cells, 1·0 G. hæmoglobin combining with approximately 1·36 ml. of oxygen. It is therefore most important that the hæmoglobin content of the blood should be maintained at its optimum for each species (see Table 2.)

Table 2

Species	Approximate Hæmoglobin (G.%)	
Horse:	10·0 ±1·5	Thoroughbreds are somewhat higher.
Cow:	12·03	
Sheep:	12·4 ±1·4	
Goat:	10·9	
Pig:	12·0	
Dog:	13·0	
Cat:	10·5	
Cockerel:	13·5	
Hen:	10·0	

Hæmoglobin consists of an iron-containing pigment and a protein, the pigment forming about 5 per cent. of the hæmoglobin molecule.

From these few facts it will be seen that the oxygen carrying capacity of the blood is proportional firstly to the number of circulating erythrocytes and secondly to the hæmoglobin content of each individual erythrocyte. The number of erythrocytes is governed by the rate of formation and of destruction of red blood cells, whilst the hæmoglobin content is determined both by the amount of available iron and also of the specific protein. A deficiency of iron or inability to utilize it because of the absence of other factors, such as copper or cobalt, and a deficiency of dietary protein, will both cause a hypochromic anæmia. Disorganization of erythropoiesis or extensive hæmolysis or hæmorrhage will result in anæmia due to a reduction in the numbers of circulating erythrocytes.

Perhaps the commonest form of anæmia in Great Britain is *piglet anæmia*, which is usually a microcytic hypochromic condition due to lack of available iron but is sometimes associated with other factors, including deficiencies of the vitamin B complex and of dietary protein. The condition is a definite penalty of intensive indoor pig rearing, though it is ironic that the cleaner and more hygienic the conditions, the higher is the

incidence of anæmia. Where free access to soil is available from birth it is uncommon to find anæmia as a rearing problem.

During the first week to ten days after birth the normal hæmoglobin level of between 10·0 and 11·0 G. per 100·0 ml. of blood decreases to between 5·0 and 6·0 G. per cent. This is due in part to a redeployment of the available hæmoglobin but also to a reduction in iron intake associated with rapid growth and increased demand for hæmoglobin. If extrinsic iron is available to supplement the daily oral intake of about 1·0 mg. from the sows milk (Luke and Gordon, 1950) the hæmoglobin level will thereafter increase; should there be no outside source of iron then the level will continue to fall and precipitate subclinical and later clinical anæmia. Symptoms may be expected when the level falls below 5·0 G. per cent. and consist most frequently of scours, in which the semi-fluid fæces are grey or yellowish, dyspnœa on exertion, a disinclination to play, a pallid skin and pale mucous membranes. These symptoms are most marked at about three weeks when the piglet may look fat and well fed: such piglets may die suddenly or become progressively thinner assuming a stunted runt-like appearance. It is the piglets which grow rapidly in their early days which are most severely affected—their requirements are proportionately greater. Post-mortem lesions include a gastro-enteritis, an enlarged heart with thin walls, pale 'thin' blood which does not clot readily, fluid in the body cavities, pale muscles, an enlarged spleen, and a liver which is usually enlarged and may be fatty with necrotic foci at the centre of the lobules. Pneumonia may also be present as well as gastro-enteritis, depending on the type of secondary infection: it is often these secondary pathogens which are finally responsible for the animals death.

Treatment should be primarily concerned with a change in husbandry, but where animals are clinically affected therapy may take the form of parenteral iron supplemented by oral intake of iron once the initial craving for iron has been overcome. If oral iron is supplied immediately, overeating may occur resulting in iron toxicity and death (Brag, 1957).

In a review of piglet anæmia, Seamer (1956) details all the suggested treatments for piglet anæmia. Of these, three or four methods, with variations, have been widely used:

1. A combination of ferrous sulphate and copper sulphate, usually in proportions of about 5 to 1, have been administered in various ways. Most popular has been a mixture of 3¾ oz. (105·0 G.) iron sulphate with ¾ oz. (21·0 G.) copper sulphate in two pints of treacle, some of which is smeared on the sows teats once or twice daily. The B.V.A. Publication 14, 3rd Edit. p. 103, suggests one teaspoonful (4·0 ml.) daily to each piglet of a mixture each pint of which contains 180 gr. of ferrous sulphate and 60 gr. of copper sulphate (21·0 G. per litre and 7·0 G. per litre respectively). In Scandinavia and elsewhere it is a common practice to spray grass sods and soil with a mixture of ferrous and copper sulphates: Moe *et al.* quoted by Seamer (*loc. cit.*) suggested 9·0 G. (125 gr.) of the iron compound

and 1·5 G. (22½ gr.) of copper sulphate for every fifty pounds of soil. This medicated soil is thrown into the pens daily. Dressing of the sow's teats is a very easy method but tends to make the skin sore and dirty, for the sticky syrup picks up straw and dirt very rapidly.

2. Oral dosing with reduced iron or iron pyrophosphate has also been widely used. The B.V.A. publication (*loc. cit.*) suggests reduced iron 0·5–1·0 G. daily or every second day for a week to ten days. Barber, Braude and Mitchell (1955) used, with good effect, the 30·0 mg. dose of iron, as suggested by Foot and Thompson (1947), daily for seven days commencing on the 7th day of life: this dose is provided by 0·3 G. (5 gr.) of pyrophosphate which may be dissolved in a teaspoonful of water (4·0 ml. or 60 m.) This method is expensive in labour and has given place to the almost universal use of intramuscular iron injections.

3. Intramuscular and intravenous injections of iron carbohydrate complexes have been used in the field of human iron deficiency anæmias since about 1948, but it was not until the introduction in 1955 of an iron-dextran injection for piglet anæmia that such preparations have been used in the veterinary field. Since that time other carbohydrate complexes including an iron-dextrin complex (Brag, *loc. cit.*) have been used extensively. These carbohydrate complexes must be administered intramuscularly, for subcutaneous injection or leakage may cause tissue staining which is unsightly until it is completely absorbed some six weeks or so later. Absorption of the dextran and dextrin complexes is sufficiently rapid to prevent any fall of the hæmoglobin content below the critical level and to restore acutely pathological levels to normal. The majority of the injected iron is used within about one week of administration (Brownlie, 1955). The normal dose is 100·0 mg. of ferric iron usually contained in 2·0 ml. of the injection; this dose is often given within three days of birth and in severe cases repeated after about ten days. However, muscular degeneration and death have occasionally followed administration of some organic iron compounds to very young pigs. In view of the rapidity of the therapeutic action of such compounds and the fact that blood iron rarely becomes depleted to danger level before about 10 days of age there seems little point in inoculating piglets before they are about 5 days old. In fact, investigations now in progress indicate that it is inadvisable to inject piglets with anything until at least five days after birth (Done, 1958). Intercurrent infections must be treated in the same manner as they would be if not associated with anæmia, for though iron injections will improve general resistance they are not in any way antibacterial agents. Likewise any protein, copper, cobalt or other deficiency must be treated concurrently with the iron therapy.

In all cases of piglet anæmia the aim should be to supply sufficient iron for the animals' needs during the first three weeks of life and to treat rationally any secondary infection. After the third week the piglets should be eating creep feed and thus obtaining some iron, although Barber, Braude and Mitchell (1953) have pointed out that significant amounts of

creep feed may not be eaten until about the fifth week of life, which may be responsible for a secondary fall in hæmoglobin levels. Brownlie (*loc. cit.*) has also shown that creep feeds may have too low an iron content and that even 124 p.p.m. (equivalent to 54·0 mg. iron per lb.) was too low, although samples of a normal creep feed and a commercial sow and weaner meal contained only 80 p.p.m. (36 mg. iron per lb.) and 110 p.p.m. (48 mg.) respectively: enrichment of such meals is essential unless other means of oral administration of iron are used.

Other iron preparations, all of which are astringent both externally and internally, include *Ferrous Sulphate, B.Vet.C.* which may be either a water soluble green crystal or powder with an astringent metallic taste, or a heavy greyish-white anhydrous powder with similar properties although it dissolves very slowly when compared with the hydrated salt. Ferrous sulphate is commonly used as an intestinal astringent in cattle and horses and also as a hæmatinic (a hæmoglobin forming and erythropoietic substance). McFadyean's treatment for Johne's disease is a typical example of the former use:

℞	Ferrous Sulphate	120 gr.	8·0 G.
	Dilute Sulphuric Acid, B.P.C.	120 m.	8·0 ml.
	Water	to 1 fl. oz.	to 30·0 ml.
	Fiat Haustus		

The *dose* of this mixture was a fluid ounce in a pint of water (30·0 ml. in 500 ml.) by mouth once or twice daily.

The dose of the exciccated salt as a hæmatinic is 60 gr. (4·0 G.) given twice daily to a horse, usually in food with gentian and nux vomica powder.

Ferrous carbonate (Blaud) is used in the form of a pill or tablet, often in conjunction with arsenic, as a hæmatinic in small animals, and *Compound Syrup of Ferrous Phosphate, B.P.C.*, is also used in doses of 30–60 m. (2·0–4·0 ml.): most of these preparations are being displaced by organic acid salts such as *ferrous gluconate* and *succinate* which are less irritant, less constipating and more effectively absorbed, especially if combined with therapeutic amounts of the vitamin B complex. *Doses* of 5 gr. (0·3 G.) may be given twice or three times daily to small animals.

Ferric chloride as *Strong Solution of Ferric Chloride, B.Vet.C.*, containing 60 per cent. of the salt, is a more powerful hæmostatic which is useful for arresting capillary and minor arterial hæmorrhage. As such it finds use in arresting bleeding during the removal of dew claws and docking puppies and in the removal of small superficial warts. When applying the solution, hæmorrhage must be arrested temporarily by pressure, for if the solution is applied to a wound covered in blood the iron merely coagulates the protein in the blood but does not cause clotting in the vessel, which it must do if bleeding is to be stopped. The strong solution is also used for preparing ferric hydroxide precipitate and Solution of Dialysed Iron, B.Vet.C., both of which are reputed to be useful in arsenic poisoning:

the former is freshly prepared and given *ad lib.*, whilst the latter is given in *doses* of ½–2 fl. oz. (30·0–60·0 ml.) to horses and cattle, 15–60 m. (1·0–4·0 ml.) to sheep, 8–45 m. (0·5–3·0 ml.) to pigs, and 5–25 m. (0·3–1·5 ml.) to dogs.

Cobalt deficiencies associated with a marked anæmia, loss of appetite, progressive wasting, decreases in blood volume and a drop of oxygen carrying capacity to 30 per cent. of normal or lower are reported in sheep. The condition is widely known as 'pine' in Great Britain and elsewhere, but also as 'bush sickness' in New Zealand, 'nakuruitis' in Kenya and 'grand traverse disease' in the United States.

Symptoms in cattle are less severe than in sheep but are similar in type. Milk yields are reduced and calves are weak when born—if they survive they are unthrifty and anæmic.

As the condition is essentially related to deficiencies in the soil and herbage, preventive measures must include pasture dressing with cobalt sulphate or cobalt chloride, the quantity and frequency of dressings will vary with the area and degree of deficiency but in Great Britain short term leys will require about 2 lb. per acre every three years (Cuthbertson, 1955); in New Zealand, 5 oz. per acre annually as a top dressing has been shown to be satisfactory (Dept. of Agric. and Cawthron Inst., 1954) and 20 oz. per acre is effective for three years (Andrews, 1953). In Australia, 4 oz. per acre per year is satisfactory (Rossiter *et al.*, 1948). Spraying solutions from the air has proved an efficient and rapid method of applying the salt. For animals not at grass, *oral* dosing twice weekly or mixing cobalt salts in the food is the best means of administration, for it has been shown that pining animals do not all use salt licks (Filmer, 1941). Parenteral injection is not effective in alleviating the effects of cobalt deficiency (Cunningham, 1955), which is not surprising for the eventual deficiency is one of vitamin B_{12} which is manufactured from cobalt in the rumen by the bacterial flora and then absorbed.

Dosage. For prophylaxis:

Cattle:	25·0 mg. (2/5 gr.)
Calves:	10·0 mg. (1/6 gr.)
Sheep:	5·0 mg. (1/12 gr.)
Lambs:	2·5 mg. (1/24 gr.)

These doses must be given orally each day either in food or as a drench.

For oral treatment:

Cattle:	0·5 G. (7½ gr.)
Calves:	0·2 G. (3 gr.)
Sheep:	0·1 G. (1½ gr.)
Lambs:	0·05 G. (¾ gr.)

Recently repository 'bullets' have been developed which are administered orally and, theoretically, because of their weight, remain in the reticulum

releasing cobalt slowly over a long period. They have proved reasonably successful in Australia and have been marketed commercially in Great Britain since early in 1958: their main disadvantage is that applying to all oral tablets in that some individuals will return the bullet some time after dosing and it is not possible to detect the offenders until clinical signs of deficiency appear.

Copper is also necessary for the normal utilization of iron in hæmoglobin formation in mammals and birds (Schultze, 1940), and various authors are quoted by Cunningham (*loc. cit.*) as showing that a microcytic and hypochromic anæmia develops in pigs, rabbits, and rats subjected to experimental copper deficiencies. Copper and iron are together associated in various enzyme activities, whilst copper is an essential component of other enzymes including ascorbic acid oxidase, polyphenoloxidase, laccase and copper protein compounds of unknown function. Through various enzymic and catalytic processes, copper is closely associated with normal wool growth, coat and skin colouring and normal bone metabolism. Derangement of all these processes are noticeable in clinical cases of copper deficiency.

Symptoms of copper deficiency in sheep vary according to whether the deficiency is complicated with cobalt deficiency or molybdenum excess, or other unidentified complications (*cf.* swayback in which no symptoms occur in adults but lambs are affected *in utero* by demyelination of the brain tissue). In uncomplicated deficiencies the wool changes its appearance and becomes straight with a steely sheen; this is followed by severe hypochromic and microcytic anæmia; lambs may be affected with demyelination of the brain and spinal cord.

In cattle, the picture of copper deficiency (peat scours) in Great Britain has been, and is being, investigated by Dr. Ruth Allcroft and her colleagues: in Caithness the pine of cattle is reported not to be associated with an excess of molybdenum (Jamieson and Allcroft, 1950), but copper deficiencies frequently associated with excess molybdenum (teart) are widespread in Great Britain (Allcroft and Parker, 1949; Allcroft, 1952) and elsewhere in the world. References to such deficiencies in Australia, New Zealand, North and South America, South Africa, Sweden, and India are quoted by Cunningham (*loc. cit.*). The symptoms in cattle are those of unthriftiness, anæmia, temporary sterility and, in some areas (Western Australia), sudden death ('falling disease'). Straightness of leg joints and stiffness are recorded, and also fading of hair colour, particularly around the eyes which is responsible for the popular name 'spectacle disease'. Scours are also a significant symptom in many areas.

Treatment has consisted of mineral licks containing 0·3 per cent. or more of copper sulphate; intravenous injections of 20·0 mg. copper (80 mg. Copper Sulphate, B.Vet.C.) for sheep, and 50·0 mg. (200·0 mg. Copper Sulphate, B.Vet.C.) for cattle, are effective for about four months. Trials initiated by Harvey, Sutherland and Moule (1953 and 1955) have resulted

in the use of copper glycinate intramuscularly in cattle and sheep, the doses being 120·0 mg. and 45·0 mg. of copper, respectively, equivalent to 400·0 mg. and 150·0 mg. of the glycinate (Allcroft, 1957). Copper sulphate may also be given as a food supplement at the rate of 2·0 G. daily for adult cattle and 1·0 G. daily for young stock. Top dressing of pastures is widely practised to offset soil deficiencies: in New Zealand, 5 lbs. copper sulphate per acre annually is found to be adequate, whilst in Australia as much as 20 lb. per acre and as little as 7½ lb. per acre have been reported adequate for a 2 year period, and 15 lb. for 3 years.

Other uses of copper sulphate are numerous. A 10 per cent. solution of copper sulphate will close the œsophageal groove of adult sheep. The anthelmintic action of copper sulphate is giving place to more efficient and less toxic drugs: 5–10 per cent. solutions are used as foot-baths after paring the feet of sheep affected by foot-rot; 0·03 per cent. of copper sulphate in sheep dips prevents the growth of Erysipelothrix and therefore prevents the post-dipping lameness which this organism may cause. Copper sulphate crystals have been used as a caustic dressing after docking lambs and after removal of warts; solutions containing up to 5 per cent. have been used as ringworm dressings.

For the destruction of *Lymnæa truncatula*, the snail intermediate host of the liver fluke, and other freshwater snails, it is usual to dissolve copper sulphate in pond water at a concentration of 5 parts per million and pastures may be dressed with the sulphate at the rate of 28 lb. per acre mixed with sand in the proportion of 1 part sulphate to 4 parts sand. The mixture should be applied twice yearly either in February and April to kill off over-wintering snails (B.V.A. publication, No. 6, 3rd Edit. 1955, p. 88), or in June and again in August when the snails are breeding most actively (B.Vet.C.). The interval between dressings should be about six weeks, according to the life history of the snail, so that the second dressing kills off snails hatched after the initial dressing has dispersed. Because of the danger of copper poisoning it is essential that at least one substantial fall of rain should occur before animals are grazed on the pasture, especially if the grass is short.

In reservoirs, copper sulphate at a concentration of 1 part per million will prevent overgrowth with algæ without killing fish, though 5 parts may be dangerous to fish.

One per cent. copper sulphate solution is also used in zinc phosphide poisoning of animals, when its action is one of precipitating the phosphorus compound as insoluble copper phosphide which can then be removed by purgatives.

Copper sulphate has been incorporated in pig food rations within recent years but there is still much that is unknown and the possibility of toxicity seems to outweigh any advantages from increased weight gains. Copper toxicity in sheep, pigs, and cattle is increasingly reported (Pearson, 1956; Bass *et al.*, 1956; O'Moore, 1956; Gordon and Luke, 1957; Marshall and Todd, 1957.)

Fluid Balance and Electrolytes

Approximately 70 per cent. of the body weight of an adult animal consists of water, of which about 50 per cent. is intracellular and 20 per cent. extracellular. Of the extracellular water, about 5 per cent. is present in the plasma and 15 per cent. is interstitial fluid. The total volume normally changes very little, although the body fluids in the different 'compartments' are constantly interchanging as metabolism proceeds: water is produced during intracellular oxidation (40·0 G., 55·0 G. and 107·0 G. of water are produced by the oxidation of 100·0 G. of protein, carbohydrate and fat, respectively), and diffuses under the influence of osmotic pressure out of the cell and into the interstitial fluid. The interstitial fluid normally accommodates the extra water long enough to allow the plasma fluid to take up the excess along with the metabolites which diffuse with it, and to carry it all to the organs of excretion—the kidneys and lungs. The interstitial fluid therefore acts as a cushion between the largest fluid compartment and the smallest, enabling intake and excretion of water to proceed without sudden stresses and strains on the limited capacity of the plasma volume.

The interchange of water between blood and tissues and the concentration of the electrolytes of the body are interdependent; an increase or decrease of one, though it may cause a temporary imbalance, is followed very soon by an equalizing increase or decrease of the other, although the concentration of the electrolytes varies only within fairly restricted limits. As with water, the electrolytes are constantly interchanging between the various body fluid compartments.

The electrolytes may be divided into cations, the most important being sodium, potassium, calcium and magnesium, and anions, principally chloride, bicarbonate, biphosphate and sulphate ions. There are also a number of organic acid anions, and proteins also ionize acidically, producing more anions. In plasma and interstitial fluids the predominant cation is sodium whilst the two main anions are chloride and bicarbonate, the former being in greater amounts. In the intracellular fluid, however, potassium, and to a lesser extent magnesium, are the only cations of significance whilst organic phosphate, protein, sulphate, and bicarbonate are the anions, the first predominating.

The method of interdiffusion of these electrolytes is not fully understood. However, it is known that the permeability of cell membranes is selective and that the permeability in one direction may be different from that in the other direction. Red blood cells are almost impermeable to sodium and calcium ions, fats and sugars, slightly permeable to amino-acids, but readily permeable to anionic radicles, phosphates, bicarbonates, chlorides and sulphates as well as bile salts, ammonia and urea. Sodium and potassium ions increase, while calcium ions decrease, the permeability. Tissue cells vary in their permeability, but in general potassium and phosphate ions are constantly interchanging between intra- and extracellular

fluids, whilst magnesium is almost static within cells, any magnesium acquired by the body or mobilized from the bone being distributed exclusively throughout the extracellular fluids.

The role of the electrolytes is complex for they influence the metabolism of the whole body. They are the major factor in the creation of osmotic pressures and take part in the buffer systems and pH mechanisms of the body; their concentrations regulate the enzyme actions and determine tissue irritability; they are essential for the transmission of nervous impulses through the polarity mechanism of cell membranes and take part in all chemical and physical reactions within the body.

It is apparent therefore that these electrolytes and the fluid necessary for their solution are absolutely essential and that any imbalance or losses will exert an influence on the whole body metabolism. This applies particularly to the young animal, in which the surface area (to which metabolic needs are directly related) is considerably greater in proportion to the extracellular water reserves: as an illustration, a cow weighing 1000 lbs. has an extracellular fluid component of about 200 lb. (20 per cent.) and a 100 lb. calf, 20 lb. extracellular fluid, thus the adult has a fluid reserve ten times greater than the calf and yet has a metabolic requirement (or surface area) only three or four times greater than that of the calf (Dukes, 1955). All young animals are similarly placed which accounts for their greater susceptibility to the effects of scouring and vomiting as well as to poisoning with electrolytes (salt poisoning, etc.).

Dehydration. The loss of electrolytes and fluid by an animal affected with severe diarrhœa and, or, vomiting can be a critical factor in deciding between life and death. Although this has been partially realized, especially when associated with surgical conditions. the full significance is not well enough appreciated and put into practice, mainly because of a general belief that the influence of a normal saline injection is too brief to be of clinical value. Where electrolyte balance is more or less unaffected the duration of effect may be short and intravenous injections of saline solution can be harmful, but in many medical conditions where dehydration is associated with electrolyte losses saline by *subcutaneous* injection should always be given. The action of such injections will be prolonged by renal saline retention so long as a negative electrolyte balance remains. In general, up to 6 per cent. of the body weight may be administered daily and chloride checks on the urine will indicate the success or otherwise, of the electrolyte replacement (chlorides precipitate with silver nitrate and do not redissolve in nitric acid but are soluble in ammonia.)

The simplest electrolyte solution available to combat electrolyte and fluid loss is Injection of Sodium Chloride, B.Vet.C., which consists of a solution of sodium chloride in water to the isotonic concentration of 0·9 per cent. w/v. A more complicated solution which is of greater value in electrolyte loss during gastro-intestinal disturbances is Compound Injection of Sodium Chloride, B.Vet.C., which contains 0·86 per cent. of sodium chloride, 0·03 per cent. of potassium chloride and 0·04 per cent of

hydrated calcium chloride; this is Ringer's solution. Where debility and starvation accompany dehydration these injections may be supplemented with 5 per cent. dextrose. The quantities of these injections used will vary with the species but the maximum daily quantity should not exceed the 6 per cent. of body weight as mentioned previously. This represents about 1½ pints for a 30 lb. dog (0·86 litres per 14·0 kg.), or about 6 pints per cwt. (3·6 litres per 50·0 kg. body weight) for farm animals. In practice a maximum single dose for horses and cattle is 3·0 litres (4¼ pints) and for dogs 100·0 ml.: these quantities can only be given subcutaneously with the assistance of hyaluronidase at a concentration of 1,000 turbidity units per litre. With hyaluronidase, 10·0 ml. per minute can be injected with no discomfort or lifting of the skin from the underlying tissues. The absorption rate is also increased.

Sodium Salts

The salts of this, the least toxic of the metals, are all white crystalline solids which are soluble in water, usually forming neutral or alkaline solutions.

Sodium Bicarbonate, B.Vet.C., is valuable externally as a dressing for the emergency treatment of burns and scalds, when it may be applied as a powder or aqueous paste: it is also included in dusting powders for its skin sedative action. Its alkalinity assists in removing ear wax and mucous from the mouth and eyes: 2 per cent. is strong enough. Internally, it may cause emesis in dogs by a local action but otherwise acts in the stomach as an antacid: in this context it is a poor compound for the treatment of hyperacidity for the carbon dioxide released by reaction with the hydrochloric acid causes distension of the stomach and reflex stimulation of further acid secretion—it thus is an *alkaline stomachic*. After absorption, the bicarbonate radicle joins the alkali reserve of the plasma, lymph and intracellular buffer mechanisms. In excess, alkalosis may occur, but the fact that the bicarbonate radicle is capable of being split with the formation of water and carbon dioxide makes elimination via the lungs relatively easy. Sodium bicarbonate is widely used in the treatment of the acidosis which frequently accompanies acetonæmia in cattle. Some of any excess bicarbonate is eliminated in the urine which is thereby rendered alkaline in reaction: this phenomenon is utilized in increasing the solubility and excretion rate of sulphonamides and uric acid. *Dosage* for horses is up to 2 oz. (60·0 G.), for cattle up to 4 oz. (120·0 G.), for sheep and pigs up to 120 gr. (8·0 G.), and for dogs and cats up to 25 gr. (1·5 G.).

Sodium Bromide, B.Vet.C., is a nerve sedative often incorporated in triple bromide tablets but rarely used on its own.

Sodium Carbonate, B.Vet.C., has a detergent and skin softening effect when applied externally though its main use is as a water softener (washing soda) and, as a 4 per cent. solution, a detergent disinfectant for routine cleansing after foot-and-mouth disease. It is rarely used internally because

of its local irritant action but this attribute may be utilized for causing emesis in poisoned dogs when a large crystal may be forcibly administered in an emergency. In other respects sodium carbonate acts in a manner similar to that of the bicarbonate.

Sodium Chloride, *B.Vet.C.*, has many other uses besides that of maintaining electrolyte and tissue fluid balance. Externally, isotonic or slightly hypertonic solutions make useful eye and wound lotions, oral and nasal washes: in markedly hypertonic solutions sodium chloride exerts a lymph lavage (lymphagogue) action by which the excessive osmotic pressure draws fluid through the wound giving it a mechanical cleansing as well as concentrating antibodies and macrophages in the area of the wound. Repeated washing with solutions of up to 3 per cent. are very effective where gross contamination is absent.

When given orally in the vomiting species emesis occurs: this is possibly the most widely used home remedy for poisoning in dogs. In the non-vomiting species sodium chloride acts as a saline purgative by the creation of a high osmotic pressure within the intestines: this draws fluid from the body and dilates the viscus, stimulating peristalsis. It is useful in all types of colic in horses and is sometimes used in cattle along with other saline purgatives. As with most purgatives small doses are laxative whilst large doses are purgative. After absorption, both the sodium and the chlorine ions enter the electrolyte system displacing equal amounts if the system is in balance but being retained along with water of solution if there is a negative imbalance. The total amount and the excretion of the salt and its water are controlled by a complex system which involves the posterior pituitary gland and the adrenal hormones. Excretion takes place through the kidney, the salt acting as a saline diuretic.

An interesting application of saline therapy concerned with the electrolyte balance is in the treatment of heat stroke and exertion cramps. During periods of excessive heat or exercise salt loss is proportionally greater than water loss through sweating and urine excretion and a negative chloride imbalance ensues which results in cramps, convulsions in severe cases, and a generalized alkalosis. Isotonic saline and concentrations of up to 10 per cent. of compound salts have been used in quantities of up to 1·5 litres for large animals; they are best given by intravenous injection. Salt is an essential dietary factor for all herbivores and rock salt should be freely available.

Toxicity following the ingestion of excessive quantities of salt by pigs and poultry has been reported, but provided water is supplied *ad lib.* these animals will tolerate relatively large quantities of salt.

Dosage for saline purgation in horses and cattle is up to 1 lb. (0·45 kg.) and as a laxative, diuretic and antipyretic in those species doses of up to 4 oz. (120·0 G.) may be given.

Sodium Citrate, *B.Vet.C.*, is mainly used as an anticoagulant in the injection of chloral hydrate intravenously for anæsthesia: a 1 per cent.

concentration of citrate is adequate. For preventing the clotting of blood taken for more or less immediate—one or two days—transfusion, 100·0 ml. of a 3 per cent. solution should be used for every 440·0 ml. of blood collected. For blood which may be kept for up to 21 days under refrigeration before use, acid citrate-dextrose solution should be used—the addition of the citric acid prevents caramelization during autoclaving. For each 500·0 ml. of blood taken 75·0 ml. of the acid citrate solution should be used: this contains 1·6 G. sodium citrate, 0·56 G. citric acid and 1·5 G. dextrose.

Since citrates are alkalizing diuretics, sodium citrate may be used in place of sodium bicarbonate when 1·5 times higher doses are required to achieve an effect equal to that of the bicarbonate.

Sodium Hydroxide, B.Vet.C., is infrequently used therapeutically although it is sometimes used as a caustic for destroying warts and in paste form for destroying the horn buds of calves and goats. It is difficult to limit the action of the preparation and disbudding collodia have widely superseded caustics.

Sodium Iodide, B.Vet.C., is used mainly for two purposes, the treatment of wooden tongue—actinobacillosis—in cattle and the treatment of ringworm in calves. Sodium iodide may be given intravenously, which is a distinct advantage over the potassium compound; it has also been given subcutaneously but this route is not recommended because of the danger of abscess formation. Wooden tongue usually responds to one intravenous injection but a second dose may be given a week after the first if necessary: the official injection, which is an 8 per cent. solution, is suitable in most areas, providing as it does about 1 oz. (30·0 G.) sodium iodide in each 400·0 ml., which is the common commercial volume. A 16 per cent. strength is used by many practitioners who find that larger doses than 1 oz. are sometimes necessary. It should be remembered that pregnant animals should not be injected if it can avoided owing to the danger of causing abortion.

The doses for ringworm in calves can be calculated on an age basis: 420 gr. (28·0 G.) may be given to the average six month old calf (younger animals should not be dosed) and 960 gr. (64·0 G.) for adults over 2 years. A linear graph will provide the dosage for any animal between these ages (Crawshaw, 1957).

Sodium Acid Phosphate, B.Vet.C., is a urinary acidifier and diuretic. In this respect it differs from other salts of sodium. The excess phosphate is excreted as sodium orthophosphate which is converted in the tubules to the acid phosphate, making sodium ions available for resorption. Sodium acid phosphate has been used as a soluble salt which can be injected intravenously to make phosphate ions rapidly available in the treatment of the hypophosphatæmia of the milk fever complex of cattle.

It is also administered by mouth, often as maintenance doses after an initial dose by injection. This therapy is less satisfactory than proprietary injections which usually contain hypophosphites.

Dosage as a urinary acidifier for use in conjunction with hexamine in dogs and cats is 5–15 gr. (0·3–1·0 G.) given three times daily. In cattle, 1 oz. (30·0 G.) may be given initially followed by half this dose twice daily.

For small animals, sodium acid phosphate is available in tablet form combined with an equal quantity of hexamine. In cattle, the dose may be dissolved in 500·0 ml. for injection and for oral dosing.

Sodium Propionate, B.P.C., is a non-irritant fungicide used against ringworm in 5–10 per cent. lotions and creams. However, the bulk of this deliquescent salt used annually is administered for the treatment of acetonæmia in cattle following reports by Schultz (1952) and Shaw and his co-workers (1952). The rationale of this therapy is related to the fact that soluble carbohydrates, including glucose and treacle, are not absorbed as such following oral administration to ruminants owing to the conversion by ruminal bacteria of these carbohydrates to volatile fatty acids (Schambye & Phillipson, 1949). In acetonæmia, increases in fatty acid absorption are to be discouraged and the absorption of the immediate precursors of glucose encouraged: glycerol, propylene glycol, lactates, and propionates including sodium propionate, are such precursors; acetates are glucose sparing substances. *Doses* vary from 2–8 oz. per day (60·0–240·0 G.) for four to ten days: a common method is to give eight ounces as an initial dose and follow it with four ounces twice daily for four days. Mineralized mixtures are available commercially, the addition of cobalt in particular is useful in promoting a healthy appetite following bacterial synthesis of vitamin B_{12}.

Sodium Sulphate, B.Vet.C., or Glaubers Salts, is a saline purgative and diuretic, but although it has been stated to be more reliable than magnesium sulphate, the latter is preferred in Great Britain and is in constant daily use.

Dosage is much the same as for magnesium sulphate.

As a purgative:	Cow:	½–1 lb. (0·24–0·48 kg.)
	Sheep:	2–4 oz. (60·0–120·0 G.)
As a laxative and diuretic:	Horse:	1–2 oz. (30·0–60·0 G.)
	Cow:	2–4 oz. (60·0–120·0 G.)
	Sheep:	¼–½ oz. (7·5–15·0 G.)
	Pig:	½–1 oz. (15·0–30·0 G.)

The drug is often given in an exciccated form to save bulk in packing. Doses are slightly greater than half those of the hydrated salt.

Sodium Thiosulphate, B.Vet.C., is familiarly known as 'hypo'. Apart from its use as a photographic fixative, this salt of sodium has very little use although it has been recommended for the treatment of arsenic and cyanide poisoning. For arsenic poisoning, doses for horses and cattle of 120–180 gr. (8·0–12·0 G.), for sheep of 15–30 gr. (1·0–2·0 G.), and of 7½–15 gr. (0·5–1·0 G.) for dogs, by intravenous injection have been suggested. The dose should be repeated twice with an interval of 6 hours between. Solutions of from 10–30 per cent have been used. The oral administration of 1–2 oz. (30·0–60·0 G.) in about ½ pint (250·0 ml.) water is suggested in horses and cows and smaller doses for other species. Recent investigations suggest that this treatment has no appreciable effect on the course of the poisoning.

It is probable that the chelating compounds such as Sodium Calcium-edetate, B.P.C., will prove more successful, in poisoning by arsenic at any rate.

In cyanide poisoning, treatment can rarely be attempted, but where it is possible a combined treatment with sodium nitrite and sodium thiosulphate may be tried. In horses and cattle, 10·0 ml. of a 20 per cent. solution of sodium nitrite should be injected intravenously followed immediately by up to 50·0 ml. of a 20 per cent. solution of thiosulphate: sheep require 10·0 ml. of a 10 per cent. nitrite solution and 20·0 ml. of a 10 per cent. thiosulphate solution: in the dog, sodium nitrite in doses of 1·0 mg. per lb. body weight (2·2 mg. per kg.) as a 1 per cent. solution should be followed by a 25 per cent. solution of sodium thiosulphate at the rate of 0·5 G. per lb. (1·1 G. per kg.). All injections should be given slowly and repeated if necessary using half the above doses.

Potassium Salts

Like sodium, potassium is an alkali metal and forms salts which possess similar characters and react similarly to their corresponding sodium salts: in general, they are more active than sodium salts. The salts of clinical importance are crystalline water soluble compounds, which are mainly white in colour although potassium permanganate and sulphurated potash are exceptions.

Although potassium ions are essential as intracellular electrolyte ions and are present in the blood to the extent of about 20·0 mg. per 100·0 ml. of serum, it must be remembered that an excess of potassium ions will first slow and disturb the rhythm of the heart and then cause a progressive ventricular block and finally cardiac arrest: if injections are given slowly, very little signs of impending heart arrest are shown until the critical blood level is reached when the cardiac effect suddenly becomes pronounced. In cattle given potassium chloride intravenously in accordance with Carlstrom's (1950) suggestions on the therapy of acetonæmia, the main signs of impending toxicity have been uneasiness and restlessness with a marked grinding of the teeth. Normally, NO POTASSIUM SALT SHOULD BE INJECTED INTRAVENOUSLY.

Potassium Bicarbonate, B.Vet.C., is used in the same way and in the same circumstances as sodium bicarbonate, which is usually preferred because it is less expensive. As a urinary alkalizer and diuretic for carnivores potassium bicarbonate, as with all potassium compounds, is superior in action to the sodium salt because of its lower renal threshold.

Potassium Bromide, B.Vet.C., is a nerve sedative that has been widely used in human medicine and finds a small place as a hypnotic sedative in dogs and very occasionally pigs. The bromide ion is pharmacologically identical with the chloride ion from which the body is unable to distinguish it, but there is one significant difference and that concerns the bromide sedative effect on the central nervous system. As the bromide ion is absorbed and excreted in proportion to its concentration in the intestines and blood respectively, it displaces chloride ions and can thereby accumulate, especially if chloride intake is relatively low. It is advisable, therefore, to have a 24 hour break periodically if dosing is protracted. The main use of potassium bromide is in the control of pubertal puppies which show signs of sexual hyperexcitability. It is also useful as a sedative for nervous and excitable animals during thunder storms and on the occasions of fireworks displays. Such uses have been largely superseded by tranquillizers.

Dosage for dogs is from 5–15 gr. (0·3–1·0 G.)

Potassium Carbonate, B.Vet.C., is very deliquescent, and though it is active in a manner similar to that of the sodium salt, it finds little use other than as a keratin softener which aids in the penetration of antiparasitic dressings: 8 per cent. was incorporated in the old sulphur lotion used against sarcoptic mange in horses.

Potassium Citrate, B.Vet.C., has an anticoagulant action but may not be used in blood transfusion work. It has been widely used in man as an oral alkalizing diuretic, for it is readily absorbed from the intestines and excreted as the bicarbonate via the kidneys. In large doses it is a saline laxative. *Dosage* for the dog is up to 30 gr. (2·0 G.) two or three times daily.

Potassium Chlorate, B.Vet.C., is an oxidizing agent and has been used as an oxidizing antiseptic for many years. More recently, doubts have been expressed concerning its efficiency because it has been shown to release its oxygen with difficulty. Nevertheless, it has been incorporated in mouth lotions and demulcent electuaries in concentrations of 1–2 per cent. Large oral doses will have a laxative and diuretic action. Potassium chlorate has also been used as a treatment for acetonæmia, mainly as a means of supplying potassium ions to ensure that intracellular potassium is adequate for normal glucose metabolism: the chlorate ion is excreted unchanged. Daily oral doses of about 2 oz. (50·0–70·0 G.) have been given for from three to five days. Glucogenic and glucose sparing compounds are superior in their effect.

If potassium chlorate is used *it must not be triturated* owing to the danger of explosion.

Potassium Hydroxide, B.Vet.C., is very hygroscopic and has a strong caustic action. Its uses and disadvantages are the same as for sodium hydroxide. Its main use is in the form of Solution of Potassium Hydroxide, B.Vet.C., a 5 per cent. solution in water, as an agent for breaking up skin scrapings to release the ectoparasites buried in the skin tissue.

Potassium Iodide, B.Vet.C., is used pharmaceutically to obtain a solution of iodine in water and alcoholic-aqueous solutions. Therapeutically its main use has been as an oral treatment for 'wooden tongue' (actinobacillosis) in cattle as an alternative to sodium iodide (*q.v.*). It is given in doses of about 120 gr. (8·0 G.) twice daily, but must not be injected intravenously. Symptoms of iodism (iodine poisoning) may develop, in which case mercuric iodide with potassium iodide in equal quantities should be given at the rate of 2–5 gr. (0·2–0·3 G.) of mercuric iodide twice daily in ½–1 pint of water (0·5 litre) until the symptoms disappear—usually about one week. Potassium iodide increases the fluidity and quantity of the secretion of bronchial, salivary, lacrimal and similar glands, and is therefore incorporated as an expectorant in cough mixtures. Potassium iodide is said to depress the production of lymphocytes and has therefore been used to treat avian lymphomatosis. Intraperitoneal injections of 5·0 ml. of a 10 per cent. solution on two successive days have been suggested: the results have been disappointing. For the same reasons it is commonly used in tonsillitis.

Dosage for horses is up to 120 gr. (8·0 G.), for cattle up to 240 gr. (16·0 G.), for sheep and pigs up to 45 gr. (3·0 G.), for dogs up to 10 gr. (0·6 G.), and for cats and poultry up to 2½ gr. (150·0 mg.)

Potassium Nitrate, B.Vet.C., is probably the widest used diuretic in cattle but is used infrequently in other species because of its irritant tendency. For this latter reason it should not be used in cases of nephritis. The diuresis is caused by a saline (osmotic) action: it is one of the strongest urinary alkalizers which is probably the reason for its irritant effect. Externally, mixed with ammonium chloride and water in a ratio of 1 : 1 : 16, potassium nitrate has a refrigerant effect.

Dosage for horses and cattle is 30–180 gr. (2·0–12·0 G.), for sheep and pigs 15–30 gr. (1·0–2·0 G.). The usual dose for cattle is about 60 gr. (4·0 G.) given twice or three times daily.

Potassium Permanganate, B.Vet.C., is known to everyone as an astringent and deodorant antiseptic for use as mouth washes and gargles. Its action is one of oxidation, during which the permanganate is reduced: it is one of the few coloured salts of potassium, the long crystals having a purple metallic lustre. Solutions when dilute are pink but concentrated ones are a deep purple; reduction changes them to a dirty brown as manganese dioxide is formed. Solutions of 1 in 1000 (¼ gr. per fl. oz. or 1·0 G. per litre)

are used for local application to ulcerated areas in the mouth, but for general washing one quarter of this strength should be used. Although potassium permanganate is said to be ineffective for snake bite it is carried by many people exposed to danger: the action is an oxidative destruction and, if crystals are rubbed into a cruciate incision over the site of the fang marks, the treatment is reputed to be life saving if applied within 5 minutes of the bite and after double ligatures have been applied (Sollmann, 1943).

Perhaps the most useful attribute of potassium permanganate is its power to liberate formaldehyde gas from formalin. For fumigation purposes, 1½ oz. (45·0 G.) of permanganate in 2½ fl. oz. (75·0 ml.) of formalin are required for every 100 cubic feet. Ammonia will clear the air after fumigation which should continue for about 12 hours. (Heat and splash proof containers are necessary, for much heat is generated and sudden evolution of gas may splash hot fluid around. Permanganate stains may be removed with hydrogen peroxide and a dilute acid (dilute acetic, oxalic or sulphurous acids.)

Calcium, Magnesium and Phosphates

Although all three ions have important electrolyte functions, especially in the acid/base buffer systems, the part these ions play in tissue metabolism is more important clinically, as a reference to pathological conditions in which the three are involved will show: rickets and osteodystrophia, milk fever, milk tetany in calves and hypomagnesæmia in adults, uterine inertia, and sterility are some of the more important ones. In many of their functions the three ions are interrelated, although this is not always the case, for in hypomagnesæmia the calcium and phosphate blood levels are unaffected whilst the magnesium levels may be almost undetectable: likewise in ordinary milk fever the calcium and phosphate levels may be extremely low whilst the magnesium levels may be normal or higher than normal.

Calcium, magnesium and phosphates are present in the extracellular fluids in relatively small amounts when compared with sodium, bicarbonate and chloride ion concentrations, but the intracellular fluids contain large amounts of magnesium and phosphate ions as well as of potassium. The normal concentrations of the minerals and phosphates in the blood are detailed on p. 195 of Banham's Vet. Surg. Vade Mecum, W. A. Greig, 8th Edit. p. 195, Bailliére, Tindall and Cox).

Should the 'mineral' concentrations in the blood fall below minimal levels (which are slightly variable according to seasonal and individual fluctuations), a condition is precipitated which is known in cows as milk fever but in most other species as eclampsia. If the magnesium level alone is affected the condition resulting is known as hypomagnesæmia.

The Milk Fever Syndrome. The variety of symptoms which collectively constitute the syndrome are related to acute pathological decreases in the blood levels of calcium, magnesium and the phosphates: the deficiencies are referred to respectively as hypocalcæmia, hypomagnesæmia and

hypophosphatæmia. Hypomagnesæmia may occur at times other than near to calving whereas the other two are always closely related to calving. The *ætiology* of the condition is still largely a matter of conjecture but, summarizing the present theories, it would appear that the main exciting cause is the drain of calcium and of phosphates into the colostrum at the time of calving, and though this occurs in normal cows at calving, the milk fever cow is unable to compensate for this drain. The inability to cope with this sudden call for minerals may be due to lack of mobilizable reserves or to disorganization of the process of mobilization either through an enzyme or a hormone imbalance, or a combination of both.

Analysis of the *incidence* of the condition shows that it occurs in both dairy and beef cattle, but that in the former the disease is predominantly a calcium and phosphate imbalance whereas in beef breeds it is the hypomagnesæmic type which seems more frequent. The majority of cases occur within two days before and three days after calving. Age, and therefore the number of pregnancies undergone, is a predisposing factor—most cases appear to occur with or after the third pregnancy, presumably as the mineral reserves become depleted. Climatic conditions appear to affect the incidence and 'magnesium' cases appear to be precipitated by cold weather, especially if such spells occur intermittently and alternate with mild wet periods. This may be partly correlated with increases in the growth rate of grass but probably also with a lowering of the animals resistance or even an induced metabolic effect on mineral levels.

Hypomagnesæmia, which is a complicating factor in the diagnosis of milk fever, is less related to calving than hypocalcæmia and hypophosphatæmia. As Barker (1948) and Allcroft (1947) indicated, magnesium blood levels show a seasonal fluctuation, being highest at the end of a normal summer and lowest at the end of winter just before the spring flush of grass. Green (1948) describes the occurrence of two types of clinical hypomagnesæmia—an acute type which usually occurs following abrupt changes of diet, especially from indoor feeding to outdoor grazing on fresh leys. Aftermath grazing may sometimes precipitate an outbreak. The subacute type is usually recurrent and indicates a border-line low blood magnesium level. Cases may be precipitated by cold, wet periods, and often follow œstrus (Smythe, 1956). Most cases occur between November and early March, but if the cold weather persists, as in the spring of 1958, the season may be prolonged. When low calcium levels also occur and the animal calves, milk fever may occur in which calcium, phosphate and magnesium are all implicated: the 1958 and 1959 calving season were unprecedented in this respect.

The *biochemistry* of milk fever is largely unknown. Calcium, magnesium, and phosphate ions are all vitally linked in blood, bone, muscle, and nerve metabolism. They work essentially in equilibrium and, should the concentration of any one member of the three-cornered equation be changed, the function of the other two, and various related coenzyme systems, are also disturbed. Calcium and magnesium are both associated with the

depression of nerve and muscle irritability: calcium depresses the stimulant effect of sodium on skeletal muscle and raises the threshold of nerve response: magnesium depresses skeletal muscle and peripheral nerve reaction—tendon reflexes are most sensitive to magnesium depression (or the lack of it). The action of magnesium on muscle and nerves appears to be exerted at the myoneural junction and the nerve synapses (Blaxter *et al.*, 1954). A lack of calcium and magnesium will therefore precipitate nerve and muscle hyperexcitability.

Magnesium is also necessary in the coenzyme system of *phosphatase 1*, which is involved in calcium and phosphate deposition in the bone, and also the coenzyme system concerned in glycogen, adenosine triphosphate and creatine phosphate reactions which are essential for producing the energy required for muscle contraction. Phosphate ions also play a large part in these enzyme systems concerned with producing energy for the muscles:

Adenosine triphosphate (ATP) → adenosine diphosphate (ADP) + inorganic phosphate → energy for muscle contraction. The ADP formed reacts with creatine phosphate to form creatine and ATP, while the creatine is reconverted into creatine phosphate, using energy supplied by the tricarboxylic acid cycle in which phosphates also play a part. If phosphate ions are not freely available the production of energy is curtailed and muscular contraction is weakened proportionally. This is reflected in the symptoms of hypophosphatæmia which are typically those of a recumbent cow unable to rise or stand.

The *blood picture* in milk fever is by no means constant. The normal values of serum calcium, magnesium, and whole blood inorganic phosphate of from 8·5–11·5 mg., 1·8–3·2 mg. and 3·5–6·0 mg. respectively (averages 10·0 mg., 2·5 mg. and 5·0 mg.) per 100 ml. show significant changes at normal parturition, with considerable falls in calcium and phosphate and a rise in magnesium. These falls of calcium and phosphate are exaggerated in milk fever animals but the magnesium levels may fall, rise or stay normal. Levels below 7·0 mg. calcium, 1·6 mg. magnesium, and 2·5 mg. phosphate may be considered pathological, although exceptions do occur and in Channel Island cattle normal magnesium levels are higher than in other breeds.

The *symptoms* of milk fever cannot easily be correlated with the blood picture. Uncomplicated milk fever is accompanied by dullness, a dry nose, a dilated pupil, a constricted anal sphincter and a disinclination to eat. 'Paddling' of the hind legs, with stiff extended joints and nervousness due to lessened muscle control, precede collapse, and a period of narcosis in which the neck may be typically kinked may follow. Finally, coma supervenes in which the head may be turned onto the flank. This sequence of symptoms is not commonly seen today.

Acute hypophosphatæmia occurs very commonly in the modern form of milk fever. The lack of blood phosphate is correlated with muscle weakness: a typical case will show acute lumbar pain, parturient œdema

of the brisket and udder, and be unable to rise. In many cases calcium injections allay the more acute signs but the animal, though apparently normal, is unable to rise; in other cases, probably where calcium levels are also low, there is a temporary improvement but the animal relapses a few hours later and rarely responds to a second injection. These cases usually become chronic if treated first with calcium and may stay recumbent for several days, even if subsequently treated with phosphorus injections.

The typical hypomagnesæmic milk fever case shows what is known in some areas as 'the blinks'—a fluttering of the eyelids: the animal is extremely hypersensitive, shows muscular tremors and may move in circles, occasionally appearing to 'attack' attendants: the pupil is often constricted and the anal sphincter flaccid. Convulsions may occur and the animal falls to the ground: the stimulus of inserting a needle may be sufficient to induce a fatal spasm.

Treatment of the uncomplicated hypocalcæmia case is fairly straightforward and failure to respond to plain calcium borogluconate injections is not frequent. It is common practice to inject 400 ml. of a 40 per cent. calcium borogluconate solution intravenously and provide a maintenance reservoir by injecting 400 ml. of a 20 per cent. solution subcutaneously.

If the cow is recumbent and suspected of suffering from hypophosphatæmia, with or without hypocalcæmia it is advisable to inject phosphorus solutions intravenously immediately—either 1 oz. (30·0 G.) of sodium acid phosphate in approximately 400 ml. of water or preferably one of the commercial phosphorus injections which usually contain small amounts of calcium as well as phosphorus, usually in the form of hypophosphites (White, 1952; Hemsley, 1957). Oral dosing with 3 oz. (90·0 G.) of acid sodium phosphate every eight hours has also been practised. Where there is acute lumbar pain and it is desirable to have the animal on her feet as quickly as 'normal' milk fever cases, intravenous analgesics (e.g. Novalgin) have been most successful (Steele-Bodger, 1957). It is possible that 'tranquillizers' may prove useful for this purpose.

Hypomagnesæmia cases can be treated by combined calcium, phosphorus, and magnesium injections, magnesium-dextrose injections, calcium borogluconate with magnesium injections, or by plain 25 per cent. injections of magnesium sulphate. Magnesium sulphate should normally be given by subcutaneous injection but the others may be given by any parenteral route. Owners should be warned before commencing treatment that hypomagnesæmic animals may die as soon as the needle is inserted—explanations are less likely to be believed after the event.

Acetonæmia is a complicating factor in milk fever. Complex calcium, magnesium, phosphorus, and dextrose solutions should be used in these cases, but where acetonæmia persists it should be dealt with by normal methods once the mineral levels are corrected. Cortisone derivatives, ACTH, glycerin and propylene glycol, propionates, acetates and lactates, as well as glucose injections, may be used.

Prophylactic measures have been investigated in recent years. Ender *et al.*

(1956) and Boda *et al.* (1956a) have shown that high protein and calcium diets during pregnancy predispose cows to attacks of milk fever. Low calcium and high phosphorus diets during the dry period before calving have therefore been suggested: this is provided by hay and concentrate mixtures supplemented by the addition of monosodium phosphate in the proportion of 1·5–5 per cent. of the basic ration (Boda, 1956). It has also been shown by Hibbs (1950), Hibbs *et al.* (1951) and Boda *et al.* (1956b) that daily doses of 10–30 million units of vitamin D_2 for up to 7 days before calving will reduce the incidence of milk fever. Swan (1952) pointed out the considerable dangers attaching to overdosing and drew attention to the widespread deposition of calcium in the blood vessels and organs. The vitamin prophylaxis is therefore limited by the inability to correctly anticipate the calving date. Prophylaxis against hypomagnesæmia is now being practiced on a large scale by the inclusion of calcined magnesite in the food at the rate of 1–3 oz. (30·0–90·0 G.) per head daily (Allcroft, 1953 and 1954). More recently it has been shown that hypomagnesæmia in grazing cattle can be controlled by the application of magnesian limestone or calcined magnesite in quantities of 2½ tons and 10 cwt. per acre respectively—these quantities supply the same amount of magnesium. (Parr and Allcroft, 1957).

Calcium Salts

The salts of this alkali metal are white or off white amorphous or crystalline powders, many of which have a low water solubility. The insoluble salts are relatively inert externally and act as skin sedatives; internally they also tend to have a gastro-intestinal sedative and anti-diarrhœic action. Absorption of calcium is conditioned by three main factors: 1. *The intestinal pH.* An acid pH tends to promote absorption by encouraging ionization, whereas an alkaline pH is detrimental to absorption by encouraging precipitation of insoluble salts. 2. *The calcium-phosphorus ratio* in the diet is an important factor in calcium and, of course, phosphate absorption. The optimum ratio is about 1·5 to 1. 3. *Adequate amounts of vitamin D* are essential for normal calcium metabolism, including absorption. If vitamin D concentrations are maintained, fairly wide calcium-phosphorus ratios can be tolerated: ratios of from 1·2 to 1 and 3·3 to 1 have been tolerated by calves when vitamin D was freely available (by sunlight). In general, vitamin D deficiency, a high phosphorus diet, excess fatty acids in the diet, alkali therapy and chronic diarrhœa are all detrimental to calcium absorption. It should be remembered that normally about 2/3 of any oral dose will be excreted in the fæces, though a small proportion of the fæcal calcium is excreted from the blood into the large intestine: the remainder is excreted in the urine. Where a calcium deficiency exists these proportions will not obtain.

In the blood, calcium exists partly as ionized calcium and partly as protein bound calcium: it is thought to be the ionized calcium which is

the active portion. The amount of calcium in the blood (9·0–15·0 mg. per cent.) is conditioned partly by the phosphate level and partly by the parathyroid hormone.

The principal functions of calcium are:

1. The provision of a rigid skeleton and teeth. About 99 per cent. of the body's calcium is found in bone and teeth.
2. The maintenance of normal function of the nervous and muscle systems; it is also essential for normal cardiac function.
3. Calcium is one of the basic ions which play an important part in the regulation of the acid-base balance: it is required in a definite ratio to potassium and sodium.
4. The clotting mechanisms of both blood and milk are dependent on the presence of adequate concentrations of calcium.

Calcium has an antagonistic effect to the cardiac stimulant action of potassium and also to the depressant effect of magnesium, although both are voluntary muscle depressants. It also has an antagonistic effect to the toxic actions of chlorinated hydrocarbons (carbon tetrachloride, tetrachlorethylene, chloroform etc.)

Calcium Carbonate, B.Vet.C., and *Chalk, B.Vet.C.*, are white or off-white powders, the former being microcrystalline and the latter, which is a native form of the carbonate, amorphous. Both are almost insoluble in water but in other respects act in the same way as any carbonate. Both may be used as cheap skin sedatives and diluents for more expensive and more active powders for external application. Internally, the antacid effects of all carbonates are exerted, including the reflex stimulation of more acid. They have a general mechanical gastro-intestinal sedative action by coating the mucous membrane with an inert, protective layer: this also has a mild antidiarrhœic effect. Chalk is also used as a calcium supplement in feeding, but steam bone flour (sterilized bone meal) is preferred because of its phosphorus content and the correct physiological ratio of the two.

The *dosages* for cattle and horses are 1–4 oz. (30·0–120·0 G.), for sheep and pigs, 120–240 gr. (8·0–15·0 G.), and for dogs and cats up to 60 gr. (4·0 G.). The doses of these compounds are determined more by their bulk than their activity.

Chalk is incorporated in Aromatic Powder of Chalk, B.Vet.C., and Aromatic Powder of Chalk and Opium, B.P. The latter contains the equivalent of 0·25 per cent. anhydrous morphine and is therefore controlled by the D.D.A. Both drugs are used in dogs at the same dosage rate as the plain chalk and for the same gastro-intestinal sedative action.

Calcium Gluconate, B.Vet.C., and *Calcium Borogluconate, B.Vet.C.*, are perhaps the most widely used salts of calcium. Calcium gluconate is only slowly soluble in cold water (1 : 30) but is slightly more soluble in boiling water (1 : 5). By the addition of boric acid in the proportion of about

1 : 5 (17 : 83) the gluconate can be changed into borogluconate, with a solubility in cold water of 1 : 5 (20 per cent.) and in hot water of over 50 per cent.; such solutions remain stable on cooling.

Calcium borogluconate is used for the treatment of hypocalcæmia in all species and by all parenteral routes. It is also useful as an antidote to overdosage with magnesium salts and chlorinated hydrocarbons. In the early days of calcium therapy of milk fever, intravenous injections of calcium chloride were used but, though the salt was suitably soluble in water, any extravascular leakage caused extensive sloughing. Attention then turned to the use of calcium lactate, which, though less soluble was also less irritant: it nevertheless frequently caused sloughs following perivascular injection and in 1930 Grieg reported on the use of calcium gluconate. This too caused some irritation and occasional sloughs following subcutaneous injection, so that the more soluble and therefore more rapidly absorbed borogluconate superseded it. The search for more suitable calcium preparations continues and within recent years the calcium salt of levulinic acid, itself a derivative of hexose sugars, has been tried experimentally. Advantages of calcium levulinate are its greater solubility and higher calcium content (13 per cent. w/v against 9 per cent. of the gluconate). Even so, its clinical effects appear to be no better than those of the borogluconate and certainly do not justify preference over the cheaper gluconate.

Dosages of calcium borogluconate are:

Horse and Cow:	2–6 oz. (60·0–180·0 G.)
Sheep and Pig:	90–300 gr. (6·0–20·0 G.)
Dog and Cat:	15–75 gr. (1·0–5·0 G.)

Aqueous solutions of up to 20 per cent. w/v strength are suitable for subcutaneous injection (10 per cent w/v is better for small animals), but stronger solutions should be administered intravenously. All injections should be given at blood heat, especially subcutaneous injections which should also be well dispersed by massage or the use of hyaluronidase at the rate of about 75 units per 400–500 ml. It is now common practice in cattle to give 400·0 ml. of a 40 per cent. w/v solution intravenously and an equal volume of 20 per cent. w/v subcutaneously, the latter injection ensuring a fairly sustained blood level. In eclampsia of the bitch, about 20·0 ml. of a 20 per cent. w/v solution is usually adequate: for lambing sickness in sheep and parturient eclampsia of the sow, 100·0 ml. of a 20 per cent. w/v solution are sufficient.

Sodium Calciumedetate, B.P.C., which is known commercially as Calcium Versenate, is described as the calcium chelate of disodium ethylenediamine tetra-acetic acid. The clinical importance of this compound is its ability to replace its calcium by the ions of heavy metals but particularly those of lead and mercury. The resulting soluble compound is un-ionized and the lead contained is therefore to all intents removed

from the circulation: actual removal occurs by renal excretion. The calcium chelate has proved extremely useful in the treatment of acute lead poisoning in horses (Holm *et al.*, 1953) and in calves (Holm *et al.*, *loc. cit;* Lewis and Meikle, 1956; O'Moore, 1956b; Todd, 1957; Hammond and Sorenson, 1957; Westermarck, 1957).

Dosage suggested for the horse was 1·0 G. per 30 lb. (13·6 kg.) given by intravenous drip of a 2 per cent. solution daily for three days followed by an interval of 3–5 days and then a further three-day course. Following experience with cattle it is probable that intermittent dosing will be just as successful as drip techniques. In calves, subcutaneous intermittent dosing appears to be just as successful as drip techniques: intermittent injections of solutions of up to 25 per cent. concentrations have been used at the same dosage rate as for the horse, but more recent experience indicates that subcutaneous injection is far too painful and that single doses of from 3·0–6·0 G. according to size, given intravenously are to be preferred: a second dose may be given two or three days later if necessary. Westermarck indicates that 0·05 G. per kg. is toxic to sheep.

Calcium Hydrogen Phosphate, B.Vet.C., an insoluble calcium salt, is used as an alternative to steam bone flour as a calcium and phosphate supplement for the treatment of calcium and phosphorus deficiencies (acalcicosis and aphosphorosis) but is not of any value in acute conditions.

Dosages of up to 180 gr. (12·0 G.) in horses and cattle, up to 30 gr. (2·0 G.) in sheep and pigs, and up to 10 gr. (0·6 G.) in dogs and cats may be used in the therapy of rickets. Attention should be paid to the calcium—phosphorus ratio in dry cows in which a low calcium—high phosphorus ratio is advisable as a prophylactic against milk fever (*q.v.*).

Calcium Hydroxide, B.Vet.C., finds a use in the form of lime water, Solution of Calcium Hydroxide, B.Vet.C. Externally, equal parts of lime water and linseed oil (Carron oil) were used as a dressing for extensive burns, but sodium bicarbonate pastes are preferable. Internally, lime water is weak antacid and gastric sedative but finds a better use as an antidote to overfeeding in calves and foals when excessive quantities of milk form large undigestible masses of curd which produce scouring. Administration of 2–4 fl. oz. of lime water prior to suckling will both diminish the appetite and aid the formation of smaller, more easily digested milk clots.

Calcium Lactate, B.Vet.C., is used mainly in conjunction with vitamin D for the treatment of rickets in small animals in doses of 5–10 gr. (0·3–0·6 G.) two to three times daily. Calcium Sodium Lactate, B.Vet.C., is used for the same purpose but is more soluble and more easily absorbed. In severe cases of rickets it is also advisable to provide bilateral support with plaster bandaging to prevent 'bowing': both legs must be bandaged, for otherwise the major part of the weight will be taken by the unbandaged leg on the opposite side and severe bowing of that leg may then occur, even when not

apparently affected in the first place. It should be remembered that parathyroid hormone is destroyed when administered orally and calcium and parathyroid tablets are therefore no better than the plain calcium tablet.

Exciccated Calcium Sulphate, B.Vet.C., is popularly known as Plaster of Paris. When mixed with water this insoluble amorphous powder contracts and sets hard. It is used as external splinting for fractured limbs and those affected with rickets. The plaster is most frequently used in the form of an impregnated bandage which may be applied in moistened strips or rolled on after moistening the whole bandage. The contraction which occurs as the plaster hardens should be remembered and joints should be protected by cotton wool or prior bandaging with ordinary bandage. In all cases the joints above and below the affected bone should be immobilized in the plaster, and the feet of small animals are best incorporated to prevent constriction and swelling. When applying bandages they should not be twisted or applied in ridges, for such applications become points of friction or stricture. Plaster casts once hardened should not be allowed to become wet or they will become soft: a full 30 minutes should be allowed for hardening.

Phosphorus Compounds

It is usual to supply phosphate along with calcium in the ratio of 1·5 or 2 parts calcium to 1 part phosphorus. Steam bone flour is the obvious substance to supply both calcium and phosphorus in the correct ratio. Acid sodium phosphate (*q.v.*) is a soluble form of phosphorus for use in acute hypophosphatæmia and may also be used orally in more chronic conditions and as a phosphate supplement for milk fever prophylaxis (*q.v.*). Most commercial injections for hypophosphatæmia contain hypophosphites.

Zinc phosphide is used as a rat poison and may be responsible for poisoning domestic animals. Symptoms are those associated with gastroenteritis and with liver and kidney damage. Antidotal treatment aims at preventing the absorption of the phosphide remaining in the intestines. One per cent. copper sulphate solution administered more or less *ad. lib.* precipitates insoluble copper phosphide which can then be removed either by saline laxatives or, in dogs, by liquid paraffin. Oleaginous purgatives should not be used for they encourage the formation of soluble phosphides and their subsequent absorption.

Magnesium Compounds

The salts of this alkali metal which are of clinical value may be divided into the amorphous insoluble salts and a single crystalline soluble compound. The carbonates, oxides, and the trisilicate are the insoluble compounds, and magnesium sulphate the soluble substance. When administered orally these magnesium salts may be divided into three groups according to their clinical effects which are dependent on their individual

solubilities in the gastro-intestinal fluids: the relatively insoluble compounds are unreactive and have an antidiarrhœic action due to mechanical coating (magnesium trisilicate); the slightly soluble salts are laxative (magnesium carbonate and magnesium oxide), whilst the soluble compounds have a strong purgative action (magnesium sulphate). Magnesium is not very easily absorbed, though a restricted water supply following the administration of magnesium sulphate to a dehydrated animal may result in the absorption of sufficient magnesium sulphate to cause severe nervous system depression and anæsthesia. The absorption of magnesium is thought to be in the form of magnesium bicarbonate ($Mg(HCO_3)_2$). This cannot be formed in the presence of excessive amounts of calcium and phosphates or fats—the calcium takes up the bicarbonate radicals, the phosphate forms insoluble triple phosphates of magnesium, and fats form dibasic soaps which are insoluble: alkaline pH's are detrimental to magnesium absorption. The magnesium ion is essential for normal bone metabolism, normal nerve and muscle irritability (low magnesium blood levels are accompanied by tetany and convulsions—milk tetany in calves, grass tetany, stomach staggers or Hereford disease in adult cattle), for normal carbohydrate metabolism, in which it links up with phosphate metabolism and the provision of energy for muscle contraction via the coenzyme system in which magnesium plays an essential part. Externally, the insoluble salts act as skin sedatives whilst the sulphate acts as a persistent lymphagogue when applied to wounds.

Magnesium Carbonate, B.Vet.C., exists in two forms, a light, fluffy, very bulky powder, and a heavy finely granular amorphous powder which is about 3½ times less bulky than the light form. From these two carbonates are prepared, by heating (calcination), the light and heavy magnesium oxides respectively.

All four may be *used* externally as skin sedatives, their action being purely mechanical. Internally, they have antacid properties: for true antacid action the oxides are preferred for they cause no reflex hydrochloric acid secretion as do the carbonates. Any magnesium chloride formed acts as a saline laxative in the intestines.

Magnesium Trisilicate, B.Vet.C., is less soluble than either the oxide or carbonate. It has good antacid properties, though the action is a slow one. Normally, any chloride which is formed by the interaction with hydrochloric acid is negatived by the mechanical sedative action of the excess silicate which coats the intestinal mucosa. Magnesium trisilicate has relatively strong toxin adsorptive properties for which it is preferred before kaolin (aluminium silicate). Magnesium trisilicate is about twice as expensive as the carbonate or oxide.

Dosages of these five compounds are more or less identical: for foals and calves up to 240 gr. (16·0 G.), pigs up to 120 gr. (8·0 G.), lambs and dogs up to 30 gr. (2·0 G.), and cats up to 10 gr. (0·6 G.). Doses for the trisilicate are usually slightly less than those for the other four compounds.

Another form of magnesium silicate, obtained from natural sources, is known as Talc, B.Vet.C., or French Chalk. It is used, preferably as the purified compound sterilized by heat which destroys bacterial spores, as a sedative skin dressing. It has been replaced by solubilized starch as a glove dusting powder: talc when introduced into the abdominal cavity has induced foreign body reactions and extensive adhesions.

Magnesium Sulphate, B.Vet.C., is the major saline purgative in cattle and other ruminants, but is less useful in other species. Its action is typical of saline purgatives but is more efficient because of the relatively slight absorption of both the magnesium and the sulphate ions. In hypotonic and isotonic solution the action is fairly rapid but hypertonic solutions of the same volume produce a slower though more powerful action; both of these factors are related to the withdrawal of more fluid from the tissues. Small amounts are laxative. Magnesium sulphate is very suitable for the precipitation of any lead remaining in the intestines when treating lead poisoning, for the excess sulphate produces purgation and expels the precipitated lead sulphate. Administered parenterally, magnesium sulphate has anæsthetic effects, and, in excess, a euthanasia action. In conjunction with chloral hydrate and pentobarbitone sodium, magnesium sulphate has been and is used for equine anæsthesia (see Non-Volatile Anæsthetics): saturated warm solutions have been used for canine euthanasia, when it must be given by rapid intravenous injection; the effect is rapid but the sudden spasm is apt to result in a loud scream as the chest is violently contracted. Magnesium sulphate is also widely administered as a treatment for hypomagnesæmia in cattle: 25 per cent. w/v solutions have a glucogenic effect and have therefore been used in the treatment of acetonæmia. When administered subcutaneously, magnesium sulphate has a local anæsthetic effect, which is a useful attribute in any subcutaneous injection.

The external actions of magnesium sulphate are relatively unimportant. When applied to dirty wounds as a paste prepared with equal parts of exciccated magnesium sulphate and glycerin (Morison's Paste) it has an osmotic lymph lavage action which cleans the wound and stimulates granulation: continued use may cause overgranulation. Magnesium sulphate is also used occasionally in concentrated solution as a lotion for bathing sprains, strains and bruises: it is probably a combination of the high osmotic pressure exerted and some local anæsthesia which is responsible for the improvement. Similarly, the beneficial effects of saturated magnesium solutions on sarcoptic mange in pigs (Daykin and Lewis, 1952) may be related to the local anæsthesia and lymph lavage action.

Heat Regulation

The normal oxidation processes of the body are constantly producing heat: it is therefore in those tissues where oxidation is a more or less continuous process that most heat is produced. It has been shown that skeletal muscle is the most important site of heat production, whilst the

liver is the next most important structure. During infection with bacteria, viruses etc., the body tissues react strongly to the attack of the organisms and the increase in metabolism results in increased heat production; this heat cannot be lost rapidly enough by the normal methods and the body temperature rises—this constitutes a fever or pyrexia. The blood is responsible for the removal of heat from the points of production and for its distribution to the various sites of elimination—the skin, lungs, kidneys, etc.

The normal methods of heat loss are:

1. Radiation, conduction, and convection, from the body surface, which together account for about 60 per cent. of the heat loss in man. These processes function only when the external temperature is below that of the body; equal temperatures produce equilibrium and higher temperatures reverse the flow of heat and warm the body. The skin circulation is the controlling factor in heat loss by these three means for a greater amount of blood circulating through the skin means more heat brought to the surface and therefore a greater chance of heat loss. As the dilatation of the vessels is controlled by the vasomotor mechanisms (vasomotor centre, adrenaline activity, etc.) this means of heat loss is directly related to nervous system reaction. In most animals the pilo-erector system is also involved, for erection of the hairs tends to restrict airflow over the skin and slows down the rate of heat loss.

2. The vaporization of water from the lungs and skin. About 25 per cent. of heat generated during rest is lost by this method. In cows and the dog, which have poorly developed sweat gland systems, the diffusion of water through the skin at low temperatures is just as important as that lost by animals such as the horse, which have a well developed sweat gland system, but at high temperatures the cow, the sheep and the dog lose far more heat by loss of water through the lungs, and these species therefore develop polypnœa (a rapid respiratory rate) during hot weather.

3. The urine and fæces are also a means by which heat is lost.

Apart from the mechanisms controlling heat loss and heat conservation, there are centres in the hypothalamus which exert a controlling influence on the total production of heat, its subsequent distribution, and the dissipation of any heat in excess of requirements. Nuclei in the anterior portion of the hypothalamus are concerned with heat loss, whereas nuclei in the posterior hypothalamus appear to be associated with heat conservation and production. These areas are very sensitive to slight changes in the blood temperature and excessive heat will stimulate the anterior hypothalamus, while a fall in blood temperature will stimulate the posterior section: these two areas act reciprocally, one being inhibited whilst the other is stimulated.

Antipyretics

These are drugs which will cause the reduction of a body temperature elevated in response to some parasitic invasion: they will not reduce a

temperature rise due to physical conditions (e.g. heat stroke). They are also referred to as *febrifuges*.

Pyrexia or fever is the natural tissue reaction to infection and it is a doubtful practice arbitrarily to reduce a high temperature without at the same time reducing the infection. However, where the temperature is very high and persistent it may be advisable to reduce the temperature in order to conserve the body's energy reserves and prevent exhaustion.

Since the advent of sulphonamides and the antibiotics the use of the historic antipyretics has vastly decreased but, nevertheless, a place in the therapeutic field still exists for them. Too frequently are the antibiotics and sulphonamides given without any attempt at diagnosis and before any significant symptoms have appeared: it is probable that antipyretics given as a placebo for the owner would hasten the recovery of the patient in many cases by allowing a correct diagnosis following the appearance of significant symptoms. Where a specific diagnosis can be made and the correct treatment applied, antipyretics are largely redundant.

Antipyretics may act in one of several ways:

1. By reducing heat production. This may be achieved either by inhibiting the heat production centre in the hypothalamus or by reducing the rate of oxidation in the tissues.

2. By increasing heat loss. The three main methods of losing body heat are involved:

(a) Increased conduction may be obtained by the use of cold baths (most useful in heat stroke).

(b) Increased evaporation losses follow dilatation of the cutaneous blood vessels, and also dilution of the blood; these result in increased sweating: an increase in respiratory rate is followed by an increase in evaporation losses via the lungs. These reactions may result from stimulation of the temperature lowering, and inhibition of the heat production and conservation, areas of the hypothalamus: most chemical antipyretics act in this way. Some of these effects, however, may be obtained independently; peripheral vasodilatation by the use of nitrites, and by the dilution of the blood by intravenous saline injections (also very beneficial in heat stroke).

(c) Increased defæcation and urine production may be obtained by the use of saline laxatives and diuretics.

Quinine and Related Antipyretics

Quinine, B.Vet.C., an alkaloid derived from the bark of the cinchona tree (Peruvian or Jesuits' bark), and the many related alkaloids (cinchonine, cinchonidine, quinidine etc.) are now infrequently used in veterinary medicine. Quinine is a typical alkaloid, forming salts with acids—sulphate, bisulphate and dihydrochloride are all official in the Codex, the last being the most soluble in water (1 : 0·6).

The main actions of quinine and its salts are a 'bitter' effect by stimulation of the taste buds during administration, and an antipyretic

action which is partly due to a reduction of oxidation processes (by inhibiting enzyme action), but mainly due to central action on the heat regulation centres. The central effects are followed by peripheral vasodilatation and hæmodilution, possibly as a result of a hyperglycæmia and osmotic withdrawal of fluid from the tissues. The slight ecbolic action, the cardiac depressant effect which results from an increased refractory period of the muscle, and the specific antiplasmodial (malaria organism) effect are of little veterinary significance.

The other antipyretics are usually preferred.

Recently reports have appeared on the use of quinine in the treatment of pyometra in the bat and, following this, in the bitch. Doses of 2½–10 gr. initially, followed by half this dose daily for 7–10 days have been claimed to give excellent results in the bitch (Cowie and Muir, 1957).

Dosage for the dihydrochloride: Horse: 30–90 gr. (2·0–6·0 G.) Cow: 75–240 gr. (5·0–15·0 G.) Sheep: 5–20 gr. (0·3–1·3 G.) Pig: 5–15 gr. (0·3–1·0 G.) Dog: 1–10 gr. (0·06–0·6 G.) Cat: ¼–2 gr. (15·0–60·0 mg.)

Salicyclic Acid, B.Vet.C.

Ortho-hydroxybenzoic acid is a light feathery, crystalline substance which is only slightly soluble in water but soluble in alcohol (1 : 4).

Salicyclic acid is only used externally where it has a *keratolytic* action, softening and assisting in the removal of hard keratin (e.g. warts), without having much effect on living tissue. Salicyclic acid is therefore useful when incorporated in ringworm ointments in strengths of up to 5 per cent., for it assists in the penetration of other more actively anti-parasitic compounds. The keratolytic effect is also made use of by incorporating the acid in disbudding collodia such as Collodion of Antimony Trichloride, B.Vet.C., the main ingredients of which are 25 per cent. antimony trichloride and 7 per cent. salicyclic acid. When included in dusting powders in concentrations of up to 5 per cent. salicyclic acid has an antiseptic action.

Methyl salicylate, popularly referred to as oil of wintergreen, is also used only externally in veterinary therapeutics. It has a counter-irritant action and for this purpose is incorporated in ointments and liniments in varying concentrations. Ointment of Methyl Salicylate, B.Vet.C., contains 50 per cent. w/w of the salicylate with 25 per cent. each of white beeswax and lanolin, but Non-staining Ointment of Iodine with Methyl Salicylate, B.Vet.C., contains only 5 per cent. of methyl salicylate: the official liniment contains 25 per cent. methyl salicylate in a bland oil.

For internal medication, sodium salicylate and acetyl salicyclic acid are available.

Sodium salicylate, B.Vet.C., may be obtained either as pearly crystalline flakes or a white crystalline powder, both of which are odourless and have an unpleasant sweetish taste. Both forms are very soluble in water, though the flakes take much longer to dissolve in cold water.

Acetylsalicyclic Acid, B.Vet.C., or aspirin, is available as a white crystalline powder which is only slightly soluble in water but fairly soluble in alcohol. Calcium salts are available commercially as Soluble Aspirin—calcium acetylsalicylate.

Both the sodium salt and the acetic ester of salicyclic acid react with the hydrochloric acid of the stomach and release a proportion of salicyclic acid, which, though somewhat antiseptic in effect, is also irritant and may cause emesis in dogs. After absorption, sodium salicylate circulates as such whilst aspirin may circulate partly as sodium salicylate (the portion which is absorbed as salicyclic acid) and probably also as acetylsalicyclic acid. Both have an antipyretic and analgesic action, although aspirin is the more effective of the two. Both also have an effect on rheumatic conditions including joint and muscular types: in this respect the sodium salt appears to be more effective.

The antipyretic action is achieved by depression of the thermal regulation centres of the brain. This is followed by peripheral vasodilatation and sweating.

Excretion in the form of salicyluric acid is rapid and may be further encouraged by the simultaneous administration of sodium bicarbonate which will also reduce gastro-intestinal dissociation. During excretion, the salicylates make the urine positive to reducing tests for sugars.

Dosage of sodium salicylate is ½–4 oz. (15·0–120·0 G.) for the horse and cow, 15–60 gr. (1·0–4·0 G.) for the sheep and pig, 5–15 gr. (0·3–1·0 G.) for dog, ½–5 gr. (3·0 mg.–0·3 G.) for the cat and up to 2 gr. (120·0 mg.) for poultry.

Dosage with aspirin is usually confined to small animals: Dog: 5–15 gr. (0·3–1·0 G.), Cat: 1½–5 gr. (0·1–0·3 G.). It is frequently administered as Compound Tablets of Codeine, B.Vet.C., which also contain phenacetin and codeine phosphate.

Aniline Antipyretics

This group contains three antipyretics of veterinary interest: acetanilide, phenacetin, and phenazone; only phenacetin is now used to any great degree.

Acetanilide or antifebrin is a white crystalline substance which is only slightly soluble in water. It is corrosive to metals. Before the advent of sulphonamides it was widely used as an antipyretic for farm animals, mainly cattle, in *doses* of about 60 gr. (4·0 G.) two or three times daily.

Phenacetin with similar physical properties and dosage to acetanailide, is used mainly as an antipyretic with analgesic actions for small animals in *doses* of up to 5 gr. (0·3 G.) three times daily for dogs, and up to 2 gr. (0·1 G.) administered at the same rate for cats. It is incorporated in Compound Tablets of Codeine, B.Vet.C., which contain 4 gr. (0·25 G.) each of aspirin and phenacetin and ⅛ gr. (8·1 mg.) of codeine per tablet.

Phenazone, or antipyrin, differs from the two preceding compounds in its chemical structure, though it contains a phenol ring, and in its water solubility (1 : 1). This compound is also an antipyretic and analgesic, though rarely used now. *Dosage* for horses and cattle is up to ½ oz. (16·0 G.) twice daily.

All three compounds are central nervous system depressants; from this there stem analgesic and antipyretic actions. The latter effect is exerted entirely through depression of the heat regulating centres in the hypothalamus. Phenazone, being soluble, acts more rapidly than the other two but its effects persist for a shorter time.

The main disadvantages of these phenolic compounds is their effect on the blood if dosing is prolonged. Methæmoglobin is formed and agranulocytosis may occur. Phenacetin is the least toxic of the three compounds.

Nitrite Antipyretics

This group of antipyretics is now also rarely used in veterinary practice. The group consists of amyl nitrite, sodium nitrite, ethyl nitrite in the form of Spirit of Nitrous Ether, B.Vet.C., or Concentrated Solution of Nitrous Ether, B.Vet.C., and glyceryl trinitrate.

The actions of individual members of the group differ only in speed of onset and duration of effect. The action is one of dilatation of all peripheral blood vessels and also the coronary vessels. Amyl nitrite, which is administered by inhalation, exerts its action within a few seconds and effects pass off within 10 minutes, whereas the other preparations are effective within ten minutes and continue their action for up to 2 hours. The vasodilatation causes a drop in blood pressure and an increased heart rate.

Dosage of amyl nitrite for the dog is up to 5 m. (0·3 ml.) by inhalation. It is rarely used.

Dosage of Spirit of Nitrous Ether, B.Vet.C., is up to 3 fl. oz. (90·0 ml.) for the horse, up to 4 fl. oz. (120·0 ml.) for the cow, and up to ½ fl. oz. (15·0 ml.) for the sheep and pig. The concentrated solution should be diluted with seven times its volume of water and is then equivalent in strength to the spirit.

Dosage of sodium nitrite for use in conjunction with sodium thiosulphate (*q.v.*) is up to 30 gr. (2·0 G.) for the horse and the cow, and up to 15 gr. (1·0 G.) for the sheep, by intravenous injection. For its diaphoretic (sweat producing) and antipyretic effects it may be given in doses of up to 30 gr. (2·0 G.) for horses and cattle, and up to 2 gr. (0·1 G.) for dogs.

Dosage of glyceryl trinitrate for horses and cattle is 1/6th–1/3rd. gr. (10·0–20·0 mg.), and for the dog is up to 1/100 gr. (0·6 mg.).

Coagulants and Blood Volume Expanders

The essential nature of the blood makes conservation of its volume of considerable importance. There are therefore physiological mechanisms

to limit the loss of blood by hæmorrhage (blood clotting mechanisms) and, following this, to replace the blood which has been lost.

Coagulation Coagulants and Anticoagulants

The essentials of the process of blood clot formation consist of the combining of thromboplastin (thrombokinase) with calcium and prothrombin to form thrombin, which, in turn, combines with fibrinogen to form fibrin. Fibrin is deposited in a fine network which ensnares first platelets (the platelets add to the firmness of the clot), and then the red blood corpuscles, blocking the blood vessels and preventing further hæmorrhage. The process is considerably more complicated than this, but for greater detail reference may be made to Jorpes (1956) or Archer and Miller (1958).

It would be only logical to expect that preparations of the substances involved in natural clotting processes would be available for arresting traumatic and surgical hæmorrhage. Such preparations are available but should only be used as local applications: they are of little value for internal hæmorrhage and should not be injected intravenously because of the danger of causing widespread intravascular clotting and death.

Thromboplastin, also known as thrombokinase, thromboplastic or zymoplastic substance, is produced naturally by platelets and damaged tissue, but commercial thromboplastin is most frequently an extract of cattle brain in normal saline. It is applied locally as a hæmostatic, being of most use in capillary oozing: it is also used for treating epistaxis and in human surgery of the nose and throat, of glandular tissue, and of bone.

Thrombin is the enzyme which converts fibrinogen into fibrin. Bovine thrombin is available commercially as a powder supplied in a dual pack with a suitable diluent. It is of value in arresting capillary hæmorrhage and may be used in conjunction with fibrinogen or fibrin foam for this purpose, for filling in 'dead space' during surgery, for grafting, in fact, for any surgical operation where it is necessary to prevent hæmorrhage or produce rapid and strong adhesion of two surfaces.

Fibrinogen from human sources is available as a white powder or friable solid prepared from human plasma by precipitation with organic solvents and freeze drying. It is readily soluble in normal saline; solutions should be freshly prepared before use. Its main use is in assisting the adhesion of grafts of skin and mucous membranes, for which 2 per cent. solutions are used: the amount of thrombin and the temperature of the solution determine the rate of clotting, and the amount of fibrinogen the strength of the clot.

Fibrin is available as Fibrin Foam (human) B.P. It is an insoluble material in the form of strips of a fine white sponge. Fibrin foam strips are useful for filling in dead space, particularly where capillary oozing occurs; the strips are soaked in a thrombin solution and placed over the site of hæmorrhage or in the cavity: coagulation will occur immediately

and the strip can then be buried by suturing. These methods have been used extensively in human lung and brain surgery.

Other Surgical Hæmostatics

These comprise Oxidized Cellulose, B.P.C., Absorbable Gelatin Sponge, B.P.C., and Calcium Alginate, B.P.C. All are heat sterilized.

Oxidized Cellulose, B.P.C., is a white gauze or cotton with a faint odour and acid taste. It is insoluble in water and acids but soluble in dilute alkalis. This oxidized cellulose is acid in reaction and must be neutralized with sodium bicarbonate if used with thrombin solutions; it also inactivates penicillin.

If used as a hæmostatic, the cellulose should be applied dry, when it will swell, forming a brown gelatinous mass which may take 7 days or more to be absorbed. It may be used to pack cavities and dead space, the wound being closed over it: surface bleeding will also be arrested by an application. The use of oxidized cellulose in bone surgery is not encouraged as it delays the formation of callus.

Calcium Alginate, B.P.C., consists of calcium, or a mixture of sodium and calcium alginates—salts of alginic acid. The white to buff powder or fibrous 'wool' is almost odourless and tasteless; it is insoluble in water but soluble in sodium citrate solution. Calcium alginate is an absorbable hæmostatic which may be applied in two ways—either sodium alginate is applied as a 4 per cent. solution over the area which is then sprayed with a 2 per cent. solution of calcium chloride, or it may be applied as a fibrous calcium alginate dressing soaked in sodium alginate solution. The dressings do not inactivate penicillin and may be buried in the same manner as other absorbable dressings. Removal of alginate dressings (aided by sodium citrate solutions) does not interfere with granulation tissue which incorporates any of the adherent dressing. Powdered alginates may be used to dust surgical gloves.

Absorbable Gelatin Sponge, B.P.C., is prepared from gelatin treated with formaldehyde, heated, whisked into a foam and freeze dried. The sponge is insoluble in water but can be wetted: it is a finely porous, white sponge-like material which will absorb about 30 times its own weight of water. The sponge may be applied dry or soaked in thrombin solution containing 100 units per ml., when clot formation occurs rapidly. It may be buried in dead spaces etc. but takes six weeks or more to be absorbed. Nevertheless, it may be used in all types of surgery where control of capillary and venous bleeding is required.

Parenteral Coagulants

There exists a great need for a safe and efficient hæmostatic which can be given parenterally. A mixture of *malonic* and *oxalic* acids in equal concentrations (5 per cent. each) has been widely used by intravenous or intramuscular injection in doses of 0·5–3·0 ml. for small animals and 5·0–20·0 ml. for large animals. For epistaxis in race horses it has been

suggested that 10·0 ml. intramuscularly on the day before and 10·0 ml. intravenously two hours before racing is effective (Scott, 1958). This coagulant effect is not altogether satisfactory and recent reports by Archer (1957) and Archer and Miller (1958) cast further doubt. Vitamin K (*q.v.*) and its water- and oil-soluble analogues are useful in checking hæmorrhage caused by hypoprothrombinæmia such as may occur with Warfarin poisoning and 'sweet clover poisoning'. Details of vitamin K therapy may be found in the section on Vitamins (fat soluble).

Local Hæmostatics

All astringent metals and plant substances will act as hæmostatics but the main one used clinically is ferric chloride (*q.v.*) which may be used as Strong Solution of Ferric Chloride, B.Vet.C. Alum has also been used but is somewhat irritant, and tannic acid may be applied. With all these astringent compounds the action is one of precipitating sufficient protein in the open end of the vessel, both to block it, and to encourage normal clotting mechanisms. They should only be applied to clean surfaces, hæmorrhage being temporarily prevented by pressure. Too much blood prevents direct application to the vessels involved and covers the area with an ineffective mass of precipitated protein under which bleeding continues. Minor arterial bleeding such as may occur during the docking of puppies can be arrested with ferric chloride solution, but only if the operation is done within the first ten days of life. Normally, only capillary oozing should be controlled with astringents. Thermocautery is often successful where other means of arresting arterial and venous hæmorrhage have been tried unsuccessfully.

Anticoagulants

The use of parenteral anticoagulants is rarely required. Heparin, B.P., Dicoumarol, B.P.C., and Sodium Citrate, B.Vet.C., may be used parenterally to delay clotting of the blood.

Dicoumarol, B.P.C., also known as Dicoumarin and Bishydroxycoumarin, U.S.P., is marketed commercially as Warfarin for destruction of rats. Its action is one of preventing the formation of prothrombin but it has no effect on that already formed. Effects are therefore not apparent for up to 48 hours and continued dosing is necessary. It has been used on man to retard the extension of coronary thrombosis but there is little clinical application in animals. Vitamin K (*q.v.*) is a physiological antagonist.

Heparin, B.P., or heparin sodium, is prepared by enzyme action on lung and liver tissue and should contain not less than 100 units per mg. Heparin delays the clotting of blood in a manner not completely understood, although it is known to interfere with the conversion of prothrombin to thrombin and also prevents the normal action of thrombin. It is rapidly inactivated in the body by enzymes, and the extent and duration of effect are proportional to the dosage. A single intravenous dose may be effective

for up to six hours. The clinical indication for heparin is in the collection of blood for transfusion when it may be given to the donor just before bleeding or mixed in with the blood as it is taken. *Dosage* for all species is not established but the average human dose is from 6,000–12,000 units by intravenous or intramuscular administration. In the dog 1·0 mg. per kg. may be given 10 minutes prior to blood collection.

Sodium citrate (*q.v.*) is used more commonly in veterinary transfusions.

Blood Volume Expanders

Variously referred to as plasma extenders, plasma expanders, and plasma substitutes, blood volume expanders may either be fluids obtained from blood by various processes or synthetic colloidal solutions which have osmotic characteristics approximating to those of plasma: they are capable of creating and maintaining an increase in the circulating blood volume and are therefore intended for the treatment of the decreases in both circulatory volume and blood pressure which are associated with shock. They cannot increase the oxygen carrying capacity of the blood and cannot replace any deficiency of blood cells, though they may be used as vehicles in which to suspend erythrocytes for intravenous infusion.

The efficiency of a substance when used as a plasma expander depends to a great extent on the degree and persistence of the osmotic pressure exerted by its macromolecules within the vessels. The persistence is determined by the rate of loss from the circulation by one of the following means: 1. across the capillary wall into the interstitial fluids, 2. by excretion from the body, 3. by selective storage in certain tissues or 4. by metabolic degradation. The value of any expander is therefore determined by the shape, structure, weight and electric charge of the macromolecule or particle, for these are the factors which govern the passage of those particles across a membrane.

The ideal plasma expander would have a molecular weight of about 70,000 (that of plasma albumin), exert an osomotic pressure equal to that of normal plasma proteins, persist in the circulation long enough to allow mobilization into the circulation of normal plasma protein, and yet be eliminated at a rate identical with that of the plasma protein mobilization so that the osmotic pressure remains constant; in addition, the solution must have a viscosity which allows free administration through the finest needle with a minimum pressure.

As regeneration of plasma protein will take place at varying rates according to the individual and the occasion, it is unlikely that a single type of synthetic macromolecule will be able to achieve this ideal, and only a natural blood fraction which can take part to the full in normal blood metabolism could comply with all the requirements. Even with the present far from complete knowledge of the reaction of macromolecules introduced into the circulation, Campbell (1956) has said that 'the ideal

macromolecule for use in a plasma expander would probably have very similar properties to those of serum albumin'.

Indications. The use of blood volume expanders is primarily indicated in the decrease of circulatory volume associated with 'shock'. Shock is an extremely complex physiological reaction to acute physical stress which may take the form of severe and sudden pain, usually associated with trauma, tissue damage, again associated with trauma or extremes of temperature, and hæmorrhage. Although plasma expanders may be of temporary value in histamine shock the specific antagonists and vaso-constrictor drugs are preferentially indicated: shock associated with bacterial toxins cannot be reversed by plasma expanders alone but must be additionally countered by antitoxic remedies.

The response to a shock stimulus follows in each instance a similar but not identical course: there is a fall in blood pressure, a progressive hæmoconcentration with a decrease in plasma volume and a fall in body temperature: other symptoms which occur less constantly are a decrease in plasma protein, a decrease in venous blood oxygenation, an increase in pulse rate, a darkening of the venous blood, a marked increase in coagulation time, hæmolysis, and a decrease in the rate and depth of respiration (Harthoorn, 1951). These conditions may persist for several hours in a reversible state, but as tissue anoxia, and especially brain and circulatory system anoxia, supervenes the state becomes irreversible and the animal dies. While the shock is reversible, treatment will save the animals life, but it should be borne in mind that the animal at this stage is very susceptible to further stimuli which may cause a rapid progression to the irreversible state.

In traumatic shock there may be extensive hæmorrhage into the traumatized area or considerable extravasation of fluid and frequently plasma protein. (Extensive burns are extremely dangerous because of marked loss of plasma into the burnt area). In all types of shock, but particularly in shock associated with nerve damage, there is a vasodilatation and an increased permeability of capillaries, and, as capillary anoxia develops, there may be protein loss also. The tissue anoxia develops owing to the decrease in circulatory volume which is followed by a fall in blood pressure, a decreased venous return, and a lower cardiac output; this in turn leads to a further decrease in blood pressure, decreased rate of circulation and therefore tissue anoxia.

The clinical symptoms of shock are primarily a collapsed animal which has cold extremities, a low general body temperature, pale or, later, cyanosed dry mucous membranes, a weak, frequent and rapid pulse, associated with shallow breathing and acute depression.

Treatment. Where shock is an established fact the immediate aim is first to remove the cause of shock, if possible, arresting any hæmorrhage and administering analgesics (*not* the tranquillizing drugs, for they will

prevent the normal vasoconstricting physiological reaction) where pain is severe—these should be given intravenously, for subcutaneous injections may not be absorbed until the shock is reversed and there may be a great temptation to give a second dose because of the lack of response; where the shock is reversed both doses would then be absorbed, with dangerous effects. One of the historic methods of treating shock has been to apply warmth: this can be dangerous and even fatal, for it may induce vasodilatation of the skin vessels and therefore decrease the volume of blood available for circulation in the vital organs. Optimum temperature would be a normal comfortable working temperature (Clarke, 1953).

Efforts to increase the circulatory volume should begin as soon as possible and should continue until the volume administered is approximately equal to that lost, if hæmorrhage has been the cause of shock. With other forms of shock, and where there is no means of estimating blood pressure beyond digital estimation of the pulse, it is difficult to estimate the amount of fluid which can be given by intravenous injection: should the plasma protein be depleted, as in hæmorrhagic shock, or should protein have been lost into the interstitial tissue, subcutaneous administration is likewise of doubtful value for there will be insufficient osmotic pressure exerted by the blood to withdraw sufficient fluid from the tissue spaces. In these circumstances one can only estimate by digital pressure on the pulse the extent of pressure and volume increase, the infusion end point being determined in conjunction with the clinical response.

The dangers of infusions are those associated with over dilution of the blood and over increase of the volume. The former results in anæmia and loss in oxygen carrying capacity—only whole blood transfusions or time can rectify this state of affairs: the latter is more serious, for, if excess of an expander is given, the volume of circulating blood increases hourly as the plasma protein is regenerated, withdrawing large amounts of fluid from the tissues, and the animal literally drowns: the capillary bed becomes overloaded and fluid is excreted into the lungs, whilst the heart becomes dilated and weakened as the cardiac reserve is exceeded. Death follows from pulmonary œdema and heart failure.

Electrolytes such as normal saline, Ringer's solution and Ringer-Lock solution have all been used as plasma volume expanders, either by intravenous drip, by intravenous injection, or by subcutaneous administration. There is evidence to show that, in all but perhaps early shock, intravenous administration of electrolyte solutions can turn reversible into irreversible shock after an initial increase in blood pressure and plasma volume (Harthoorn, 1953). It would seem that infusions of such solutions remain in the circulatory system for only a short time and, as they diffuse across the capillary membrane into the interstitial fluid, they remove some of the remaining plasma protein and severely prejudice an animal's recovery. It is probable, however, that intravenous saline may be useful when given before the onset of shock and as a prophylactic blood volume expander. These electrolytes may be used in conjunction with

5 per cent. dextrose solution which will maintain blood sugar levels and provide a readily available source of energy.

Gum acacia has been discarded as a colloid plasma expander in human shock therapy owing to the danger of allergic reactions and because of prolonged tissue storage; it also interferes with plasma protein regeneration. The last two effects occur in dogs and acacia should therefore not be used. *Pectin* has been discarded for similar reasons.

Gelatin is a modified protein which is not metabolized in the body owing to the lack of essential amino-acids in its structure. Gelatin containing molecules with weights varying from 20,000 to 70,000 is used in 6 per cent. concentration. It achieves maximum hæmodilution in 3–4 hours after intravenous injection, producing a 70 per cent. increase over the injected volume. The hæmatocrit (packed cell volume) is lowered and the concentration of plasma protein is also lowered. The majority is excreted in the urine within 24 hours. Harthoorn (*loc. cit.*) was unimpressed by the action of gelatin and found an adverse effect on animals already affected by shock.

Dextran. Solutions of 6 per cent. and 10 per cent. concentration are available, the former either with saline or 5 per cent. dextrose and the latter only with dextrose. Dextran itself is a complex polysaccharide prepared by growing a bacterium, *Leuconostoc mesenteroides*, in a medium containing sucrose: the dextran for infusion is further hydrolyzed to reduce the length of the saccharide chain and the molecular weight, which can be as high as 450,000 in British Dextran (Campbell, *loc. cit.*). Infusion produces a volume expansion which is slightly greater than the volume injected, but is equal to the infusion volume after one hour: after 12 hours the increased volume is about 50 per cent. of the infusion volume. Commercial solutions are claimed to be effective for up to 48 hours, over 60 per cent. remaining in the circulation after 24 hours. It would seem that the dextran molecule is slowly broken down into glucose, though some is excreted unchanged in the urine, mainly during the first six hours: it is probably those molecules in the lower weight range (less than 10,000) which are thus excreted. Dextran solutions may be infused at the rate of 10·0–25·0 ml. per minute, about 500 ml. being the average initial dose for an adult human, with a further 500 ml. half hour later, given at a rate determined by clinical response. Doses varying from 2·0 ml. up to 20·0 ml. per lb. body weight have been suggested in dogs but the normal range varies between 75 and 250 ml. Reactions have occasionally been noticed in dogs and in no case should the volume injected exceed one third of the plasma volume which may be taken as approximately 7·2 per cent of the body weight: if this proportion is exceeded the dextran has an heparin-like action and severe widespread haemorrhages may occur, leading to the animal's death (Lawson, 1958).

Polyvinylpyrrolidone (P.V.P.) is a complex organic polymer which was developed by Germany during the 1939–45 war. It is water soluble and has macromolecules varying in molecular weight from 30,000 to 50,000.

Following infusion of 3·5 per cent. solutions there is an initial increase of blood volume equal to about 90 per cent. of the infused volume. As much as 50 per cent. is excreted, mainly unchanged in the urine, within 3 or 4 hours and by 12 hours the increase in volume falls to about 30 per cent. of the infusion volume. Volumes used should be much the same as for dextran solutions.

Whole blood transfusions are more frequently administered than formerly. The blood may be collected immediately before use or, if properly citrated, it may be kept refrigerated for up to three weeks. For blood to be used immediately, 100·0 ml. of a 3 per cent. sodium citrate solution for every 400 ml. of blood should be adequate, but for prolonged storage 75·0 ml. of acid sodium citrate (*q.v.*) should be used for every 500·0 ml. of blood.

Although more information on blood groups in animals appears annually, (Ferguson, 1955), so far little attention is paid to them in practice, for single infusions rarely cause trouble and repeated infusions are uncommon. However, cross matching of citrated samples can be carried out on a slide, any agglutination being an indication of incompatibility.

Dosage:

Horse and Cow:	2–4 pints (1·25–2·5 l.) or more (McGeady and Bourke, 1953)
Calf:	400·0 ml. (Holmes, 1949)
Dog:	80·0–100·0 ml. (Holmes, *loc. cit.*) given at the rate of 7·0–14·0 ml. per minute.

Blood plasma may be obtained by centrifuging citrated blood or decanting off the plasma after sedimentation. The plasma will keep for up to 2 years if refrigerated. *Doses* of up to 20·0 ml. per lb. bodyweight have been suggested, given either intravenously or subcutaneously (Holmes, *loc. cit.*).

Blood serum is obtained by allowing blood to clot naturally and pouring off the serum. It may be used in the same way as plasma (Holmes, *loc. cit.*), and in the same dosage.

The difficulty associated with the use of homologous blood products in veterinary medicine and surgery is the lack of blood banks and the scarcity of suitable donors at the right time. This has encouraged the search for a blood product which is suitable for use in all species and capable of being stored. Bovine serum has been used (Crowther and Petris, 1958; Petris, 1959) in the treatment of shock of surgical and toxic origin in sheep, goats, dogs, and cats in doses of 40·0–60·0 ml. for sheep and goats, and 10·0–40·0 ml. for dogs and cats. The effects have been extremely good, in fact, spectacular, especially when supported by glucose-saline subcutaneously. Allergic reactions have not occurred and disease transmission has been avoided by observing the donor for two weeks before collecting blood. The serum has been filtered through a Seitz filter and then refrigerated.

Despecified bovine albumin is being used experimentally and clinically but its expense is hindering development, though modern techniques are enabling a reduction in cost to be made. This albumin is obtained from bovine blood by refrigeration techniques and is sterilized by heat. The advantage of despecified albumin is that it will keep almost indefinitely, it does not induce allergic reactions, but, above all, it can be given intermittently as a concentrated solution in small volume intravenously, the blood volume being made up by oral intake or subcutaneous injection of electrolyte solutions. There is thus little chance of overloading the vascular system and the intermittent method of administration is eminently suitable for veterinary practice.

Dosage for dogs (Harthoorn, 1953) is at the rate of 1·0 G. per kg. An initial intravenous dose of 1·25 ml. of a 20 per cent. solution per kg. followed by half this at two or three hourly intervals up to a maximum of 1·0 G. albumin (equivalent to 5·0 ml.) per kg. was recommended. As a rule, far less than this was required to return the blood volume to normal. The albumin injections must be supported by glucose-saline subcutaneously or by mouth.

In all intravenous injections in shocked animals, raising the vein and introducing the needle offers difficulties. If a limb is used a tourniquet is required above the injection site and the limb should be alternately flexed and extended until the vein becomes engorged. In small animals, it may be found that the sublingual veins are easy to enter, as they lie superficially below the mucous membrane.

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CHAPTER 12

NERVOUS SYSTEM DEPRESSANTS

(i) GENERAL SURVEY

THE definitions of terms used to describe the drugs which cause depression of the central and peripheral nervous systems are disputed and confusing. The following definitions will serve as a general guide and provide a reasonable understanding of terms used to describe the type and degree of nerve depression caused by a particular drug.

1. *Sedatives.* These are agents which will cause a lowering of cerebral perception and reaction, whilst not preventing the patient from taking part in the normal life surrounding it. Until recently this term has been applied to such compounds as ethyl alcohol, potassium, sodium, and ammonium bromides, but these are now being displaced by a group of drugs known collectively as *tranquillizers* or *ataraxic drugs*. Some of these tranquillizers have been advertised as 'non-sedative', which is perhaps not a little peculiar when they have been professionally described as 'chemical restraining agents' (Knowles, 1957).

2. *Hypnotics or Soporifics.* This series of nervous system depressants produces a state of central nervous system depression equivalent to sleep, and in some cases very similar to sleep. Most of the non-volatile anæsthetics will produce this state when given in suitable doses. The barbiturates are perhaps the most useful.

3. *Narcotics.* The stage of C.N.S. depression called narcosis is one of profound sleep from which the animal can only be roused with difficulty: as soon as the rousing stimulus ceases the patient immediately relapses into its former state. Such drugs are usually, but not always, analgesic. Where an animal under the influence of a narcotic is later subjected to complete anæsthesia by the application of an anæsthetic, the term *basal narcotic* is often used to describe the drug. Light, medium and deep narcosis are terms used to describe the depth of narcotic depression. In some cases the level of light narcosis is accompanied by excitement and struggling, which may result in self-inflicted injuries: the incidence of narcotic excitement is highest during the induction of, and recovery from, general anæsthesia, but may also occur when narcotized animals are hurt or stimulated by noise and movement.

4. *Analgesics or Anodynes.* These are simply described as 'pain killers'. They may act centrally and systemically, as do salicyclic acid derivatives,

chlorbutol, morphine and pethidine, or they may act locally. This latter group are the local anæsthetics (*q.v.*).

5. *Anæsthetics.* These are agents which are used to render a patient insensible to all sensation either locally, as with local anæsthetics, or completely, as with general anæsthetics. The local anæsthetics are described in Chapter 15 and the general anæsthetics in Chapters 13 and 14.

From these definitions it will be seen that simple sedatives, hypnotics, narcotics and anæsthetics are successive stages of increased nervous system depression and progressive loss of consciousness. Analgesia, though closely allied to, and a natural corollary of this scale of depression, is a distinct phenomenon. This may perhaps be illustrated by referring to nitrous oxide which is a particularly good analgesic and yet has a relatively low anæsthetic potency; and also by reference to the barbiturates which are powerful sedatives, hypnotics, narcotics and anæsthetics and yet relatively poor analgesics.

From the realization of this division has arisen the concept of modern 'anæsthesia' in which the control of a patient during an operation is achieved by the employment of drugs having three different pharmacological actions: 1. analgesia, 2. narcosis, used in the sense of the elimination of consciousness, and 3. muscular relaxation. These three actions may be effected unselectively by the use of one drug only, as with chloral hydrate or barbiturate intravenous injections, but in most cases the doses which will achieve all these effects are so large that undesirable side effects such as depression of respiration, body temperature, or blood pressure, may also occur. *Balanced anæsthesia*, which involves the use of a different drug for each of the three effects mentioned, makes it possible to ensure a complete loss of pain sensation, both from a surgical point of view and from conscious appreciation, by the use of an analgesic such as pethidine; makes it possible also to maintain a stage of *light* narcosis so that medullary depression is minimal—the general anæsthetics used in small doses are indicated for this purpose; and makes it possible to obtain complete muscular relaxation which cannot be produced by anæsthetics used in narcotic doses—muscle relaxants, such as curareform and the succinylcholine groups of drugs, are used for this purpose. When balanced anæsthesia is used it is essential that all three phases should be correctly applied, for the use of narcotics and muscle relaxants with incomplete analgesia will cause severe surgical shock when the operation begins. Similarly, if either of the other two phases is incomplete considerable distress and shock will result.

The anæsthetics are described in Chapters 13, 14, and 15 but other depressants and muscle relaxants which may be given prior to or during anæsthesia, using the term in its broadest sense, will be described here.

Sedatives and Hypnotics

The drugs which cause sedation will usually, in larger doses, cause hypnosis.

The *barbiturates* of the long, medium and short acting types will all exert sedative and hypnotic effects when given in small doses either orally or by parenteral injection: the oral route is the most suitable one for the routine administration of all sedatives and hypnotics. Phenobarbitone, methylphenobarbitone and butobarbitone are the most commonly used of the barbiturates, but small doses of pentobarbitone will have sedative effects. The dosage of the first three compounds varies from about ½ gr. (30·0 mg.) three times daily for small breeds of dogs or for light sedation in larger breeds, to 1½ gr. (90·0 mg.) three times a day for heavy sedation in the larger breeds. Higher or more frequent doses may cause motor inco-ordination. In large animals barbiturates are not used commonly, but thiopentone sodium has been used in 2·0 ml. doses of a 5 per cent. solution in a sow (Clover, 1955): phenobarbitone sodium in cattle (Sladden, 1958) given by intramuscular injection, and pentobarbitone sodium in horses (Arthur *et al.*, 1953) and cattle (Toosey, 1959) have given excellent sedation.

In general, the barbiturates are not satisfactory when pain is present and must be combined with analgesics. Phenobarbitone and methylphenobarbitone have the most marked anticonvulsant properties of the group and are therefore of most value in the treatment of epileptiform fits in dogs. Other details may be found in the section concerning barbiturates in Chapter 13.

Bromides

The bromide salts of potassium, sodium and ammonium are effective sedatives for dogs and have occasionally been used in pigs, although there is little call for sedatives in this species.

The bromides have sedative and anticonvulsant actions on the brain and are administered to dogs in doses of 5–15 gr. (0·3–1·0 G.) two or three times daily: 10 gr. (0·6 G.) doses are adequate and should normally not be exceeded. The salts are absorbed rapidly, are metabolized in a manner similar to chlorides, and have actions identical with chlorides in all respects other than effects on the C.N.S.: bromide ions are depressant on the C.N.S. and, as they displace chloride ions and are more slowly excreted, there is a danger of *cumulation*, indicated clinically by progressive depression and inco-ordination. Both motor and sensory nervous activities are depressed, but side effects relating to respiratory and circulatory depression are insignificant.

Bromides are used for general sedation of dogs prior to travelling, and on November 5th (Guy Fawkes night) or other occasions when fireworks are let off. Bromides are also useful in depressing sexual excitement in puppies.

Toxicity. This is uncommon and can be discounted providing the bromides are not used for periods longer than a week. Local gastric irritation may occur following tablet administration, but emesis subsequent to administration is uncommon.

Chlorbutol, B.Vet.C.

This white crystalline solid with a characteristic odour is more soluble in organic solvents than in water, and is particularly soluble in alcohol, which could be anticipated from its formula—trichlorodimethyl ethyl alcohol.

Actions and Uses. The actions of chlorbutol are similar to those of chloral hydrate but it is far less irritant to tissues. Its action following topical administration is sufficient to ensure its mention as a local anæsthetic and antiseptic, but once absorbed it has a central depressant effect on both cerebrum and medulla. Amongst the medullary centres, it depresses the vomiting and respiratory centres.

Chlorbutol is *used externally* in dusting powders (1–2 per cent.) for its analgesic and antiseptic effects: it is also used at a 0·5 per cent. concentration as a preservative for certain parenteral injections, both as an antioxidant (adrenaline injections) and as a bactericide. *Internally*, chlorbutol has a gastric sedative action both by local analgesic effects and by central depression of the vomiting centre after absorption: it is incorporated in arecoline worm tablets and capsules for this purpose (2½–3 gr. 160·0–195·0 mg.) chlorbutol with ¼ gr. (15·0 mg.) arecoline hydrobromide). Chlorbutol is also a useful prophylactic against travel or motion sickness in dogs, though hyoscine is becoming more popular: for this purpose, capsules containing 2–10 gr. (130·0 mg.–0·6 G.) chlorbutol, and sometimes compound formulations consisting of chlorbutol, potassium bromide, and dried extract of belladonna are used. This last formula is very useful in motion sickness. Chlorbutol is usually given in capsule form mainly because of the slow and difficult disintegration rate of tablets containing this compound.

Dosage. Dogs 2–10 gr. (0·13–0·6 G.). It is rarely used in other species. The normal dose for travel sickness is a 3 gr. (0·2 G.) capsule given 15–10 minutes before the journey begins. More will be required for large breeds of dogs.

Alcohol has no place as a nerve sedative in veterinary practice.

Anticonvulsants. This term is applied to a group of drugs which may be considered as a subdivision of nerve sedatives in which hypnotic effects are minimal. They are of less importance in veterinary medicine than in human medicine, and the study of these drugs for veterinary purposes is not extensive. They are nevertheless widely used to control the epileptiform convulsions which occur as a symptom of the neurotropic virus syndrome of dogs and which are also associated with digestive disturbances during teething.

The *barbiturates* are widely used in the control of epileptiform convulsions, but usually hypnosis and inco-ordination are seen before convulsions are controlled and the newer compounds are preferred.

Phenytoin Sodium, B.Vet.C., also known as Diphenylhydantoin Sodium, U.S.P., and commercially as Epanutin or Dilantin, has been widely used. Phenytoin sodium has less hypnotic and greater motor effect than the barbiturates and may be used on its own or combined with phenobarbitone. It is more expensive than phenobarbitone, which more than outweighs the slightly better effect, and the drug has never attained great popularity in the veterinary field.

Dosage. The dose for dogs is 0·1–0·3 G. given by mouth three to four times daily, followed by a decrease when the convulsions have been controlled.

The oxazolidine derivative *Troxidone*, B.P., or Trimethadione, U.S.P., known commercially as Tridione, has been effectively used in veterinary medicine to control epileptiform convulsions in dogs. The dosage is 5–15 gr. (0·3–1·0 G.) by mouth three times daily, the dosage being varied in the range according to reaction. Doses are increased in size until the convulsions are controlled, or until signs of toxicity are seen: once control has been established doses can be reduced to a maintenance level. The compound is available in capsules and is relatively expensive.

Toxicity. The main sign of toxicity is photophobia. As this is a common symptom of distemper or hard-pad the only way of determining the presence of toxicity is to withdraw the drug and see if the phobia remains.

Primidone, B.P., is probably the best anticonvulsant now used for controlling the convulsions of the canine virus diseases. It has been used extensively under the commercial name of Mysoline in *doses* of 12·0–50·0 mg. per lb. body weight daily in divided doses. The usual method is similar to that used for troxidone in that doses are progressively increased until convulsions are controlled and are then reduced until a maintenance dose is established. By such a method dosing has been continued for months without any deleterious effect. Apart from its use in the treatment of the nervous symptoms of virus diseases, primidone has also been recommended and used for teething convulsions, hysteria, and motion sickness in dogs. Tablets containing 0·25 G. are available. *Toxicity* is very low and appears clinically as a progressive sedation and hypnosis. Symptoms usually disappear on decreasing the doses, though spontaneous recovery may occur due to acquired tolerance.

Tranquillizers. This is a term which has been applied comprehensively to a group of drugs described in a report by the Council on Drugs of the American Medical Association (1958) as 'psychotherapeutic drugs'. The term has been held synonymous with 'peace of mind', and thus designates a drug which will, by action on the central nervous system, alter the temperament of a patient, thereby making it less responsive to outside stimulation. Another term, 'ataractic' or 'ataraxic', is being increasingly used to describe these drugs.

The application of such drugs in the sedation of temperamentally

unstable and nervous patients provides an obvious and logical use, but the side actions of many of the group are numerous and in some cases are more important therapeutically than the tranquillizing effect. These side effects include antihistaminic; general and local anæsthetic effects; 'sparing' effects or synergism with narcotics, analgesics and both general and local anæsthetics; antispasmodic effects; antipyretic and hypothermic properties, antemetic and anti-autonomic actions. The comprehensive nature of these side actions and the varying individual susceptibility to each and all of them makes clinical prescribing difficult and clinical assessment very protracted and involved. Much still remains to be learnt of the pharmacology of these tranquillizing drugs.

The *classification* of tranquillizing drugs is made extremely difficult by the fact that many drugs which are primarily associated with other effects may also indirectly relieve anxiety, and the nervous tension it induces, by removing or suppressing the cause. The analgesic drugs provide an excellent example. Other drugs which also complicate the classification are those which are primarily active in one direction but as a secondary action cause depression of the central nervous system and have a direct tranquillizing effect. The antihistaminics belong as a group to this type, though some are stronger than others in their tranquillizing effects. The Council on Drugs of the American Medical Association have therefore issued the following tentative classification (slightly modified) in which the drugs are segregated according to their known pharmacological actions:

Classification of Psychotherapeutic Drugs (Modified). Report of Council on Drugs, American Medical Association, published in the *Journal of the American Medical Association* (1958) **166**, 1040.

1. Antihistamines.
   - A. Psychotherapeutic antihistamines.
     1. Hydroxyzine hydrochloride (Atarax).

2. Central Nervous System Depressants.
   - A. Non-selective Depressants.
     1. Analgesics.
     2. General anæsthetics.
     3. Hypnotics and sedatives.
   - B. Selective Depressants.
     1. Anticonvulsants.
     2. Antihistamines.
     3. Antitussives (cough sedatives).
     4. Central (skeletal) muscle relaxants—non-sedative.
        (a) Mephenesin and its derivatives.
     5. Central (skeletal) muscle relaxants—sedative.
        (a) Meprobamate (Equanil, Miltown).
        (b) Phenaglycodol.
        (c) Promoxalane.

6. Central parasympathetic suppressants.
   (a) Benactyzine hydrochloride (Suavitil).
7. Central sympathetic suppressants—phenothiazine derivatives.
   (a) Chlorpromazine hydrochloride (Largactil, Thorazine).
   (b) Mepazine (Pecazine) hydrochloride (Pacatal, Paxital).
   (c) Perphenazine hydrochloride (Trilafon).
   (d) Prochlorperazine maleate (Compazine).
   (e) Promazine hydrochloride (Sparine).
   (f) Trifluprομazine hydrochloride (Vesprin).
8. Central sympathetic suppressants, rauwolfia derivatives.
   (a) Alseroxylon (Rauwiloid).
   (b) Deserpidine (Harmonyl).
   (c) Rauwolfia (Raudixin, Rauserpa).
   (d) Rescinnamine (Moderil).
   (e) Reserpine (Serpasil, Serpiloid).

3. Central Nervous System Stimulants.
   (a) Methyl phenidate hydrochloride (Ritalin).
   (b) Pipradol hydrochloride (Meratran).

4. Miscellaneous Agents.
   (a) Azacyclonol hydrochloride (Frenquel).

Only three or four of the drugs mentioned have been used to any appreciable extent for veterinary purposes: they are the sedative muscle relaxant meprobamate and the three phenothiazine derivatives, chlorpromazine, promazine and mepazine. Only the phenothiazine derivatives have received much veterinary attention in Great Britain and the therapeutic indications are mainly those of pre-anæsthetic sedation in the case of chlorpromazine, and 'chemical restraint' or tranquillization in the cases of promazine and mepazine. Further indications are becoming evident, as experience with the drugs increases.

Meprobamate is known commercially as Miltown and Equanil. Chemically it is 2-methyl, 2 n-propyl, 1,3-propanediol dicarbamate. It is administered orally and has an *action* similar to that of mephenesin (*q.v.*) on 'the transmission of impulses between association neurones in the spinal cord', causing a cessation of all but monosynaptic motor transmissions in the spinal cord. Mephenesin has also been credited with actions on the higher centres and these are sufficient to warrant its inclusion in the psychotherapeutic drug classification: meprobamate is similarly active on these 'higher centres', and by its oral activity and prolonged effect is superior to mephanesin for tranquillizing purposes. In some respects its insolubility and restriction to the oral route of administration are a disadvantage, for dosing is followed by a delay of about one hour before any tranquillizing effects are apparent. Knowles (1957), however, found it most useful for stopping the fretting and barking which occurs when

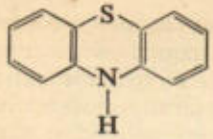
some dogs are kennelled, and for alleviation of car sickness, thunder and explosion fright, as well as for restraining those animals which interfere with stitches and bandages. He found no signs of inco-ordination or hypnotic effect and considered it safe to dispense to clients for tranquillizing purposes. *Dosing* twice or three times daily was recommended by Knowles but no dosage was suggested. Human dosage is from 0·4–0·8 G. (6–12 gr.) up to four times daily and Huebner (1956) found 100·0–400·0 mg. orally two to four times daily quite satisfactory in dogs.

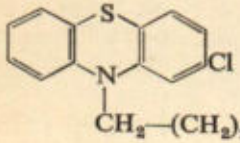
Phenothiazine Derivatives. The observation of the central actions of the antihistaminic promethazine led to investigation of other derivatives of phenothiazine with a view to finding compounds with more intense central activity. This has led to the discovery of a number of compounds of important veterinary as well as human medical significance. Two of these drugs, chlorpromazine and mepazine, are now widely used for veterinary purposes in both the United States and Great Britain: a third, promazine is of less significance. All three have tranquillizing properties but chlorpromazine has been developed mainly as an agent for pre-anæsthetic medication; mepazine (pecazine) was introduced in September 1957 as a tranquillizer only, but investigations are proceeding to determine its value in pre-anæsthetic medication; promazine has received little attention in Great Britain though its use as a tranquillizer is not unknown. The actions of all phenothiazine derivatives including promethazine, chlorpromazine, mepazine and promazine would appear to differ quantitatively rather than qualitatively. For example, promethazine has marked antihistaminic actions and reasonable local anæsthetic effect, but less sedative and tranquillizing action: chlorpromazine on the other hand has much less antihistaminic effect but is a very effective sedative and tranquillizer and has a stronger local anæsthetic action.

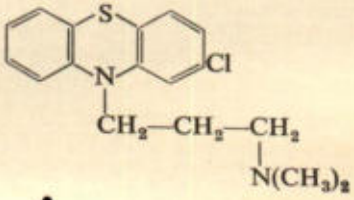
Chlorpromazine Hydrochloride, B.P.C.

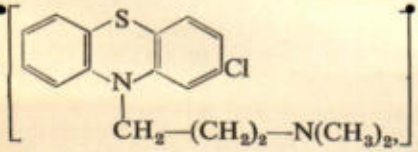
This synthetic organic compound (marketed as Largactil and Thorazine) is a white or cream, crystalline powder with a slight pungent odour and an intensely bitter taste which is followed by a numbing sensation as the local anæsthetic action becomes effective. It is extremely soluble in water (1 : 0·4), alcohol (1 : 1·3), and chloroform (1 : 1), but is insoluble in benzene and ether. Both the salt and its solutions are susceptible to light and oxidation, and solutions should contain antioxidants such as hydroquinone, ascorbic acid, or sodium metabisulphite.

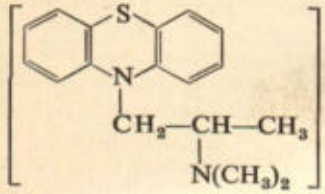
Chemically the compound is a relatively simple amino-alkyl derivative of halogenated phenothiazine; it will be seen that chlorpromazine differs from promethazine (10-(2-dimethylaminopropyl)-phenothiazine) the potent antihistaminic, only in the attachment of the chlorine atom at carbon 2 in the nucleus and in the attachment of the dimethylamino group at carbon 3 of the side chain instead of carbon 2.

(i)  Phenothiazine

(ii)  Chlorpromazine base or 2-chloro-10-(3-dimethyl aminopropyl)-phenothiazine.

This may also be written as: (iia) 

(iii)  HCl Chlorpromazine hydrochloride.

(iv)  HCl Promethazine hydrochloride (antihistaminic).

Actions. Chlorpromazine is fairly rapidly and completely *absorbed* by whatever route the compound is administered. Maximum blood levels are obtained about three hours after oral dosing and somewhat more than 1½ hours after intramuscular injection. Effects occur within five minutes of intravenous administration and become maximal shortly after, remaining so for about one hour; the duration of effect depends upon the indicator used, for most effects may persist as long as six hours, whereas hypothermic effects may be evident even after twenty-four hours. The 6 hour limit for the main action suggests a dosage rate of three times daily where repeated oral medication is indicated.

The *metabolic fate* of chlorpromazine is unknown, but only traces are found in the blood and urine, suggesting a rapid and widespread dissociation of the compound. The fact that hepatic and kidney disfunction prolongs and intensifies the action indicates that these organs are probably involved.

The *pharmacological actions* of chlorpromazine are still incompletely known is spite of the wide use and valuable therapeutic effects achieved.

The major action is a marked depressant effect on the brain stem; very little action seems to be exerted on the cerebral cortex and spinal cord. Subsidiary but important actions include the potentiating effect on general and local anæsthetics and analgesics, slight antihistaminic effects, adrenolytic and anti-acetylcholine actions, hypothermic and antipyretic effects, and a marked antemetic action where emesis is due to stimulation of the vomiting centre by certain chemicals.

Central sedative effects result in drowsiness and an inclination to sleep, and it has been shown by electro-encephalography that brain activity approximates more closely to that of normal sleep than the activity present during barbiturate depression. In spite of the drowsiness induced, mental acuity is not impaired. From this central sedation arises the 'sparing' or potentiating action which chlorpromazine exerts when administered prior to general anæsthesia, local anæsthesia, or analgesia: the anæsthetic dose of a barbiturate is cut by as much as 50 per cent when chlorpromazine premedication is practised. Although it has been shown that chlorpromazine has a local anæsthetic potentiating action it is not usual to reduce the amount of local anæsthetic administered. Also associated with the sedative action, and closely integrated with the analgesia potentiating effect, is the tranquillizing action: apprehension is reduced or abolished and the reaction to pain decreased. This last aspect of chlorpromazine action has not received the emphasis in Great Britain that it has elsewhere.

The *antemetic* effect of chlorpromazine, which is associated with depression of the vomiting centre, makes the compound remarkable in that it was the first drug discovered to have an antagonistic action to the emetic effect of apomorphine. It has been found to antagonize the emetic effect of many chemicals which act centrally, but has no limiting effect on the action of local emetics.

The *antihistaminic* action is relatively weak (over 100 times less) when compared with that of promethazine, in spite of the very small difference in chemical structure.

The *autonomic* effects of chlorpromazine on the other hand are quite significant. The compound has both adrenolytic (sympatholytic) and anti-acetylcholine (parasympatholytic) actions.

The *adrenolytic* action is of major importance in anæsthesia, for in addition to causing some peripheral vasodilatation, chlorpromazine causes an inhibition of the pressor response to adrenaline. If, during the course of anæsthesia, shock supervenes, with vasodilatation and a drop in blood pressure, the autonomic reflex vasoconstriction cannot occur when the pressor response is abolished by premedication with chlorpromazine; the fatal tissue ischæmia which might result is therefore avoided. It has been pointed out (Hall, 1957) that administration of chlorpromazine *after* the onset of shock can prove fatal, probably because a further and fatal

drop in blood pressure may result. This 'lytic' effect does not apply to noradrenaline and, where a pressor response is required in an animal subjected to chlorpromazine medication, injections of noradrenaline can be used.

The *parasympatholytic* effect of chlorpromazine is less prominent than the adrenolytic effect; it is also less than that of atropine. Nevertheless, the action is sufficiently great to reduce intestinal spasm and peristalsis. The flow of bronchial and salivary secretions is reduced.

On the *respiration*, chlorpromazine has been demonstrated to have a stimulant effect when administered to anæsthetized rabbits, but this action is not established in other species and, in fact, respiratory depression is a clinical feature of sedation, though not a marked one.

The *thermo-regulator* centre is depressed by chlorpromazine. This means that the body will tend to adopt the temperature level of the immediate environment, and chlorpromazine is therefore useful in assisting the achievement of *induced hypothermia* as an anæsthetic technique. The *antipyretic* action stems from this effect on the thermo-regulatory centre, and excessively high temperatures can be reduced in the same way that hypothermia is obtained.

Chlorpromazine has other less well defined actions which will no doubt be clarified as experience increases.

Uses. A considerable number of publications have appeared, and still are appearing, concerned with the veterinary applications of chlorpromazine.

These applications may be briefly classified under four headings:

1. Pre-anæsthetic medication.
2. General restraint.
3. Psychoneurotic disturbance therapy.
4. Specific disease therapy.

1. *Pre-anæsthetic Medication.* The use of chlorpromazine as a pre-anæsthetic sedative has been reported in cattle and horses (Troughton *et al.*, 1955; Guillon, 1955; Owen *et al.*, 1957), in sheep prior to local anæsthetic injection (Martin *et al.*, 1958), in pigs (Ritchie, 1957), in dogs (Schweizer, 1954; Troughton *et al.*, *loc. cit.*; Estrada, 1956; Weaver, 1956; Brodey *et al.*, 1956; Schmitterlow *et al.*, 1956; Bardens, 1957; Graves, 1957), and in the cat (Troughton *et al.*, *loc. cit.*).

The advantages of premedication with chlorpromazine are numerous and include:

(a) A tranquillizing effect, which besides reducing reaction to pain and irritation, and therefore allowing intubation to be achieved without causing obvious discomfort, also reduces by as much as 50 per cent. the quantity of anæsthetic and analgesic required. The sedation allows uneventful anæsthetic induction and recovery, particularly when barbiturates are used as anæsthetics.

(b) Since less anæsthetic is used, the toxic effects which might result

from anæsthesia are considerably reduced. This is especially valuable in poor risk patients, though it should be realized that sedation may be prolonged in such animals.

(c) Bronchial and salivary secretions are diminished.

(d) Although rapid intravenous injection may cause a drop in blood pressure, chlorpromazine, as explained previously, helps to avoid irreversible surgical shock when administered prior to the induction of a shocked state.

(e) The anti-emetic effect assists in cases showing emesis due to central action. (e.g. pyometra cases in bitches.)

(f) Chlorpromazine causes some skeletal muscle relaxation which assists in carrying out abdominal operations, in the reduction of fractures and luxations, etc.

Most reports indicate that chlorpromazine is preferred before morphine, partly because of the lower toxicity of the phenothiazine derivative, and partly because of the impaired mental acuity that accompanies morphine but not chlorpromazine medication. Chlorpromazine can also be used for Cæsarian operations, for the compound does not pass the placental barrier.

It must be realized, however, that chlorpromazine sedation is uncertain, particularly in horses (Owen *et al.*, *loc. cit*; Hall, 1958), and cases will occur where excitement rather than sedation follows administration. These workers also point out that the larger doses, which will produce obvious sedation, have a tendency to prolong the anæsthetic recovery period. Owen and Neal indicated that intravenous injection gave more predictable results, more rapid onset of sedation, and a shorter duration of effect.

2. *General Restraint.* In all species small doses will produce tranquillization and so facilitate the handling of otherwise intractable animals. In *small animals*, chlorpromazine administration will make the scaling of teeth, dressing of eczema patches, abdominal palpation, general handling, restraint for x-ray, opening of abscess, injection of local anæsthetics, and many similar manipulations, relatively simple in cases where such processes were previously difficult or impossible.

In *large animals*, the handling of feet, clipping, shoeing, transportation including loading and unloading, teeth rasping, the drawing of the penis in the bull, and similar operations, will all be facilitated by chlorpromazine.

3. *Treatment of Psychoneurotic Conditions.* Although such affections have not received the same attention in the veterinary as in the human medical field, according to various reports certain emotional disturbances have benefited from chlorpromazine therapy.

Troughton *et al.* (1955) record the case of a terrier bitch which developed hysteria when taken out walking and was treated with 30·0 mg. daily, decreasing to 10·0 mg. daily, for three weeks. It suffered no further attacks in the seven months subsequent to cessation of treatment.

Hoerlein *et al.* (1957) report that chlorpromazine medication was beneficial in the emotional disturbances associated with weaning in calves.

Martin and Beck (1956) described the case of a thoroughbred mare which refused to suckle her foal after the third day but which, when treated with one dose of chlorpromazine at the rate of 1·0 mg. per kg. body weight (50·0 mg per cwt.), gave no further trouble.

Many authors agree on the benefits conferred by chlorpromazine on kennelled and confined animals. Restlessness and noisiness decrease, and the animals eat, drink, and sleep normally, with no sign of fretting or apprehension. In season bitches which refused to stand, cases of pseudo-pregnancy, and similar conditions which may be associated with psychotic disturbances all benefit from chlorpromazine therapy.

4. *Use in Specific Diseases.* Those skin diseases of small animals which are associated with pruritis respond very well to chlorpromazine therapy combined with specific agents, for the phenothiazine derivative appears to remove the animals incentive to scratch and nibble so that the skin is not continually damaged by self-inflicted trauma.

In large animals *tetanus* is perhaps the most important disease to respond to repeated chlorpromazine therapy at the rate of 1·0–2·0 mg. per kg. in single daily doses (Troughton *et al.*, *loc. cit.*; Tait *et al.*, 1957), or 250·0 mg. twice daily (van den Heever, 1955). Tetanus in other species has also been successfully treated—dogs, donkey, bull and pig (Owen *et al.*, 1959).

Colic cases in horses, particularly of the spasmodic type, have responded excellently to 1·5 mg per kg. (75·0 mg. per cwt.) given intramuscularly, symptoms disappearing within thirty minutes (Troughton *et al.*, *loc. cit.*).

The relief of *choke* in cattle is greatly facilitated by chlorpromazine (Cartmell, 1956; Martin *et al.*, 1958) given intramuscularly in doses of 250·0–500·0 mg., depending on the size and state of health of the animal. Liver fluke, it must be remembered, damages the liver and may be responsible for excessive depression following the administration of small doses of the drug. The same authors report the successful use of chlorpromazine as a muscle relaxant in the reduction of shoulder luxations in cattle, using a 500·0 mg. dose for a 1,000 lb. animal; also 250·0 mg. doses in sheep prior to Cæsarian section under local anæsthetic were found to be very effective.

Toxicity. In itself chlorpromazine is not highly toxic but it is somewhat unpredictable in its sedative effects, especially in horses, and following intramuscular administration. Excitement and struggling during the onset of action and during post-anæsthetic recovery are the most important possibilities. Barbiturates or other sedatives may be used to control these idiosyncratic responses. Should nephritis or hepatitis be present animals will show an exaggerated and prolonged response to chlorpromazine. Chlorpromazine is contra-indicated in deeply anæsthetized animals.

Dosage. For pre-anæsthetic medication and general sedation, the dose for all species lies between 1·0 and 2·0 mg. per kg. body weight (50·0–100·0 mg. per cwt.) when administered intramuscularly and between 0·5 and 1·0 mg. per kg. (25·0–50·0 mg. per cwt.) by the intravenous route. Wide variations in dosage have, however, been reported, up to 4·0 mg. per kg. having been used in most species without serious consequences. In the dog, Miss Weaver suggests that 1·1 mg. per kg. given intramuscularly followed by anæsthesia 1½ hours later is the optimum method of applying chlorpromazine as a pre-anæsthetic sedative. Oral dosage to achieve pre-anæsthetic sedation in dogs and cats is optimum at 4·0 mg. per kg. according to Troughton *et al.* (*loc. cit.*).

The following dosage scheme has been recommended commercially:

Small animals:	Oral:	4·0–5·0 mg. per kg. daily. (2–2½ mg. per lb. approximately)
	Parenteral:	2·5 mg. per kg. daily for sedation. 2·0 mg. per kg. for premedication given either intravenously or intramuscularly.
Horse and Cow:	Parenteral:	1·0 mg. per kg. daily for sedation. 1·0 mg. per kg. for premedication, given by the intramuscular route only*. 10·0 ml. for a 1,000 lb. horse given intramuscularly 1½ hours before anæsthetizing is suggested as a standard dose.
Pig:	Parenteral:	2·0 mg. per kg. by intravenous or intramuscular injection for either sedation or premedication.

* Note the preference of Owen and Neal for intravenous injections, mentioned at the end of section 1, p. 229.

Administration in large animals is normally by intramuscular injection of a 5 per cent solution. This is sometimes followed by painful but temporary reactions at the sites of injection. In small animals intravenous injection of 2·5 per cent. solutions can be given, but this concentration is irritant when given intramuscularly and should be diluted to 0·5 per cent. concentrations whenever this is possible.

In small animals collapse of the third eyelid and wrinkling of the face provides an indication of the point when further procedures may commence following administration of chlorpromazine. In all species it is usual to allow about 10 minutes to elapse after intravenous injection and thirty minutes or more (up to 90 minutes has been suggested) after intramuscular injection: oral dosing may not give maximum effects for up to three hours after dosing.

Duration of effect will vary with the individual and dose. Normal dosage gives sedation periods of about six to eight hours, but the higher

doses mentioned may provide obvious sedation for up to 24 hours or longer. For sedative purposes doses may be repeated from two to four times daily depending on results and requirements.

Chlorpromazine is available as 10·0 mg. and 25·0 mg. tablets, as a 2·5 per cent. solution in 1·0 ml. ampoules and a 5 per cent. solution in 5·0 ml. ampoules.

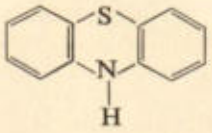
Promazine has been reported to be an extremely effective tranquillizer in dogs (Gradess, 1956; Knowles, *loc. cit.*; and Greer, 1958). *Doses* of about 3·0 mg. per kg. (1·5 mg. per lb.) give sedation for a period of up to six hours when administered either orally or by the intramuscular and intravenous routes.

Mepazine or Pecazine

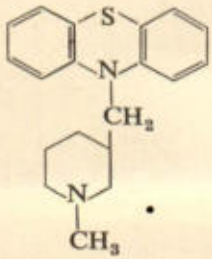
This phenothiazine derivative has been developed as a tranquillizing sedative and marketed under the names of Paxital in the United States and Pacatal in Great Britain. Recently it has been marketed for veterinary purposes, and reports on its clinical effects are increasing in number.

Chemically it differs from the phenothiazine derivatives already mentioned in having a heterocyclic ring in the side chain and has the formula 10-(N, methyl-3-piperidyl-methyl) phenothiazine, graphically written as in (v)

(v)



Phenothiazine.



Mepazine.

The salts of mepazine which are used commercially are white, water soluble powders which darken on exposure to light. Solutions are incompatible with alkalis and chlorides and should therefore not be diluted with saline solutions but only glucose solutions or sterile water.

Actions. Absorption is rapid no matter what the route of administration. Effects are apparent one hour subsequent to oral dosing, five to ten minutes after intravenous and about thirty minutes after intramuscular injection. Mepazine is thus very similar in this respect to the other phenothiazine tranquillizers. The action following oral administration

persists for about twelve hours, but the duration will vary according to size of dose and the condition treated; it is usual to dose three times daily.

As with chlorpromazine the metabolic fate is unknown but the effects of kidney and liver dysfunction are similar to those of chlorpromazine, indicating a similar fate.

The *pharmacological* actions of mepazine are similar in quality to those of other phenothiazine derivatives but quantitative differences exist. Thus the tranquillizing, sedative, and anæsthetic and analgesic potentiating effects are good, but when combined with the general anæsthetics in particular, the respiratory depressant action is intensified. Mepazine shows weak anticonvulsive effects and differs from chlorpromazine in the intensity of its autonomic effects: mepazine has a weak hypotensive action, and the sympatholytic and parasympatholytic effects are about equal in intensity: the adrenolytic effect is incomplete, but on the parasympathetic side mepazine inhibits secretory activity of the salivary and bronchial mucosa glands; normal and artificially increased peristalsis is inhibited. The hypothermic effect is appreciable.

Uses. So far mepazine has been recommended only for pre-anæsthetic medication, general restraint with sedation, and the treatment of psychoneurotic disorders in dogs. Its use in the cat for the same purposes is recorded (Traynor, 1958); treatment of zoo animals is also favourably reported (Jones, 1957). Further investigations are proceeding.

Dosage:

In the dog, oral and parenteral routes are used:

Oral:	5·0–10·0 mg. per lb. (11·0–22·0 mg. per kg.) in three divided doses daily.
Parenteral:	50·0–100·0 mg. as a single dose by all normal parenteral routes.

The commercially available forms are 50·0 mg. and 100·0 mg. tablets of the hydrochloride, and 50·0 mg. mepazine acetate in 2·0 ml. ampoules.

Narcotics

The production of this state of C.N.S. depression, which borders on anæsthesia, may be achieved by the use of subanæsthetic doses of barbiturates or chloral hydrate and by the administration of morphine or opium extracts such as papaveretum. Cannabis Indica, or Indian hemp, was at one time used for this purpose but is now rarely if ever used in Great Britain owing to its irregular and unpredictable action. A new addition to the range of narcotics is thiambutene hydrochloride, described in an early publication as an analgesic and hypnotic (Green, 1952), but shown to produce narcosis: its action is reversed by the intravenous injection of nalorphine hydrobromide.

These narcotics may be used alone for restraining hysterical animals or

for general sedation but are most frequently administered prior to anæsthesia by general or local anæsthetics. In view of the increasing use of combinations of non-volatile basal narcotics and non-volatile anæsthetics it should be stressed that, though this practice is safe in normal animals, the liver and kidneys of the toxic animal may be unable to tolerate the increased work entailed in detoxicating and excreting these compounds. It is therefore advisable in these cases to use volatile gaseous anæsthetics in conjunction with the non-volatile narcotics.

These narcotics cannot be administered universally and indiscriminately in all species. Chloral hydrate is suitable for adult farm animals; the barbiturates can be used in farm animals and household pets; morphine and opium extracts are suitable only for dogs: pethidine (meperidine) may be used in cats, but its sedative action in this species is not as powerful as that of morphine in the dog.

The barbiturates and chloral hydrate have been described elsewhere (see Chapter 13) but morphine, opium and thiambutene may best be mentioned here.

Opium, B.Vet.C. (*D.D.A.*)

Unprocessed or raw opium consists of the dried exudate obtained by the incision of the growing unripe seed capsules of a poppy, *Papaver somniferum L.*, cultivated for this purpose in the Middle East, the Indian continent, and China. It is imported as brown resin-like masses which have an aromatic and characteristic odour. Opium should contain at least 9·5 per cent anhydrous morphine, but a great number of other alkaloids are present: these may be classified into *phenanthrene* derivatives, of which morphine and its esters, both natural and synthetic, such as methyl-morphine (codeine), dimethyl-morphine (thebaine) and diacetyl-morphine (heroin), are examples, and the *isoquinoline* derivatives such as papaverine and narcotine. The former group are predominantly sedative in their effects but the latter group tend to cause relaxation of smooth muscle and have relatively low narcotic effects.

Actions and Uses. The greatest part of the action of opium is related to its morphine content which provides analgesic, sedative, and hypnotic actions. The isoquinoline derivatives add the smooth muscle relaxant effects, giving a broader application to a combination of alkaloids than is possible with the individual alkaloids. It is for this reason that opium has a greater constipatory effect than pure morphine: there is little local anæsthetic action, but direct action on the intestinal muscle combined with central action causes closure of the sphincters and a slowing of peristaltic waves.

Opium is used mainly as an intestinal sedative in gastro-enteritis of all species other than the cat. It is also a useful cough sedative in the same species.

For intestinal sedation, powdered opium may be given combined with

chalk, kaolin, and catechu, but such preparations should not be given in obstructive colics. The tincture may be used in drenches of similar formulation. In large animals, these opium compounds are not as reliable as in man or the dog, but personal experience with morphine indicates that the possibility of causing maniacal excitement in horses is less likely than is generally believed. Amadon *et al.* (1937) have shown that morphine and its derivatives are not entirely satisfactory in the horse.

For cough sedation, the tincture, alone, or combined with other drugs as in camphorated tincture of opium and Dover's powder, has been used, but cases should be chosen with care for the depression of the cough centre in an animal with profuse bronchial secretions would obviously be wrong. Opium is therefore indicated for the treatment of harsh, painful, dry coughs. Codeine phosphate is usually preferred in small animals.

Dosage:

Tincture of Opium, B.Vet.C. (Laudanum) (*D.D.A.*)

Horse: 1–2½ fl. oz. (30·0–80·0 ml.)
Cow: 2–4 fl. oz. (60·0–120·0 ml.)
Sheep: 90–320 m. (6·0–20·0 ml.)
Dog: 5–30 m. (0·3–2·0 ml.)

This compound contains 1 per cent. anhydrous morphine.

Camphorated Tincture of Opium, B.Vet.C. (Paregoric)

Dog: 30–90 m. (2·0–6·0 ml.)

This formulation contains only 0·05 per cent. w/v anhydrous morphine and is therefore not controlled, but Concentrated Camphorated Tincture of Opium, B.Vet.C. is controlled as it contains 40 per cent. w/v of tincture of opium and consequently 0·4 per cent. w/v of anhydrous morphine: its dose is 4–12 m. (0·25–0·75 ml.) for the dog, which is ⅛th that of the normal tincture.

Powdered Opium, B.Vet.C. (*D.D.A.*)

Horse: 45–120 gr. (3·0–8·0 G)
Cow: 90–180 gr. (6·0–12·0 G.)
Sheep: 8–30 gr. (0·5–2·0 G.)
Pig: 5–15 gr. (0·3–1·0 G.)

Powdered opium is standardized to contain 10 per cent. w/w anhydrous morphine and is controlled.

Powder of Ipecacuanha and Opium, B.Vet.C. (Dover's Powder.)

Dog: 1½–10 gr. (0·1–0·6 G.)

This powder was used by Dr. Dover, the celebrated pirate, during his expeditions along the South American Coast and through the islands of the West Indies. It contains equal parts (10 per cent.) of powdered opium and ipecacuanha in lactose. It contains 1 per cent. w/w morphine but is not controlled by the Dangerous Drugs Act because of its ipecacuanha content.

Morphine (*D.D.A.*)

This alkaloid, extracted from opium, is mainly used in the form of either the hydrochloride or the sulphate. These two salts are white crystalline powders which are odourless but have the typical bitter taste and the water solubility of alkaloidal salts. They are far less soluble in alcohol, although the hydrochloride, with a solubility of 1 in 100 is about ten times more soluble than the sulphate.

Actions. There are no external actions. Following oral or parenteral administration, *absorption* is rapid and the actions are clinically evident within two or three minutes. In all species there is at least an initial period of stimulation but this soon passes in the dog: in the cat, however, stimulation predominates throughout, whilst in other species restlessness may give way to depression. This irregularity of response makes morphine unpopular in all species but the dog.

In the *dog*, clinical signs following subcutaneous injection consist of restlessness with nausea, salivation, and finally emesis and defæcation. Subsequently, depression deepens to narcosis and a drop in body temperature occurs due to peripheral vasodilatation: during narcosis sudden noises will cause muscle spasms which can be very dangerous if local anæsthesia is being used instead of general anæsthesia—even the dropping of an instrument into a tray causes a jerk. Narcosis is achieved in about 20 minutes and will last 2 or 3 hours unless the animal is toxic, when it may persist for as long as 24 hours.

A knowledge of the pharmacological actions in the dog would enable these clinical effects to be predicted. The main action of morphine is exerted on the central nervous system and consists largely of stimulation followed by depression.

1. The *cerebral cortex* is initially stimulated, but depression of both motor and sensory cortex soon follows. The sensory cortex is particularly depressed, giving a powerful analgesic and sedative action.

2. The *medullary centres* are affected in two ways:

(a) Group 1 consisting of the vagal, vomiting and oculomotor centres (V.V.O.) are initally stimulated and later depressed. This selective stimulation is mainly responsible for the salivation, emesis, defæcation, and a constricted pupil (this effect is irregular). The heart rate initially increases due to nausea, but is then slowed by the stimulated vagus.

(b) group 2 comprising the respiratory, vasomotor, and cough centres (R.V.C.) are depressed without any initial stimulation. This depression is responsible for peripheral vasodilatation and loss of heat but there is little effect on the blood pressure; respiration is slowed but may be deeper than normal, and reaction to carbon dioxide is lowered: the cough reflex is materially affected even by small doses. These effects on respiration are very important if morphine is used as a basal narcotic and may affect the choice of anæsthetic.

The *alimentary tract* is quite strongly affected, the action being both

central and local. The sphincters are closed and the intersphincter muscle remains in tonic spasticity so that food does not pass and constipation results. These effects follow the initial period of stimulation which results in emesis and defæcation. Opium, due to the muscle relaxant effects of the isoquinoline derivatives, has a much stronger constipating effect.

Tolerance. An acquired tolerance to morphine will develop in animals subjected to repeated dosing but it is unusual to administer morphine in this manner.

Idiosyncrasy. Individual animals of all species will show unusual reactions to morphine. In large animals, restlessness and excitement may result when sedation is expected. In the dog, the most common idiosyncratic reaction could be classed as inherent tolerance, for doses as large as 1½ gr. (97·0 mg.) have been given with no effect other than a slight drowsiness when deep narcosis would have been anticipated.

Excretion. The major part of a morphine dose is excreted via the urine in the 24 hours following administration. It is present in the urine mainly in a conjugated form, but partly unchanged. A small quantity is excreted into the intestines.

Uses. Morphine has three main uses:

1. *Premedication.* Morphine has a place in balanced anæsthesia of dogs. Its powerful analgesic effect makes it very suitable for this purpose and the narcotic effect enables smooth and easy induction of anæsthesia with either a non-volatile or an inhalant anæsthetic. Further advantages are the reduction of the amount of anæsthetic required and an uneventful recovery period. Morphine is compatible with hyoscine (scopolamine) which may be administered simultaneously to reduce salivation and nausea.

Morphine is not the ideal basal narcotic. Its *disadvantages* include the incidence of vomiting and salivation, the constipatory effect, elimination of pupil reflexes, and respiratory depression. In toxic patients the relatively slow excretion rate makes full recovery very slow and provides a problem in maintaining body temperature and freedom from hypostatic pneumonia.

Hall and Weaver (1954), and Hall (1957), have recommended Papaveretum, B.P.C., in the form of a 2 per cent. injection obtainable alone or with hyoscine. This strength is equivalent to ⅓ gr. (20·0 mg.) per ml., which is reputed to be equivalent in activity to ¼ gr. (15·0 mg.) morphine. Papaveretum contains 50 per cent. w/w anhydrous morphine, with codeine (2·5–5·0 per cent.), narcotine (16·0–22·0 per cent.), and papaverine (2·5–7·0 per cent.). It is reputed to cause less nausea and emesis.

Morphine and papaveretum, with or without hysocine, should be given subcutaneously 30–45 minutes before induction of anæsthesia, and doses should be in the region of 1/180 gr. per lb. (0·66 mg. per kg.) body weight, which is equivalent to about 1/6 gr. for a 30 lb. dog. (8·5 mg. for 13·0 kg.).

2. *Intestinal sedation.* Morphine is a constituent of many scour drenches, including *Tincture of Chloroform and Morphine, B.Vet.C.*, (chlorodyne) which contains 0·229 per cent. morphine hydrochloride but is exempted from control under the Dangerous Drugs Acts. Chlorodyne is frequently combined with chalk, kaolin, catechu, and ginger, as a treatment for diarrhœa in cattle, horses, and dogs, and morphine as the hydrochloride, acetate, or sulphate is similarly used. These preparations are especially useful in spasmodic colic and where diarrhœa is accompanied by painful straining (tenesmus).

3. *Cough sedation.* Codeine is superior to morphine for this purpose, but nevertheless morphine is a constituent of many cough mixtures, pills, and tablets, used in veterinary practice in both large and small animals. It depresses the cough reflex and is therefore indicated in the 'non-productive', harsh, dry cough usually occurring at the beginning of bronchopneumonia.

Dosage:

Morphine Salts (*D.D.A.*), by subcutaneous injection.

Narcosis:	Dog:	1/12–1/6 gr. (5·0–10·0 mg.)
Sedative:	Horse and Cow	2–10 gr. (0·14–0·6 G.) (normally 2–4 gr. or 0·14–0·3 G)
	Sheep and Pig:	½–1 gr. (30·0–60·0 mg.)

Solution of Morphine Hydrochloride, B.Vet.C. (*D.D.A.*)
By mouth:

Horse and Cow:	½–2 fl. oz. (15·0–60·0 ml.)
Sheep and Pig:	30–120 m. (2·0–8·0 ml.)
Dog:	5–20 m. (0·3–1·3 ml.)

This solution contains 1 per cent. w/v morphine hydrochloride.

Tincture of Chloroform and Morphine, B.Vet.C.

Horse and Cow:	1–2 fl. oz. (30·0–60·0 ml.)
Foal and Calf:	½–1 fl. oz. (15·0–30·0 ml.)
Dog:	5–25 m. (0·3–1·5 ml.)

The tincture contains 0·229 per cent. w/v of morphine hydrochloride.

Note. These compounds are not recommended for use in cats.

Toxicity. Cases of morphine toxicity are now rare. When it is seen it is usually associated with faulty renal filtration and occurs with toxæmic cases. The delirious symptoms rarely occur and respiratory stimulants with tannic acid or potassium permanganate (0·2 per cent.) by mouth are the main features of treatment. Picrotoxin or nikethamide by intravenous injection may be given, but Nalorphine Hydrobromide, B.P.C., in doses of 1/6–3/5 gr. (10·0–40·0 mg.) is a specific antagonist for use in opiate respiratory depression; it may be given intravenously or subcutaneously.

Animals should be kept warm and quiet; oxygen with carbon dioxide plus artificial respiration may be useful in acute cases, but manual manipulation is not usually practicable for the long periods of depression normally met.

Other alkaloids of opium *viz.* codeine and diacetylmorphine appear in Chapter 9—Respiratory System.

Thiambutene Hydrochloride

This compound known commercially as Themalon is a member of a group of narcotic and analgesic drugs classed as amino-alkyl-tertiary-carbinols (Adamson, 1950; Adamson and Green, 1950). It has the formula [3-diethyl-amino-1:1-di-(2′-thienyl)but-1-ene hydrochloride] and is a white, water soluble, bitter tasting powder that gives unstable solutions which, though they can be sterilized by boiling at 100°C., turn brown on keeping for a few days. Solutions are prepared for injection by dissolving a hypodermic tablet in sterile water immediately prior to administration.

Actions. Thiambutene is similar to morphine in many ways, but has several interesting additional effects. It should be used only in dogs and there are no *external* actions. *Orally* the compound is irritant in solid form and may cause emesis but this does not occur when solutions are given. Following *subcutaneous* administration a local anæsthetic effect prevents pain. Intravenous injection is also suitable. Given by these parenteral routes, thiambutene causes analgesia and sedation, hypnosis, or narcosis, the degree depending on the size of the dose and the route of administration. Small doses will cause mild analgesia and sedation, whereas doses may be increased to give strong analgesia and deep narcosis: subcutaneous administration will tend to give a slower onset but more prolonged duration of effect and lighter level of C.N.S. depression, whereas intravenous injection will give stronger analgesia and deeper narcosis in a shorter time and for a shorter period.

Normally no emesis follows parenteral injection but salivation may occur which, however, can be prevented by the use of atropine or hyoscine.

Idiosyncrasy. Individual cases have occurred where normal doses have caused hysteria and convulsions, or, at the other extreme, deep and fatal narcosis.

Antagonism. The morphine derivative nalorphine hydrobromide acts in its convulsant capacity as a stimulant for animals depressed by morphine and morphine-like substances, including thiambutene hydrochloride. An intravenous injection of about 20·0 mg. causes awakening of the depressed animal in a minute or so: in some cases full recovery occurs but in others the animal relapses into a hypnotic state and only recovers fully several hours later.

Uses. The main indication for the use of thiambutene is in place of morphine, as a basal narcotic. Barbiturates and inhalant anæsthetics may

be used in conjunction with thiambutene: Owen (1955) reports on its successful use with thiopentone for anæsthesia of bitches with pyometra. It has also been used as a sedative and analgesic for minor manipulations and surgery.

Toxicity. Thiambutene must not be used in cats, which react to the convulsive effects in much the same way as they do to morphine. In the dog, subcutaneous overdosage produces rapid analgesia and hypnosis followed by convulsions (Green, 1952). Intravenous overdosage causes convulsions, a rapid drop in blood pressure and sudden death. Nalorphine will only antagonize the depressant effects of thiambutene: convulsions should be controlled with pentobarbitone or thiopentone sodium salts.

Dosage. As with most narcotics and sedatives, the highly nervous animal will require more thiambutene than the placid animal. Small dogs will require slightly more in proportion to their weight than the large dog. Solutions containing from 25·0–100·0 mg. per ml. may be used.

Subcutaneous injection:

Mild analgesia and sedation:	2·5 mg. per lb. (5·5 mg./kg.) body weight. Effects will be seen in 10–20 minutes, be maximal in 30 minutes, and disappear in about 2 hours.
Deep analgesia and narcosis:	10·0 mg. per lb. (22·0 mg./kg.) Effects will appear and reach a maximum more rapidly and may persist for as long as 10 hours.

Intravenous injection:

Doses will vary from 0·5–2·5 mg. per lb. (1·1–5·5 mg./kg.) and will usually give narcotic effects within a few minutes. Recovery is rapid with small doses and prolonged with large doses (15 mins.–3 hours.)

Thiambutene hydrochloride is available in packs of 20 hypodermic tablets each of 50·0 mg.

Analgesics

The analgesic drugs may be divided into several groups:

1. Opium and derivatives of opium (*q.v.*).
2. Synthetic morphine substitutes such as Pethidine Hydrochloride, B.Vet.C., Phenadoxone Hydrochloride, B.P., and Methadone Hydrochloride, B.P. Only the first has found a place in veterinary medicine and surgery.
3. The gaseous anæsthetics (*q.v.*), particularly nitrous oxide and trichlorethylene.
4. Salicylic acid derivatives, the para-amino phenol derivatives acetanilide and phenacetin, the pyrazolone antipyretics phenazone, amidopyrine and the related phenylbutazone. This group is not used primarily for analgesia in veterinary medicine or surgery.

Pethidine Hydrochloride, B.Vet.C. (*D.D.A.*)

Known in America as Meperidine Hydrochloride, U.S.P., pethidine hydrochloride is a synthetic white crystalline powder with little odour and a bitter taste. It is soluble in water, less soluble in alcohol and chloroform, and almost insoluble in other organic solvents.

Actions. Pethidine was originally developed as a smooth muscle relaxant—antispasmodic or spasmolytic—but besides having this power it is also analagesic, though only 1/10th as active in this respect as morphine. *Absorption* is rapid. Following oral administration in dogs, the maximum analgesic effect is given in approximately 45 minutes and lasts 4–6 hours: after subcutaneous injection, maximal effects follow in about 20 minutes and persist for from 3–4 hours. The duration of effect varies according to the severity of the pain—the greater the pain the shorter the period between doses.

The *antispasmodic or spasmolytic* action of pethidine is due to a relaxant effect on smooth muscle of the large intestine, the uterus, bladder and the bronchi, partly by an atropine-like action on the parasympathetic nerve endings but mainly by a direct action on muscle fibres similar to that of papaverine or narcotine. Through these two effects it will be seen that the greater the tonicity of the muscles the more marked will be the action. This is amply supported by clinical observations. The effect on the small intestine is one of decreased tonus which results in a delay in the passage of food though this is less marked than with morphine. The *analgesic* action is similar to that of codeine but more pronounced; it is exerted centrally and there occurs a raising of the pain threshold.

The *sedative* action is slight when compared with that of morphine, but hypnosis will follow the administration of large doses, especially if hyoscine is administered simultaneously.

Excretion is mainly via the kidneys after inactivation in the tissues either by hydrolysis or methylation. Traces will be found in saliva within 30 minutes of intramuscular injection and some may be found in the fæces. Very little passes the placental barrier, making the compound suitable for premedicating Cæsarian section cases.

Uses. The main advantage of pethidine over morphine is its usefulness as a sedative analgesic in cats: other advantages lie in its freedom from any emetic action, its relatively short action, and its lack of constipatory effect. Pethidine has been used as a sedative and antispasmodic in cattle and horses (Archer, 1947), as a sedative in large sows and boars (Hall, 1957), and as a premedication sedative in dogs and cats (Carlson, 1955; Meyer, 1945; Hall, 1957). In horses the action is a little irregular, the sedative action being absent and transient excitement occurring occasionally (Raker, 1955), but its use in spasmodic colic has been recommended. As a premedication drug in dogs and cats it has been found quite useful, and Albrecht *et al.* (1951) found that pethidine combined with pentobarbitone sodium was far safer in dogs than an ether-pentobarbitone

combination: less anæsthetic is required and post-operative excitement is eliminated.

Dosage. Intravenous injection is not recommended for animals owing to the vasomotor effects which may result.

Horse and Cow:	100·0 mg. per cwt. (50·0 kg.) by subcutaneous or intramuscular injection.
Pig:	1·3–2·25 mg. per lb. (3·0–5·0 mg./kg.) by intramuscular or subcutaneous administration.
Dog:	2·0–5·0 mg./lb. (10·0 mg./kg.) orally or by subcutaneous injection.
Cat:	12·5 mg./lb. approx. (25·0 mg./kg.) orally. 2·0–5·0 mg./lb. approx. (4·0–10·0 mg./kg.) subcutaneously.

The oral dose in cats is far greater than the parenteral dose.

Toxicity. This is relatively insignificant. Overdosage may cause a drop in blood pressure, and convulsions which can be counteracted by pentobarbitone sodium injections. Nalorphine hydrobromide will counteract respiratory and generalized depression in cases where overdosage causes sedative effects only.

Muscle Relaxants

One of the requirements of surgery, but particularly of abdominal and orthopædic surgery, is muscular relaxation. Local anæsthetic blockade of the nerve supply to muscles situated in, or affecting, the site of operation, will cause muscular relaxation, but the procedure involved in paravertebral nerve blocking, for example, is protracted and somewhat specialized. The development of skeletal muscle relaxants in the field of human surgery has provided the veterinary profession with a means of causing total skeletal muscle relaxation by a single low volume parenteral injection.

Muscle relaxants are increasingly used in the medical field but so far application in veterinary surgery has been mainly confined to small animals, although a relaxant specifically intended for casting horses without anæsthesia is now available (Montgomerie, 1958).

Certain risks and obligations attach to the use of muscle relaxants on animals. Hall and Weaver (1954) observed that 'normal clinical' doses do not prevent some movement following a painful stimulus, but, as the controversy raised by the issue of a relaxant for casting horses shows, everyone is not agreed on the humanity of applying these drugs to conscious animals: Hall (1957) unequivocally states that relaxants should be administered only to unconscious animals which must be maintained in that state throughout the effective period of the relaxant.

A real danger attaching to the use of relaxants is that of intercostal muscle paralysis. Because of this danger, means of applying sustained

artificial respiration must be available for immediate use. This has undoubtedly been one of the deterrents to a wider veterinary use.

A further danger, which has received full attention in human surgery, is that of over-extending joints and limb attachments, which may result in the tearing of, or pressure on, nerves and other tissues. Radial paralysis due to stretching of the brachial plexus when strapping down is particularly to be guarded against. It may be as well to know that circulatory collapse of an idiosyncratic nature has occurred following the use of relaxants in man, and that a relaxant is not used unless it offers distinct advantages in particular cases.

There are two main groups of muscle relaxants, both of which may be considered to be quaternary ammonium derivatives.

1. *Competition blocking agents*, which compete with acetylcholine at the motor end-plate and so prevent depolarization of the end-plate and stimulation of the muscle.

2. *Depolarizing agents*, which maintain the neuromuscular junction in a state of depolarization (see Local Anæsthetics: Ionic Theory of Nerve Impulse Transmission) so that further impulses are blocked. This may be described as a sustained refractory period. As these compounds must first depolarize the end-plate, they cause an initial stimulation and are, in this way, similar to acetylcholine.

These two groups are to a certain extent antagonistic and should not be used together. It is also important to remember that antagonists to the acetylcholine competitors (neostigmine) will in some cases (succinylcholine) prolong the action of depolarizing agents by preventing the rapid hydrolysis of the relaxant.

A third, minor group, unrelated chemically and pharmacologically to the previous two, acts by depression of the lower motor neurones, which are responsible for transmitting impulses to the muscles and are situated in the anterior horn of the spinal cord. They are therefore spinal cord depressants.

Competition Blocking Agents. The members of this group of compounds are also referred to as *curarizing agents* since the alkaloids of curare were the first of these agents to be investigated and used surgically. The important members of this group are Tubocurarine Chloride, B.Vet.C., Dimethyl Tubocurarine Iodide, N.F., and Gallamine Triethiodide, B.P.

Tubocurarine Chloride, B.Vet.C.

This white, odourless, microcrystalline alkaloidal salt is soluble in water to the extent of 1 : 20, and in alcohol of 1 : 45. It is insoluble in chloroform and ether. The preparation is standardized biologically and the British Unit is contained in 1·0 mg. of the Standard Preparation maintained by the Medical Research Council. The American Unit potency is equivalent to the activity of 0·15 mg. δ.tubocurarine chloride pentahydrate.

Action. Tubocurarine chloride affects the myoneural junction by preventing the access of acetylcholine to the motor end-plate: this may

also be expressed as raising the stimulation threshold of the end-plate. This results in a paralysis of skeletal, or voluntary, muscle, commencing in the eyes and then affecting successively, muscles of the face, neck, limbs, abdomen and respiratory muscles (intercostal and diaphragm). Recovery takes effect in the reverse order. The action is rapid following intravenous injection, the first effects appear in about a minute and maximum action in 3–5 minutes: duration of effect is about 45 minutes, depending on individual reaction and dosage. Where respiratory paralysis is going to occur it may be expected 7–10 minutes subsequent to administration.

Dogs and cats appear to tolerate tubocurarine better than other species.

Note: Tubocurarine has no sedative or analgesic effect and should therefore be used in conjunction with an anæsthetic: non-volatile anæsthetics and relaxants should not be mixed together in the syringe and administered simultaneously because of the possibility of precipitation.

Excretion. Tubocurarine is excreted mainly in the urine, partly unchanged and partly metabolized.

Toxicity. The side actions of tubocurarine are mainly those associated with histamine production, which occurs in a number of cases. The chief symptoms of histamine release are salivation, a drop in blood pressure, bronchial secretion, and bronchial spasm: the administration of antihistaminics will counteract these effects. Intratracheal intubation is advisable in all cases submitted to relaxant injections.

Overdosage produces death from asphyxia; occasionally a large drop in blood pressure is an aggravating factor. Relaxation of the cardiac sphincter and œsophageal muscles may allow regurgitation of food from the stomach.

Treatment consists of artificial respiration using oxygen, combined with intravenous Edrophonium, N.N.R. and neostigmine injections. The action of the neostigmine is reputed to be one of preventing acetylcholine destruction and causing the build up of a concentration which exceeds the stimulation threshold of the motor end-plate.

Uses. Tubocurarine is chiefly indicated as a muscle relaxant for use in surgery and should always be used in conjunction with anæsthetics. It is compatible pharmacologically with all anæsthetics but should be used in reduced doses with ether, which has itself some curare-like effects; it should not be mixed with non-volatile anæsthetic solutions as precipitation may occur.

Tubocurarine is indicated for abdominal surgery, repair of fractures, anal and perianal surgery, mainly in dogs and cats; for spastic paralysis in dogs (Davidson, 1950), tetanus in the dog (Ripps, 1950) and the horse (Booth and Pierson, 1956). In the treatment of tetanus, intramuscular injections of oil and beeswax suspensions of 3 per cent. tubocurarine are

used: the effect of a single intramuscular injection should last for about 24 hours.

When used for Cæsarian section there should be no effect on the young (Pickett, 1951).

A standardized curare, the main active ingredient of which is tubocurarine, has been used in dogs (Dinsmore, 1950; Jones, 1950; Harris, 1951; Pickett, 1951), in the horse (Cella *et al.*, 1952; Booth *et al.*, 1953), when it was found that it was inadvisable to use it in conjunction with chloral hydrate anæsthesia, and in calves, lambs, and pigs (Jones, 1950).

Dosage and Administration. It must be remembered that the American unit is equivalent to 0·15 mg. tubocurarine chloride pentahydrate. Dosages are not satisfactorily determined and administration should be slow and continued until the desired effect is achieved. With aqueous solutions the intravenous route is preferred but with oily suspension the intramuscular route must be used.

Horse:	Up to 112·5 mg. per 1000 lbs. (500·0 kg. approx.) may be used in tetanus (Booth *et al.*, 1956). Normally 35·0 mg. per 1000 lbs. would be considered as a maximum.
Calf, Lamb, and Pig:	0·035 mg. per lb. (0·075 mg. per kg.) body weight (maximum)
Dog and Cat:	0·045–0·09 mg. per lb. (0·1–0·2 mg. per kg. body weight).

Note: Doses should be reduced to ⅓rd the above if ether is used concurrently with tubocurarine.

Dimethyl Tubocurarine Iodide, N.F., is similar in character and actions to tubocurarine chloride but it is about six times as potent as the chloride in rabbits and cats: in man it is only three times as active. Clinically in man it has been shown to cause little respiratory depression, little tendency to produce histamine or cardiovascular shock, and to possess a slightly longer duration of effect; it has therefore been advocated for thoracic surgery (Wilson, 1950). The dosages should be estimated on the basis of one sixth of those suggested for tubocurarine chloride initially, but administered up to and beyond these, according to effect.

Gallamine Triethiodide, B.P., is a white amorphous or granular powder which is hygroscopic and therefore very soluble in water: it is slightly soluble in alcohol and acetone but insoluble in other organic solvents. Gallamine acts in a similar manner to tubocurarine but improves both blood pressure and heart rate rather than depresses them, causes little histamine release and has a potency about five times less than tubocurarine. Duration of effect is the same or slightly longer. Administration is by intravenous injection to effect. *Doses* will be proportionally larger, but clinical reports are not available. In man 80·0 mg. are given as an initial dose, followed by 40·0–80·0 mg. 20 minutes or so later, if required: with the larger repeated dose respiratory assistance is often required.

Antagonists. Both gallamine triethiodide and dimethyltubocurarine iodide are antagonized by physostigmine and neostigmine.

Though both these relaxants have been used in veterinary anæsthesia no clinical reports are available (Hall, 1957).

Depolarizing Agents. The members of this group of compounds all have a chemical similarity in their quaternary ammonium structure. The most important members of this group are Decamethonium Iodide, B.P., Suxamethonium Chloride, B.P.; suxethonium iodide has also been used (Hall, 1952). *It must be remembered that physostigmine and neostigmine potentiate the action and may not be used as antagonists for the depolarizing agents.*

Decamethonium Iodide, B.P., is now rarely used in anæsthesia (Hall, 1957), but has been used extensively in the field of human surgery in Great Britain, while the bromide is likewise used in America. It is a white, bitter-tasting crystalline powder which is soluble in water (1 : 10) and alcohol (1 : 50). The *action* is typical of the group, causing depolarization of the motor end-plate. Following intravenous injection, muscle paralysis begins in 2–3 minutes and is maximal in 4–8 minutes; the duration varies from 15–25 minutes and is therefore shorter than that of tubocurarine. Muscle cramps, salivation, and laryngospasm are disadvantages: no safe antidote is available. Decamethonium, however, has the advantage of not causing histamine liberation or blood pressure reduction and, because of its shorter duration, is more suitable for controlled dosing by small repeated injections. The short-acting succinic acid derivatives of choline have displaced it because of their greater suitability for intravenous drip administration and therefore more accurate control of relaxation. Toxicity is of a low order but overdosage can only be counteracted with artificial respiration and oxygen.

Decamethonium is more active in the cat than tubocurarine and *doses* should be about 1/5th of those of tubocurarine. In man, doses of 1·0–2·0 mg. initially by intravenous injection are followed by further doses of 0·5–1·0 mg. every five to ten minutes for as long as relaxation is required.

Suxamethonium Chloride, B.P.

This muscle relaxant is a white crystalline powder which is soluble in water and alcohol. Acid solutions are stable but in alkaline solution destruction is rapid even with refrigeration.

Action. Known also as succinylcholine chloride, this compound, in common with the iodide, acts by depolarization of the motor end-plate or myoneural junction. Its effects following intravenous injection are seen within 15 seconds and consist of irregular unco-ordinated muscular contractions which, in the absence of an analgesic, would be painful: these contractions last about ½ minute and, along with the profuse salivation, are an indication of the progress of depolarization with its stimulatory effects. Respiratory paralysis frequently follows and the drug

must not be used unless facilities are available for administering artificial respiration. Duration of action varies in the species according to the concentration of the enzymes cholinesterase and pseudo-cholinesterase in the red blood cells and plasma respectively (Evans *et al.*, 1952: Hall *et al.*, 1953). Thus, in cats 1·0 mg./kg. (0·45 mg approx. per lb.) causes respiratory paralysis for about three minutes, whereas a third of this dose will cause a paralysis in dogs lasting five times longer (Hall, 1957). In the horse, quantities necessary to produce muscular paralysis and casting (0·13–0·17 mg./kg. or 6·5–8·5 mg. per cwt.) will give a duration of up to 8 minutes. Cattle are much more susceptible to the effects of suxamethonium, and doses about 1/8–1/10th of those for the horse will cause recumbency for about fifteen minutes (Stowe, 1955a; Hansson, 1956). Stowe (1955b) goes so far as to say that the use of succinylcholine is contra-indicated in cattle. The difference between the reaction of the cow and the horse is attributed to the low pseudo-cholinesterase in the plasma of cattle (Stowe, 1955b). In pigs, 2·0 mg./kg. (approx. 0·9 mg. per lb.) produces only transient paralysis.

All investigators stress the need for pre-sedation before the relaxant is administered, and also the danger of aspiration of ruminal contents in cattle, although Hansson (1956) reports negative findings in 30 cattle destroyed and examined after succinylchloine casting: however, if artificial respiration is to be applied in cattle œsophageal blockage is essential.

Uses. Suxamethonium may be used in small animals to obtain muscular relaxation in all types of surgery, for examination by X-ray, or manipulation, in conjunction with narcosis, but it is particularly suited for use in thoracic and orthopædic surgery (Hansson and Edlund, 1952; Hansson, 1956). In large animals, with prior sedation, it has been used for casting (Hansson and Edlund, 1954; Belling and Booth, 1955; Stowe, 1955a; Hansson, 1956).

Hall (1952) has also reported the use of suxethonium iodide in 24 dogs with no deleterious effects attributable to the relaxant.

Toxicity. The side actions of suxamethonium and suxethonium are those associated with the initial depolarization, and consist of incoordinated muscular contractions, salivation, and possibly bradycardia (slowing of the heart), though Hall (1952) observed no change of rhythm or rate in 24 dogs subjected to suxethonium relaxation. Bovet (1949) was able to give 300 times the normal lethal dose to dogs without killing them provided artificial respiration was given. Toxicity is therefore extremely low.

Antagonists are not available but are usually not necessary if a means of providing sustained artificial respiration is available.

Dosage and Administration. These muscle relaxants have been administered by intravenous, intramuscular and intrathoracic injections, but only the first route is entirely satisfactory (Belling and Booth, 1955).

Suxamethonium chloride:

Horse: 6·5–8·5 mg. per cwt. or 50·0 kg.
Cow: 0·8–1·06 mg. per cwt. or 50·0 kg.
Pig: 0·9 mg. per lb. (2·0 mg. per kg.) repeated as required.
Dog: 0·03–0·07 mg. per lb. (0·06–0·15 mg. per kg.)
Cat: 0·45 mg. per lb. (1·0 mg. per kg.) repeated as required.

Suxethonium may be given to dogs at the rate of 1·0 mg. per 9–18 lbs. (1·0 mg. per 4·0–8·0 kg.).

No accumulation occurs and doses may be repeated after an interval of 10–15 minutes if required. Ether anæsthesia should not be used with these as with other relaxants but otherwise all normal anæsthetics may be used with them.

Miscellaneous Relaxants. Only one further relaxant is of veterinary interest.

Mephenesin, B.P.C.

This compound is chemically 3-(2-methyl-phenoxy) propane-1-2-diol and is therefore entirely different from the previous muscle relaxants mentioned. It is a white crystalline compound almost odourless but with a bitter taste followed by local anæsthesia. It is soluble 1 : 100 in water but freely soluble in organic solvents.

Actions. Mephenesin produces muscular relaxation following oral or intravenous administration. In normal doses facilitation and spreading of impulses up and down the spinal cord are reduced, but monosynaptic transmission is unaffected. This would account for the fact that muscular relaxation is neither so marked nor so complete as with tubocurarine and similar relaxants. In addition to muscular relaxation mephenesin has sedative, hypnotic, and ataractic effects: it also has some local anæsthetic action. Respiratory depression is unlikely unless large doses are given, when a fall in blood pressure and heart block may also be anticipated.

Subsequent to intravenous injection the compound takes effect quickly and lasts for up to 30 minutes, but the duration may be extended up to 2 hours by giving the drug orally.

Uses. Mephenesin may be used in cats and dogs as a muscle relaxant during anæsthesia. Satisfactory use has been reported in cats (Sheppard, 1951), dogs (Kingma, 1951), and it has been used in horses. The dose of anæsthetics is reduced by $\frac{1}{3}$–$\frac{1}{2}$. More clinical information may now be forthcoming since the introduction in Great Britain of a combined pentobarbitone-mephenesin injection for small animal anæsthesia (Pentolissin). This follows the pattern of an American injection which contains 1 gr. of each per ml. (60·0 mg. per ml.): the dosage of this mixture is 1/6–1/7 ml. per lb. body weight (approx. 1·0 ml. per 3·0 kg.) administered

intravenously to effect. Frequently only three-quarters of the calculated dose is required, due to the varying individual response to the mephenesin.

In the horse, intravenous doses of 4·0 G. given over a period of up to 10 minutes have caused sedation, inco-ordination, and casting: effects have persisted for up to 30 minutes. Oral doses of 3½–5 oz. (100·0–150·0 G.) have caused similar reactions and sedation for 3–5 hours. (U.S.D., 25th Edit., 1955., p. 1992.)

Mephenesin will abolish the convulsions of strychnine poisoning and it has been used in tetanus in the horse in oral doses of 50·0–70·0 G. per 1000 lbs. or 450·0 kg. (Detweiler *et al.*—quoted by U.S.D. 25th Edit, 1955, p. 1992.)

Toxicity. Side actions when given orally are nausea and emesis. Solutions given intravenously at concentrations greater than 5 per cent. may cause intravascular hæmolysis, hæmoglobinuria, and venous thrombosis at the site of injection. In overdosage, respiratory collapse, heart block, and a fall in blood pressure, should be treated by artificial respiration and intravenous injections of methylamphetamine in doses of about 15·0 mg.

Dosage:

Dog and cat: 1/6th gr. (10·0 mg.) per lb. (22·0 mg. per kg.) given intravenously to effect.
7½–15 gr. (0·5–1·0 G.) orally three times daily.

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CHAPTER 13

NERVOUS SYSTEM DEPRESSANTS

(ii) THE ANÆSTHETICS

ANÆSTHETICS are agents which eliminate body sensation. The term anæsthesia is now broadly applied in the human surgical field to a complex procedure by which the patient is prepared psychologically for the operation and then rendered insensible to all feeling in the operation area; by which blood pressure and oxygenation of the blood are maintained at their optimum levels, by which physiological means are used to keep the field of surgery clear of blood, and by which muscle tonus is decreased so that manipulations may be carried out easily and quickly. This procedure involves extensive premedication and the administration of ancillary therapeutics after anæsthesia has been induced. Drugs are used which aim at achieving the following:

(1) A reduction in the likelihood of the incidence of shock:

(a) by lowering the blood pressure and preventing the physiological constriction of the peripheral blood vessels: this maintains normal capillary function under conditions which would otherwise result in peripheral vasoconstriction followed by capillary anoxia and an increased vascular permeability—the normal reaction to traumatic shock. Concurrently with the use of these hypotensive drugs the blood volume must be maintained by the injection of blood-volume expanders should a state of shock appear imminent. *Note*. These hypotensive agents should not be administered after the onset of shock, for they will then only serve further to reduce the blood pressure, possibly to a fatal level.

(b) by reducing apprehension and voluntary struggling due to fear.

(2) A reduction in the amount of anæsthetic required:

(a) by lowering the level of brain activity, and

(b) by the use of muscle relaxants.

(3) A reduction in salivary and respiratory secretions.

(4) A reduction of hæmorrhage in the operation field. This is achieved by the use of the hypotensive drugs mentioned under 1a. above.

Hexamethonium bromide and chlorpromazine have hypotensive actions, the long and medium acting barbiturates, chloral hydrate, morphine, pethidine, and also chlorpromazine, have general sedative effects, and in addition some have analgesic actions. Muscle relaxants include tubocurarine chloride and succinylcholine, whilst atropine and hyoscine (scopolamine) have a depressant action on secretions.

This complicated procedure is not entirely applicable to veterinary anæsthesia, but many of the features are being adopted in the teaching schools and the general principles are universally accepted.

There are two main groups of anæsthetics:

1. *General anæsthetics* which, besides causing the loss of sensation also induce sleep, or a level of central nervous system (C.N.S.) depression equivalent to sleep.
2. *Local anæsthetics* which merely desensitize one area of the body and have no direct effect on the C.N.S.

General Anæsthetics

An ideal general anæsthetic would possess a number of essential characteristics. It must: 1. Be easily and painlessly administered; 2. induce a rapid loss of consciousness without causing voluntary or involuntary struggling; 3. not cause any physiological changes such as a drop in blood pressure, depression of respiration and heart action, or an increase in respiratory and salivary secretions; 4. give adequate analgesia and muscular relaxation at the minimum level of dosage required to cause loss of consciousness; 5. be completely non-toxic; 6. be easily neutralized by a non-toxic antidote so that the duration of anæsthesia can be shortened at will; 7. have a short recovery period without excitement; 8. be compatible with premedication and other ancillary therapeutics; 9. be reasonably and economically priced.

No single anæsthetic is known which possesses all these attributes but by combining drugs with complementary pharmacological actions, an approximation to the ideal can be achieved. This combination of complementary drugs is now spoken of as 'balanced anæsthesia'. For example, *premedication* with relaxing, analgesic and C.N.S. sedative drugs such as pethidine or morphine, along with hyoscine, *a light anæsthesia* produced by some general anæsthetic such as pentobarbitone sodium, and a *muscle relaxant* such as tubocurarine chloride or suxamethonium chloride, will together produce something approaching perfect anæsthesia.

In this suggested combination for balanced anæsthesia the pethidine and morphine provide basal narcosis (C.N.S. sedation at the level of narcosis prior to the induction of anæsthesia by another substance) and also lower the amount of pentobarbitone sodium required. This lower dosage of anæsthetic means a duration of anæsthesia and period of recovery shorter than that which follows the use of the barbiturate alone. The hyoscine, besides taking part in the C.N.S. sedation also, by its atropine-like effect, reduces respiratory and salivary secretions. The muscle relaxant ensures relaxation of abdominal muscles with only light barbiturate anæsthesia and greatly facilitates intra-abdominal manipulation or visualization.

There are still great imperfections attaching to the use of these combinations. In most cases, for example, paralysis of the respiratory muscles

Anæsthetic reflexes in the approximate order of disappearance:

1. (a) Ear twitch.
   (b) Jaw and tongue.
2. Front pedal.
3. Body reflexes—scratch and panniculus response.
4. Hind pedal.
5. Tail relaxation.
6. Palpebral.
7. Corneal.
8. Pupillary.

The stimuli which initiate these reflexes are touch in the cases of 1a, 6 and 7, forcible opening of the mouth in 1b, light in 8 and pain in 2, 3 and 4. The jaw reflex is not readily applicable in large animals.

The most important are the corneal and pupillary reflexes for these give the final warnings against overdosage. In light anæsthesia the eyelids are open, the corneal response (closure of lids on touching the cornea) is rapid and the pupil is usually dilated, but will frequently respond to light. In deep anæsthesia the pupil is tightly constricted and the lids are closed: in dogs and cats the corneal reflex may be absent, but in cattle and horses anæsthesia should not be continued to this stage. Sudden dilatation of the pupil is an indication of overdosage and that death is imminent if not already a fact.

Control of Oxygenation. The state of oxygenation and circulatory well being are normally estimated by examination of the oral and ocular mucous membranes, the pulse and respirations. The membranes should be light pink in colour, not dark red or blue; the vessels should not be engorged and pressure on the gum should produce a white mark which disappears within a few seconds. It must be remembered, however, that where hypotensive agents such as the hexamethonium salts are used, the blood pressure will be low and mucous membrane recovery will be relatively sluggish. Details now considered essential are intubation, whereby a tube is introduced into the trachea to ensure a clear air flow, premedication with atropine or similar drug to reduce salivary and respiratory secretions, and positioning the animal with its head lower than the body so that fluid, whether of gastro-intestinal or salivary and respiratory origin, will drain out of the mouth and not back into the lungs.

Non-Volatile Anæsthetics. The use of non-volatile anæsthetics is sharply divided between the species, chloral hydrate being used exclusively in the large animal field and the barbiturates being used almost entirely in dogs and cats, although their use in farm animals and exotic species is increasing. Nevertheless, these anæsthetics have certain group characteristics, though each individual anæsthetic has attributes which are not shared by the rest of the group.

occurs with muscle relaxants and positive pressure breathing apparatus is required: this, even in its simplest form, requires special apparatus which is not normally possessed by veterinary surgeons. There are also dangers inherent in the induced muscle relaxation, including that of over-extension of joints and the stretching of nerves, ligaments, and tendons, when the animal is tied to the operating table.

However, in small animal surgery these methods of anæsthesia are becoming established as the best that have so far been devised. In large animals, the use of muscle relaxants is still in the early experimental stages.

The general anæsthetics now available each possess one or more of the attributes of a perfect anæsthetic. They are classified into three types according to their physical characters:

1. Non-volatile anæsthetics which are mostly water soluble solids and must be given orally or by parenteral injection:

(1) The Barbiturates.
(2) Chloral hydrate.

2. Volatile anæsthetics which are liquids. They give off vapours which have anæsthetic properties and are therefore administered by inhalation:

(1) Chloroform
(2) Ether and vinyl ether
(3) Trichloroethylene
(4) Bromochlorotrifluoroethane

3. Gaseous anæsthetics, which are stored under pressure in some cases as liquids, but which are administered as gases at normal temperature and pressure:

(1) Nitrous oxide
(2) Cyclopropane

Control of Anæsthesia

During the *induction* of anæsthesia and *recovery* the depth of effect is determined by repeated tests of the animal's reflex response to stimuli and the degree of relaxation of appendages such as the tail.

During *anæsthesia* the depth of anæsthesia and the circulatory condition are determined by frequent examination of mucous membranes, pupillary and other reflexes, respiratory rate, depth and regularity, pulse character and rate.

Reflexes in Anæsthesia. The majority of anæsthetics are spoken of as 'descending anæsthetics', indicating that the reflexes of the head and forepart of the body are eliminated before those of the hind-quarters. An exception is Betanaphthoxyethanol, B.Vet.C., which induces an ascending reflex paralysis in which the reflexes of the head are the last to disappear.

All non-volatile anæsthetics must be administered either parenterally or by mouth. If given parenterally, the intravenous route is the one of choice, for dosage may then be judged according to individual reaction: some of the injections will cause irritation and sloughing if given subcutaneously or intramuscularly (chloral hydrate and possibly thiopentone sodium) but all give unreliable and unpredictable depths of narcosis or anæsthesia if given by any other route than the intravenous one. The oral route also suffers from the same disadvantages as the non-intravenous parenteral routes, but to a greater degree, for the absorption rate and the blood levels achieved (and therefore depth of narcosis or anæsthesia) will depend on the amount of food in the gastro-intestinal tract, and on whether the drug is given as a solution, powder, tablet, or in capsules.

A further attribute common to chloral hydrate and most of the barbiturates is their suitability as basal narcotics prior to the induction of anæsthesia by a volatile, gaseous, or local anæsthetic. Chloral hydrate has been widely used for this purpose in cattle and horses and pentobarbitone sodium is useful in small animals, whilst thiopentone sodium is widely used in the medical field and in veterinary schools for inducing anæsthesia which is then maintained with nitrous oxide, ether or cyclopropane.

With the barbiturates, the induction of anæsthesia is usually rapid and unaccompanied by struggling, providing the correct techniques are used, but with chloral hydrate struggling occasionally occurs. A disadvantage of considerable importance which applies to chloral hydrate and the short and medium acting barbiturates is the length of the recovery period, during which excitement and voluntary struggling may cause considerable distress and even death in some species: the convalescent period may be lengthened and damage to, and breakdown of, the operation wound may occur. In some cases the recovery period may be so long that frequent turning over may be required to prevent the occurrence of hypostatic pneumonia.

Neither chloral hydrate nor the barbiturates are analgesics (pain reducers) and in balanced anæsthesia pethidine or morphine are used for their additional analgesic effects. Similarly, neither of them produces good muscular relaxation and for this reason they are frequently used only as narcotics, volatile or gaseous anæsthetics being used to bring about anæsthesia.

All non-volatile anæsthetics are detoxicated and eliminated by the liver and kidneys, and where these organs are functioning inadequately prolonged anæsthesia and slow recovery may result. This is not a problem with anæsthetics given by inhalation which are also excreted via the lungs.

Fœtal anæsthesia due to placental diffusion makes all non-volatile anæsthetics unsuitable either as narcotics or anæsthetics for Cæsarian section.

Greater skill is required in the administration of the non-volatile anæsthetics but the injections can be given with the help of unskilled assistance and once the required depth of anæsthesia is reached no further

help is needed. In emergencies, anæsthesia can be induced without any assistance whatsoever if non-volatile anæsthetics are used.

Chloral Hydrate, B.Vet.C.

This white crystalline substance has a characteristic pungent odour sometimes compared with that of melons. The crystals gradually turn yellow if kept in clear glass containers for long periods: they are very soluble in water, alcohol and other organic solvents: exposure of solutions to light over a period may result in some decomposition, and alkalis such as the barbiturate sodium salts cause rapid decomposition with the formation of chloroform and a formate. Solutions should therefore be prepared immediately before they are needed.

Actions. The anæsthetic effect following the administration of chloral hydrate is widely attributed to trichlorethyl alcohol produced by reduction following absorption. Sollman questions this production of trichloroethyl alcohol (Manual of Pharm., 6th Edit., p. 781, 1943, Saunders,) which in turn puts in question the whole theory accounting for the action of chloral hydrate. Whichever of these two compounds is responsible for the anæsthetic effect the precise mode of action is unknown.

The *systemic* effect of chloral hydrate is one of C.N.S. depression affecting the motor impulses of the brain and spinal cord. The sensory routes are only mildly affected short of anæsthesia. This selectivity results in a loss of motor function before sensory perception ceases, and incoordination due to loss of muscle control may result in fright and struggling, with possibly serious consequences. It is for this reason that, in horses at any rate, there should be a minimum of noise and the eyes should be covered during induction and the early recovery stages. When the stage of anæsthesia is reached dosage is such that the medullary centres and particularly the respiratory and vasomotor centres are depressed: this results in a slowing of respiration and peripheral vasodilatation with a drop in blood pressure. There is no direct action on the heart except where toxic doses are given, and occasionally during the recovery stages (see toxicity). In doses short of those required to give anæsthesia there is little analgesic (pain killing) effect except in so far as cerebral perception is dulled. The *local* effect of chloral hydrate is one of irritation, whether given by mouth, applied externally in liniments or inadvertently injected extravascularly. External applications and oral dosage make use of this action as well as the slight local anæsthetic effect.

Uses. Chloral hydrate is used mainly in the horse for:

(1) a *light cerebral sedative* action, as in the treatment of colic
(2) a *basal narcotic* effect prior to anæsthesia with volatile or local anæsthetics.
(3) *general anæsthesia* by intravenous injection either alone, with magnesium sulphate, or with magnesium sulphate and pentobarbitone sodium.

It is also used in the cow as a treatment for acetonæmia but only rarely for other purposes. Chloral hydrate should not be used during Cæsarian section, for it passes the placental barrier and depresses fœtal respiration.

For *sedative effects*, chloral hydrate may be administered as a drench, as a bolus, in drinking water after a period of water starvation (18–48 hours), or given by stomach tube. It is useful in colic for its central and local sedative, carminative and antizymotic actions: frequently it is combined with chlorodyne in doses of ½ fl. oz. of each (15·0 G. and 15·0 ml.), given every six hours, or given as a single dose with aloes and turpentine in a vehicle of linseed oil. As a sedative for fractious horses which object to clipping, or a fractious bull which must be handled, ½–1½ oz. (15·0–45·0 G.) chloral hydrate should be given orally in water about half an hour before, or by intravenous injection immediately before handling. In the treatment of acetonæmia 1 oz. (30·0 G.) has been given initially followed by ½ oz. (15·0 G.) twice daily, further dosing at reduced rates following according to reaction: the use of chloral hydrate is only indicated in the 'nervous type' of acetonæmia.

For *basal narcosis*, chloral hydrate may be given in drinking water after starvation, by stomach tube, or by intravenous injection; when the first two methods are used, dosing should take place about 20 minutes prior to anæsthesia, and the dosage should be at the rate of 45–90 gr. per cwt. (3·0–6·0 G. per 50·0 kg.) body weight in all species. Narcosis varies when the oral route is used, and intravenous dosage to effect is preferred. Subsequently, anæsthesia may be induced by a volatile or local anæsthetic. In light narcosis the animal will remain standing, but will become cast in medium and deep narcosis: the last of these approaches light anæsthesia Narcotic effects will persist for up to 2 hours, depending on dosage and depth.

For *anæsthesia*, chloral hydrate should be administered only by the intravenous route. It has been used for this purpose in horses, cattle, sheep, and pigs, but is rarely used for any species other than horses and cattle. For intravenous injection a 10 per cent. solution (60·0 G. (2 oz.) in 600·0 ml.) in water or saline should be used and it is usual to include 1 per cent. sodium citrate (6·0 G./600·0 ml., or 90 gr. per 20 fl. oz.) as an anticoagulant. On all occasions it is advisable to make up more solution than is required according to the estimated dose: this is the normal practice in all cases of non-volatile anæsthetic administration; it is intended as an emergency reserve for use in animals which are idiosyncratic and tolerate doses greater than the average.

Injection should be carried out by gravity apparatus in the normal manner over a 5–10 minute period, but extra care must be taken to see that the needle is in the vein and that its point is some distance from the point of entry. These precautions, aimed at preventing perivascular leakage, are necessary because of the strong irritant effect of the hydrate on the tissues.

A further important point which must be observed during chloral

hydrate administration is that injection should cease at a point when the depth of anæsthesia is just short of that required, as anæsthesia continues to deepen for 10–15 minutes after injection has stopped.

Following anæsthesia the animal may be recumbent for 3 hours or more.

Excretion is via the kidneys in the form of urochloralic acid which is formed in the liver by the conjugation of chloral hydrate with glycuronic acid; some is excreted unchanged. The presence of urochloralic acid in the urine causes a strong Fehling's or Benedict's reduction which should not be interpreted as a sign of glycosuria.

If the drug is administered by the oral route the animal should be starved for up to 24 hours in order to empty the stomach and small intestine so that absorption, and therefore nervous system depression, may not be affected by dilution and dispersion in the food.

Whether orally administered, injected intravenously or intraperitoneally (this route has been used in pigs but it is not the one of choice), chloral hydrate should be well diluted in order to avoid irritation.

Dosage and Administration:

Oral:	Sedative:	Horse and Cow:	½–1 oz. (15–45·0 G.)
		Sheep and Pig:	30–60 gr. (2·0–4·0 G.)
		Dog:	5–15 gr. (0·3–1·0 G.)
		Cat:	2–10 gr. (0·12–0·6 G.)

Narcosis (Wright):	Light.	Medium.	Deep.
Horses: Hunter	1¼ oz (37·0 G.)	1¾ oz. (52·0 G.)	2¼ oz. (67·0 G.)
Vanner	1½ oz. (45·0 G.)	2 oz. (60·0 G.)	2½ oz. (75·0 G.)
Heavy draught	1¾ oz. (52·0 G.)	2½ oz. (75·0 G.)	3 oz. (90·0 G.)

Intravenous injection: Anæsthesia: Farm animals: 90–120 gr. per cwt. (6·0–8·0 G. per 50·0 kg.).

Narcosis: Light—half, Medium—two-thirds, Deep—five-sixths, } of the anæsthetic dose.

In all cases dosage will be judged according to effect.

Toxicity. At one time chloral hydrate was thought to be converted into chloroform, which then caused liver changes. Though this is now proved wrong, prolonged dosage with chloral hydrate at near toxic strengths will produce liver damage similar to that caused by chloroform.

Apart from overdosage, and death from respiratory failure or occasionally circulatory collapse, the main danger in chloral anæsthesia results from cardiac fibrillation and sudden death during the recovery period. Fowler (1947) reported 12 such cases out of 2000 mules anæsthetized. This has been attributed to cardiac fibrillation and heart block produced by vagal action. The vagus reacts reflexly to the increase in blood pressure which follows the release of adrenaline by fright and struggling during the recovery period. Because of this *adrenaline is*

contra-indicated as a stimulant in choral hydrate anæsthesia and animals must not be encouraged to rise until it is reasonably certain that they can do so and remain on their feet.

In an endeavour to overcome the disadvantages of chloral hydrate various combinations are used, including mixtures with magnesium sulphate alone or along with pentobarbitone sodium.

Combined Formulations

Chloral Hydrate–Magnesium Sulphate. There are several suggested formulations containing various proportions of chloral hydrate and magnesium sulphate. These proportions vary from 3 : 1 to equal parts, but probably the most popular is the proportion of 2 : 1 used by Danks (1943), who preferred a solution containing 12 per cent. of chloral hydrate and 6 per cent. magnesium sulphate. This solution is used only in the horse and must be given slowly (30·0 ml. per minute) if overdosage is not to occur, for the progressive deepening of the depression found with chloral hydrate also occurs with this mixture, and there is the added danger of magnesium depression of the heart and respiration if too rapid an injection is given.

The magnesium in this formulation gives a more rapid induction of anæsthesia with less excitement, and the depth of anæsthesia is increased if equal volumes of the plain solution and combined formulation are compared. As magnesium sulphate is excreted rapidly, duration of anæsthesia is less (30 minutes) and recovery is more rapid, inco-ordination being less and of shorter duration because of the reduced dose of chloral hydrate.

Dosage is according to reaction, allowance being made for the post-injection deepening of anæsthesia. The quantity of a 12–6 per cent. solution required varies from 200·0–400·0 ml. (7–14 fl. oz.) according to size and condition of the horse. Injection should take a minimum of 10 minutes.

This mixture of chloral and magnesium sulphate is not as safe as one would wish and the addition of pentobarbitone sodium was suggested by Millenbruck *et al.* (1946) as a means of reducing further the proportions of each component of the anæsthetic and therefore reducing the toxic effect of the combination.

Chloral–Magnesium–Barbiturate. The original solution of Millenbruck and his colleagues contained 30·0 G. (1 oz.) chloral hydrate, 15·0 G. ($\frac{1}{2}$ oz.) magnesium sulphate, and 6·4 G. (100 gr.) pentobarbitone sodium, per litre of aqueous solution. A modification by Groves (1951) doubled and quadrupled the amount of chloral hydrate and magnesium sulphate (60·0 G. with 30·0 G. or 120·0 G. with 60·0 G., respectively, per litre), retained the same dose of pentobarbitone salt, and added 200 ml. ethyl alcohol per litre. The addition of alcohol made the product more stable and the more highly concentrated solution made the volume required

very much lower, which in turn decreased the injection period. This solution must be prepared and used within an hour or so because of the hydrolysis of the pentobarbitone sodium and its reaction with the chloral. More stable solutions containing the acid barbiturate in place of the sodium salt, and using high proportions of propylene glycol and ethyl alcohol, are marketed commercially, usually in concentrations similar to those suggested by Groves.

This combination of drugs combines the rapid induction properties and muscular relaxation of the barbiturate with the short anæsthetic period (30 mins.) and rapid recovery rate of the chloral–magnesium mixture. Return of consciousness is approximately paralleled by return of muscle control.

Dosage and Administration. Horses and cattle: approximately 650 ml. of the Millenbruck solution. Proportionately less will be required of the more concentrated solutions.

Administration follows the pattern of barbiturate anæsthesia in small animals in which half the dose is given fairly rapidly (5 minutes) and the remainder slowly until the required depth of anæsthesia is reached. Half the dose is usually sufficient to approach medium narcosis. In cows it is advisable to cast the animal by Reuff's method before attempting anæsthesia. Where animals are cast prior to anæsthesia injections can be made slowly, as the initial 'knock-down' effect is not required.

The Barbiturates

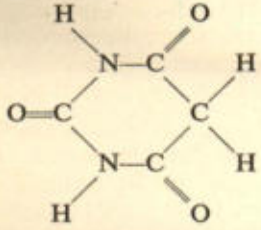
This group of organic C.N.S. depressants are either white or yellow (sulphur containing compounds), odourless, bitter tasting crystalline powders. The acids are only slightly soluble in water, but are soluble in alcohol and other organic solvents: their sodium derivatives are very soluble in water, usually soluble in alcohols, but insoluble in other organic solvents; these sodium salt solutions are frequently highly alkaline. All powders are hygroscopic and hydrolize in aqueous solution; they are also decomposed by air, heat, and light.

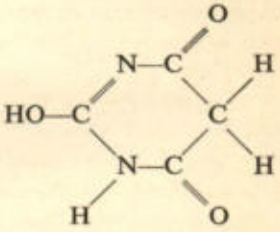
Classification. The barbiturates are classified according to their duration of effect, for in most other respects they have few distinguishing features, their mode of action in particular being the same for all members of the group. There are four classes:

		N_1	C_2	R_1	R_2
1. Long Acting:	Phenobarbitone	H	O	C_2H_5	C_6H_5
	Methylphenobarbitone	CH_3	O	C_2H_5	C_6H_5
2. Medium Acting:	Butobarbitone	H	O	C_2H_5	C_4H_9
3. Short Acting:	Pentobarbitone	H	O	C_2H_5	$(CH_3)C_4H_8$
4. Ultra-Short Acting:	Thiopentone	H	S	C_2H_5	$(CH_3)C_4H_8$
	Thialbarbitone	H	S	C_3H_5	C_6H_9

The long and medium acting compounds are usually given as the parent acid but the short and ultra-short acting compounds are normally administered as sodium salts by injection.

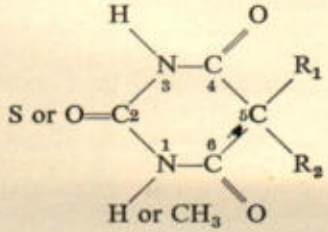
Chemistry. The whole group are based chemically on barbituric acid (malonyl urea) which has a pyrimidine ring as a nucleus. Its formula may be written in two ways (i) by the '*keto*' and (ii) by the '*enol*' method:

(i) 

(ii) 

The formulæ of the salts are represented in British literature by attachment of sodium or calcium atoms through the oxygen atom at Carbon 4, whereas American literature attaches the sodium or calcium through either the oxygen or sulphur associated with Carbon 2.

The chemical structure of the barbiturates is varied by means of substitution of organic or combined inorganic and organic groups at one, two or all of three sites in the acid structure: a. Nitrogen 1; b. Carbon 2; and c. Carbon 5. The whole group may therefore be represented by the graphical formula (iii)

(iii) 

Action. The action of the barbiturates can be divided into two distinct parts, each of which is closely identified with a certain part of the chemical structure.

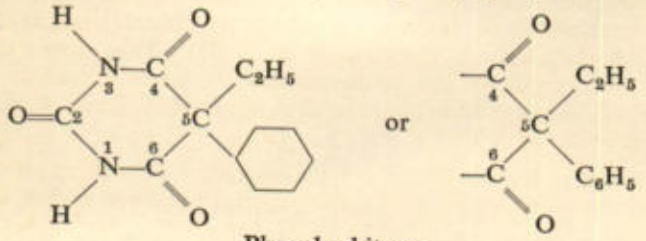
1. The C.N.S. depressant action, which is common to the whole group, is related to the common barbituric acid nucleus, and if this nucleus is disrupted the depressant action is lost. It is interesting that barbituric acid alone has no depressant action, but, when aliphatic and/or cyclic groups are substituted for the hydrogen atoms at R_1 and R_2, the resulting compound has a C.N.S. depressant action.

2. Just as the character of the group is linked with the nucleus, so are the individual differences linked with the side-chains that may be substituted in any or all of the sites indicated above. These side chains are

responsible for individual differences in metabolism and therefore determine rates of absorption, detoxication, and excretion, and hence duration of depression, dosage, and indications etc.: they have very little influence on the nature of the action, affecting only the degree.

For example, a barbiturate with the shortest and most stable side chains commensurate with activity will be long acting, as with Phenobarbitone, B.Vet.C. (iv) where hydrogen atoms are attached at nitrogens 1 and 3, oxygen at carbon 2, and ethyl and phenyl groups at carbon 5.

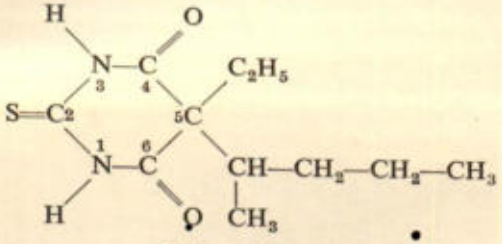
(iv)



Phenobarbitone

Conversely, if nitrogen 1 has a methyl group, carbon 5 having one relatively long unsaturated or branched chain, and/or carbon 2 has sulphur substituted for oxygen, the resulting compound will be metabolically unstable and therefore short acting, as with thiopentone (v). Between these two extremes, by variation of the side chains, a whole scale of compounds can be produced with a more or less predictable and graduated degree of effect.

(v)



Thiopentone

C.N.S. Depressant Action. The action of the barbiturates on the brain cells is generally accepted as one of interference with oxidation processes, probably in connection with the breakdown of glucose, but the precise details are unknown. Nor is the exact site of action known, but Morgan (1953), quoting Leiter *et al.* and Masserman, suggests that the action is 'subcortical and probably located in the thalamus'.

The clinical action is one of C.N.S. depression, mainly of the motor functions of the brain and spinal cord, preceded, in the case of the medium and short acting compounds, by a period of excitation. Sensory functions, and therefore pain perception, are appreciably affected only by near

anæsthetic doses (*cf.* chloral hydrate). These details may be illustrated by reference to phenobarbitone, which will produce marked inco-ordination without materially dulling the animal's sensitivity to pain, and to pentobarbitone sodium which may produce narcotic excitement in the dog or cat if given by slow intravenous injection.

The intensity of clinical effect and its rate of onset and duration will vary according to the individual barbiturate used, its dosage, and its method and route of administration.

The central nervous system actions are prolonged by the administration of many derivatives of glucose, especially phosphate derivatives, and occasionally glucose itself (Lamson *et al.*, 1951). This means that the administration of glucose and its derivatives in plasma extenders for the treatment of shock must be carefully considered when barbiturate anæsthetics are used.

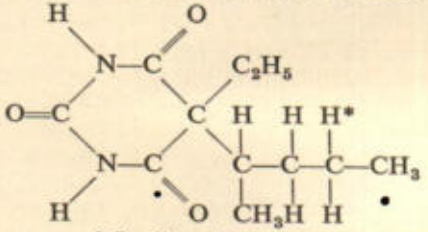
Other Systems. The barbiturates have no appreciable effect on systems other than the respiratory and cardiovascular systems, except in near toxic doses. During the induction of anæsthesia, the injection of barbiturates is almost invariably accompanied by a temporary cessation of respiration (apnœa); this is an acknowledged fact and is particularly apparent with the ultra-short acting barbiturates, with which the induction period is of only one or two seconds duration. In the normal animal this apnœa is only temporary and respiration restarts spontaneously: where the apnœic period is prolonged artificial respiration should be applied until the breathing becomes spontaneous once more. The phenomenon is due to a temporarily high concentration of barbiturate in the brain which affects the respiratory centre, but as soon as the drug is adequately circulated the temporary high concentration becomes reduced to a sub-paralytic level. The cessation of respiration is not the catastrophe that one normally associates with respiratory paralysis, for in barbiturate over-dosage the heart will continue to function satisfactorily for sufficient time to allow the institution of normal respiratory resuscitation—artificial respiration and analeptics.

Depression of the vasomotor centre in the medulla during deep anæsthesia results in peripheral vasodilatation and a fall in blood pressure which, with toxic doses, may be reduced to shock level. Vasodilatation of peripheral vessels results in heat loss which cannot be replaced by normal mechanisms because of anæsthesia and animals should therefore be kept reasonably, but not excessively, warm.

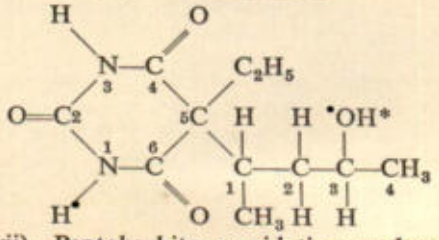
General Pharmacology. The individual metabolic fate determines whether the compound is a long, medium, or a short acting barbiturate. This duration bears an inversely proportional relationship to the reversible binding of the barbiturate to plasma albumin (Goldbaum *et al.*, 1954), which means that long acting compounds are adsorbed onto protein in the lowest degree, whilst the ultra-short acting compounds are adsorbed in the highest quantity. *Long acting barbiturates*, of which phenobarbitone

is probably the most widely used, are readily and completely absorbed from the intestines but, whether given orally or parenterally, the onset of effect is slow and in general the depth of C.N.S. depression is not so great as that caused by the shorter acting compounds. The duration of effect is prolonged due to the slow rate of renal clearance, for no disruption of the molecule occurs *in vivo* and the compounds are excreted via the kidneys unchanged. It takes from 7–10 days for a single dose of barbitone to be eliminated; consequently, this and the other long acting compounds are cumulative and should be used circumspectly when dosing should be continued for long periods. If any signs of inco-ordination are shown the daily dosage rate should be cut immediately. Any renal blockage will seriously impair renal clearance, and prolonged action will result.

Medium and short acting barbiturates are rapidly and well absorbed when given by any route. Their effects are relatively rapid in onset and their duration limited to a period of a few hours. C.N.S. depression can be varied from light sedation to deep anæsthesia by varying the dosage or route of administration. Unlike the long acting group, these barbiturates undergo detoxication mainly in the liver and are excreted neither completely disintegrated nor unchanged: the metabolic products vary according to the individual barbiturate, but from radioactive isotope investigation it would appear that oxidation of the longer chains at carbon 5 is one of the important methods of detoxication. For example, by using C_{14} labelled pentobarbitone (vi) it has been shown that this barbiturate is excreted by mice in at least five different forms, none of which is urea or the unchanged compound (Roth *et al.*, 1949). Meynert *et al.* (1949) showed that one of these excretion products was 5-ethyl 5(3-hydroxy-1-methylbutyl) barbituric acid (vii). These medium and short duration barbiturates are therefore



(vi) Pentobarbitone



(vii) Pentobarbitone oxidation product

not solely dependent, as are the long acting compounds, on renal clearance for a limitation of the duration of effect: this responsibility is shared with the liver. Consequently any liver damage will slow up the detoxication of these barbiturates and activity will be prolonged.

The *ultra-short acting* barbiturates are inactivated so rapidly that absorption from the intestines is too slow to build up a therapeutic brain-tissue concentration. They are therefore administered only by the intravenous route, when their effect is exerted within seconds of administration and is of only a few minutes duration unless special methods are used to ensure a continuous flow of drug into the blood stream.

The cause of the very short duration of effect, of the thiobarbiturates at least, appears not to be simply one of rapid breakdown but to be related more to the rapid passage of the drugs from the blood stream into the fat depots of the body from whence they are slowly released and broken down by the liver. A small proportion only of any dose is therefore taken up by the brain and spinal cord and exerts a depressant effect. This information provides part of the answer to the question of why young animals and those in lean condition are more susceptible to the depressant action of these very short acting barbiturates. (Very young animals have difficulty in detoxicating the barbiturates). Following breakdown in the liver thiopentone, by the use of S_{35} labelling, has been shown to be excreted in approximately twelve different metabolite forms.

Toxicity. Normally these drugs are not very toxic but cumulation of the long acting compounds may occur: this is indicated by increased general depression and the onset of inco-ordination. With the short and ultra-short acting barbiturates, toxicity is mainly that of C.N.S. depression with respiratory and circulatory collapse due to temporary or permanent overdosage, the former resulting from too rapid an injection rate. Treatment consists in the first place of artificial respiration, if the heart is still beating, and the administration of analeptics (convulsants) to stimulate (but see p. 319) the respiratory and vasomotor centres in the medulla.

Individual Uses, Dosages and Administration. In general, the long and medium duration barbiturates are used orally as anticonvulsants and routine nerve sedatives: the short acting compounds may be used by all routes as anticonvulsants and sedatives, but their main indication is for intravenous injection as basal narcotics and general anæsthetics: the ultra-short duration barbiturates are of no use other than as general anæsthetics for intravenous administration.

Long Acting Barbiturates

These comprise phenobarbitone, methyl phenobarbitone, and their sodium salts; barbitone is also available but is now rarely used in veterinary medicine.

Phenobarbitone B.Vet.C., Phenobarbital U.S.P.
(5-ethyl, 5-phenyl barbituric acid)

This barbiturate is a typical example of a long acting barbiturate. It is therefore absorbed slowly and excreted slowly; between these pharmacological mile posts is a long period of C.N.S. sedation, for excretion of a single dose takes several days.

Uses. The main use of phenobarbitone is as an anticonvulsant in the treatment of the neurotropic virus syndrome of dogs (distemper, hard-pad etc.), and in the sedation of puppies suffering from convulsions and hysteria associated with teething and the digestive upsets related to teething or other causes. Its power in these respects is greater than that of other barbiturates, with perhaps the exception of methyl phenobarbitone. Where pain or severe skin irritation is present, these barbiturates are relatively useless and must be combined with analgesics which may be the aspirin type of compound or the more active pethidine (Meperidine, U.S.P.). There is practically no indication for its use in other species.

Sodium phenobarbitone has been used by intravenous injection as a sedative in the horse in doses up to 12·5 G., but its effect is of long duration and it is therefore infrequently used. In cattle it has been used to control the nervous symptoms of scrapie (Sladden, 1958) by intramuscular injection in doses of approximately 1/6th gr. per lb. body weight (19 gr. per cwt. or 1·25 G. per 50·0 kg.).

Dosage. Dogs: orally ½–2 grains (30·0–130·0 mg.) given three times daily. This dosage may occasionally result in cumulation, especially if liver or kidney malfunctions are involved: indications of this are the development of inco-ordination, with an inability to negotiate furniture or steps. Cessation or reduction of the dosage is usually followed by a return to normal and no other measures are required.

Methylphenobarbitone, B.Vet.C. (Mephobarbital, N.F., 5-ethyl-1-methyl-5-phenyl barbituric acid), in which a methyl group is substituted for the hydrogen atom at nitrogen 1, may be used instead of phenobarbitone, as its cerebral sedative action is less than that of its parent and its anticonvulsant action is superior. Dosage is the same.

Medium Duration Barbiturates

There are several of these but only butobarbitone has been used to any degree in Great Britain.

Butobarbitone, B.Vet.C., Butethal, N.F.(U.S.),
(5-ethyl-5-n-butylbarbituric acid)

This medium duration barbiturate is a slightly more effective cerebral sedative than phenobarbitone but its anticonvulsant action is weaker

(Morgan, 1953). The indications and dosages are similar to those for, phenobarbitone. It has the advantage of being eliminated in about half the time of phenobarbitone.

Short Duration Barbiturates

Pentobarbitone sodium is by far the safest and most widely used of these short acting barbiturates.

Pentobarbitone Sodium, B.Vet.C., Pentobarbital, U.S.P., (5-ethyl-5(1-methylbutyl) barbituric acid)

This white, bitter tasting, water soluble barbituric acid derivative is typical of the short acting group of compounds. It is therefore reasonably quickly absorbed when given by all but the subcutaneous route and can be used to induce all stages of cerebral, medullary, and spinal depression. The degree of effect is related to route of administration and dosage.

The major use of pentobarbitone in the veterinary field is as a surgical anæsthetic. It may, however, be used as an antidote to eliminate the tonic spasms associated with strychnine poisoning, for which purpose often five times the normal anæsthetic dose is required: the affected animal is kept anæsthetized until the alkaloid is metabolized and excreted. It is also widely used for euthanasia of dogs and cats, being injected intravenously or intraperitoneally as an aqueous–alcohol–glycol solution containing 3 gr. (195·0 mg.) per ml.: the dose used varies but is approximately 1·0 ml. per 3 lbs. body weight (0·7 ml./kg.) given intravenously.

Oral administration should be used routinely only if the barbiturate is required for cerebral sedation and hypnotic (sleep-producing) effect in small animals. Narcosis in small animals can be achieved by this route, but if there is a large amount of food in the gastro-intestinal tract this will affect the absorption rate and the maximum blood and tissue levels. There is always the danger of producing a state of almost unmanageable narcotic frenzy, which though not of common occurrence is never pleasant to meet. Anæsthesia in cats is frequently achieved in single handed practice by administering an estimated dose (twice the intravenous dose, i.e. 2/5 gr. per lb. or approximately 60·0 mg. per kg.) in capsular form, keeping the cat in a small cat basket until anæsthetized. Euthanasia can be conveniently performed in this manner. Anæsthesia in dogs should not be attempted by this route unless all other routes of administration are disallowed. In these cases the animal may be starved overnight and the pentobarbitone sodium given in solution: anæsthesia should follow in 15–20 minutes. This method can be used for euthanasia where help is not available and the animal will not allow injection. The application of a tape-muzzle and the spraying or pouring of a solution into the mouth can prove an easy, humane, and reasonably quick method of anæsthetizing a dog prior to destruction with cyanide.

In general, narcosis or anæsthesia should not be induced by the oral

route, because it is impossible to compute a dose which will provide a predictable level of C.N.S. depression.

Parenteral administration, excluding the use of intravenous injections, gives results almost as unpredictable as the oral route. The *subcutaneous route* may be suitable for small doses intended for prolonged cerebral sedation, but for other purposes, such as the induction of anæsthesia or narcosis, absorption is too slow; though narcosis or anæsthesia may eventually be achieved, providing the dose is large enough, a period of excitement may occur lasting as long as 30 minutes.

The *intramuscular route* is not practicable because of the volume of solution required.

The *intraperitoneal route* is very useful where intravenous injection is not possible, for narcosis or anæsthesia may be obtained within 15 minutes. The usual disadvantages of intraperitoneal injection apply (see Chapter IV).

The *intrathoracic route* can be used to induce rapid anæsthesia in hysterical dogs where intravenous injection is not possible. Anæsthesia can be obtained within five minutes, but great care must be taken in computing the dosage, for absorption is rapid, and the time lag which occurs following intraperitoneal injection is not present to act as a buffer and prevent temporary overdosage. A fine needle should be used and the injection made fairly high on the chest wall, behind the shoulder and just anterior to a rib (see Chapter IV).

The *intravenous route*, including intracardiac injection, is used routinely for inducing anæsthesia and performing euthanasia. All the precautions normal to intravenous injections must be observed (see Chapter IV), but there are a number of points concerning procedure which are peculiar to pentobarbitone sodium: unless certain principles are adhered to, serious consequences may follow.

The induction of anæsthesia should be performed as follows: Prepare the animal in the normal manner. Dosage should be computed according to weight (1/4–1/7 gr. per lb. or 20·0–33·0 mg. per kg.) and an extra 1 gr. (65·0 mg.) or more in the case of large doses, included to allow for idiosyncrasy. When the needle is in the vein inject about half the computed dose taking about 10 seconds; the animal will tense and then relax, possibly extruding the tongue, curling it up over the nose. Lie the animal on its side making sure that the needle remains in the vein. Proceed to inject the solution in fractions of a ml., allowing about 20 seconds to elapse between injections, during which time the various reflexes should be tested: this second part of the induction period should take five to ten minutes and proceed until the required depth of anæsthesia is reached.

This method is both suitable and advisable in healthy dogs and cats but should not be used for toxic animals, sheep, or pigs, for which the normal method is a slow continuous injection until narcosis is achieved, when slow intermittent injection should continue until the required level of C.N.S. depression is reached.

Where light anæsthesia has been induced, a period of 15–20 minutes

per ml. for anæsthetic purposes and 3 gr. (195·0 mg.) per ml. for euthanasia and large animal anæsthesia. Capsules are also available.

Ultra-Short Duration Barbiturates

Numbers of this type of barbiturate have been synthesized, including thiamylal sodium, thialbarbitone, and thiopentone, but only the latter is in general use in Great Britain.

Thiopentone Sodium, B.Vet.C. (Thiopental Sodium U.S.P.)

This is a yellow, unstable, water soluble salt, marketed in ampoules sealed under nitrogen. When made up with water for injection, the solution should normally be used within a few hours, for hydrolysis occurs fairly rapidly. No solution should be used after 3 days at room temperature. Chemically the compound is identical with pentobarbitone sodium except for the substitution of sulphur for the oxygen at carbon 2.

The action is typical of the ultra-short duration barbiturates, and though it has anticonvulsant properties which are superior to those of pentobarbitone, it can only be used as an intravenous injection for the induction and maintenance of anæsthesia. To control the spasms of tetanus in man, it has been used successfully over a period of 10 days by intravenous drip techniques in conjunction with intramuscular pethidine (Grant *et al.*, 1953), but similar applications in the veterinary field are not reported.

Thiopentone sodium is used in all species of domestic animals for the induction of anæsthesia. Once anæsthesia is achieved it may be maintained by further intermittent or continuous flow injections of thiopentone or by changing to volatile or gaseous anæsthetics. Thiopentone may be used with or without prior sedation and analgesia (with chlorpromazine, morphine, or pethidine), and may also be combined with muscle relaxants. It is compatible with atropine and hyoscine which may be administered in a combined solution with pethidine or morphine.

Intravenous administration follows much the same pattern as pentobarbitone sodium, but it should be remembered that the ultra-short acting barbiturates exert their effects immediately following injection and the impact of a temporarily excessive dose is immediate. Considerable care should be taken when giving the injection; as the anæsthetic is a strong respiratory depressant the major sign of overdosage is the cessation of breathing. This apnœa is usually temporary and breathing recommences after 15–60 seconds, though sometimes artificial respiration may be required.

In *dogs and cats* it is usual to give the preparation as a 5 per cent. solution, ampoules of 0·25 G. being dissolved in 5·0 ml. water for injection, 0·5 G. in 10·0 ml., and 1·0 G. in 20 ml. of water. Half the dose is given fairly quickly (about ten seconds), followed by a wait of up to a minute, during which the breathing should become even and regular. If apnœa is protracted, artificial respiration should be given by pressure on the chest

will be available for operational purposes. Medium anæsthesia will provide a 'safe' period of 15–30 minutes, and deep anæsthesia will normally last for up to 45 minutes. The recovery period will last for up to eight hours, by which time the animal should be able to stand. Inco-ordination may persist for 24 hours and in extreme cases as long as 48 hours. During this recovery period animals should be kept quiet and warm. Should the animals be stimulated during the medium and light narcosis recovery stages, appreciable narcotic excitement can result and self-inflicted damage may be considerable. Pentobarbitone sodium *alone* is not suitable for inducing anæsthesia in horses, is of doubtful value in large adult cattle, should not be used in young calves which may remain anæsthetized for up to forty-eight hours, but has been used successfully in sheep and pigs, although thiopentone is preferred in view of its short post-anæsthetic recovery period. A recently discovered compound β methyl β ethylglutarimide sodium, known commercially as Megimide Sodium in Great Britain and Australia and as Mikedimide in the United States, makes it possible to antagonize pentobarbitone and cut short the recovery period. It is possible that pentobarbitone may become even more widely used if experience with this compound shows that the main drawback is removed. (Current investigations indicate that this is so in adult cattle and calves; Jennings, 1958; Toosey, 1959.) Pentobarbitone sodium with chloral hydrate (*q.v.*) and magnesium sulphate has proved to be a useful combination for inducing surgical anæsthesia in horses and cattle.

In *balanced anæsthesia* pentobarbitone anæsthesia may be combined with morphine or, better still, pethidine narcosis. This reduces the quantity of pentobarbitone required by as much as two thirds, but usually one half, of the normal requirements, and therefore increases the chances of survival, as it gives a lighter level of anæsthesia and a shorter recovery period. Another type of premedication drug which will reduce the amount of anæsthetic is chlorpromazine; this potentiates the barbiturate effect, reducing dosage and recovery period: it should not be used for pre-medication of shock cases, however, for it may cause a further, and fatal, drop in blood pressure. Muscle relaxants are useful in conjunction with pentobarbitone sodium for, as with all barbiturates, muscle relaxation is not marked and may make prolonged and involved abdominal surgery difficult.

Dosage by intravenous injection to give anæsthesia:

1/4–1/7 gr./lb. (20·0–35·0 mg./kg.)

In general, large animals will require about 1/9 gr. per lb. body weight and small dogs and cats may require as much as ¼ gr. per lb. body weight. The dosages for intraperitoneal and intrapleural injection are the same.

Doses given orally for sedative purposes are much the same as those of other barbiturates. Doses injected intramuscularly for sedative purposes should be about half those given for anæsthesia. Pentobarbitone sodium is commercially available as stable solutions containing 1 gr. (65 mg.)

every three or four seconds or by other suitable methods. After assessing the depth of C.N.S. depression, injection is continued intermittently until the required depth of anæsthesia is reached. This may take up to five minutes. Duration of anæsthesia will depend on the dose given: with light anæsthesia, usually requiring a dose of approximately 1/10 gr. (6·0 mg.) per lb. body weight (13·2 mg./kg.), anæsthesia lasts about ten minutes, but 1/5 gr. per lb. (26·4 mg. per kg.) will normally give deep anæsthesia with an anæsthetic duration of up to 25 minutes. Recovery is usually complete within 1–2 hours and struggling is not common. Old animals may show idiosyncrasy with protracted inco-ordination.

It is now common practice, when an operation is scheduled to take 30–60 minutes, to strap the syringe onto the leg with the needle in the vein, using elastic or zinc adhesive tape, so that an assistant may reinforce the initial injection by further intermittent injections. By this means, anæsthetic duration similar to that obtained with pentobarbitone is achieved without the prolonged recovery period attaching to the latter drug, though some extension of the recovery period must be expected.

By varying the method of injection, thiopentone sodium can thus be used for operations and manipulations of short duration, such as x-ray procedures, dental surgery, minor surgery, and abdominal palpation: it may also be used for protracted abdominal or thoracic surgery, surgical repair of fractures, and similar procedures which require prolonged anæsthesia but in which it is desirable to avoid the prolonged recovery period which follows anæsthesia induced by pentobarbitone sodium or chloral hydrate.

Pigs have been successfully anæsthetized with thiopentone sodium. The method of choice, and the one which gives the most consistent results, is intravenous administration using the procedure described above for dogs and cats (Muhrer, 1950; Clover, 1955;). Intraperitoneal administration has been used successfully (Henderson *et al.*, 1950), but Clover (*loc. cit.*) quotes cases of widely varying response and considers it inadvisable to use this route.

Sheep can be anæsthetized quite safely and satisfactorily with thiopentone sodium (Hall, Phillipson & Jennings, 1955; Titchen *et al.*, 1949), but allowance should always be made for excessive salivation and the possibility of regurgitation; defæcation may also occur.

Cattle of all ages and sizes have been narcotized and anæsthetized with thiopentone sodium (Henderson *et al.*, 1950; Wright, 1947; Ford, 1951). If small doses are given rapidly by the intravenous route narcosis is usually achieved, but Ford (1951) was unable to obtain consistent results when trying to obtain anæsthesia in adult cattle and reported heavy falls when anæsthesia supervened. Boukaert *et al.* (1950) found that thiopentone sodium was satisfactory for anæsthesia in calves, periods of anæsthesia ranging from 10–12 minutes being obtained by normal methods using doses of up to ½ gr. per lb. body weight (15·0–20·0 mg./kg.) given over a period of 5 minutes.

Horses are not good subjects for thiopentone anæsthesia. (Ford, 1951), although Longley (1950), Waddington (1950), and Belonje (1949) have advocated its use in small doses given within 10 seconds. Although anæsthesia is achieved in the majority of cases, heavy falls may occur, Cheyne-Stokes breathing is common and violent struggling during the recovery period is frequent (Henderson et al., *loc. cit.*; Ford, *loc. cit.*). It is therefore not to be considered as an anæsthetic for routine use in horses though Faustini (1954), and Hall (1957), indicate that the post-anæsthetic excitement and struggling is practically eliminated by the use of chlorpromazine premedication.

Dosage:

Horse (Longley)	Old and debilitated horses:	1/15–1/13 gr./lb. (9·0–11·0 mg./kg.)
	Healthy adults:	1/10 gr./lb. (13·0 mg./kg.)
Foal (Belonje):	150 lb:	0·5 G.
	200 lb:	1·0 G.
Yearling:	400 lb:	3·0 G.
Cow Adult:		1/12–1/9 gr./lb. (11·0–15·4 mg./kg.)
Calf:		1/9–1/7 gr./lb. (15·4–19·8 mg./kg.)
Sheep:		1/12–1/9 gr./lb. (11·0–15·4 mg./kg.)
Pig (Muhrer):	10–50 lb:	5·0 mg./lb. (11·0 mg./kg.)
	50–100 lb:	4·5 mg./lb. (9·9 mg./kg.)
	100–200 lb:	4·0 mg./lb. (8·8 mg./kg.)
	200–300 lb:	3·5 mg./lb. (7·7 mg./kg.)
Dog and Cat:		1/8–1/5 gr./lb. (8·0–12·0 mg./kg.)

Thiopentone sodium is available commercially in 0·25, 0·5, and 1·0 G. ampoules. The suitable sizes of ampoules of water for injection (5·0, 10·0, and 20·0 ml., respectively) are usually included in the packs.

Thialbarbitone Sodium, B.Vet.C. (Kemithal Sodium)

This is another thiobarbiturate with an ultra-short anæsthetic duration. It is a pale yellow hygroscopic powder with a characteristic odour. It is soluble in water and solutions are stable for only 4 or 5 hours. As an intravenous anæsthetic its potency is approximately half that of thiopentone, and though it has been used as an anæsthetic in sheep (Titchen *et al., loc. cit.*) at the rate of 20·0–30·0 mg./lb. (44·0–66·0 mg./kg.), and to dogs and cats at a slightly higher rate, it is not used very frequently.

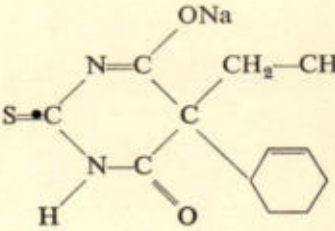
Ampoules containing 1·0 G. are available: 10·0 ml. of water should be used in preparing solutions (10 per cent).

The parent drug, Thialbarbitone, B.Vet.C. (Kemithal), is more widely known due to its use in conjunction with betanaphthoxyethanol in the form known commercially as Anavenol K. Thialbarbitone is a white or creamy white powder which is odourless and insoluble in water but soluble in organic solvents. Its actions and dosage are similar to those of the sodium salt.

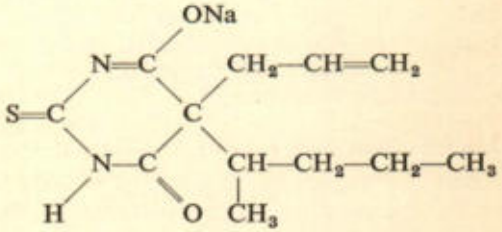
Thiamylal Sodium, N.N.R. (1955)

This thiobarbiturate differs from thialbarbitone in having a (methyl-butyl) side chain at Carbon 5 in place of the (cyclo-hex-enyl) ring. It is therefore also closely related to thiopentone sodium.

(viii) Thialbarbitone Sodium



(ix) Thiamylal Sodium



This anæsthetic, known commercially as Surital Sodium, is a pale yellow hygroscopic crystalline substance which, in aqueous solution, (it is freely soluble), has a strong sulphurous odour. It may be used as a 2·5 per cent. solution (pH about 10·8) or a 4 per cent. solution, which correspond to 1·0 G. (15 gr.) in 40·0 ml. and 1·0 G. in 25·0 ml. respectively, but stronger concentrations have been safely and successfully used: Crawshaw (1955) used a concentration of approximately 7 per cent. (1·0 G. in 15·0 ml. or 1 gr. per ml.) in 37 dogs and eight cats. The compound has been widely used in the United States as an ultra-short acting barbiturate anæsthetic for dogs and cats (Reutner *et al.*, 1948; Brinker *et al.*, 1951; Lumb *et al.*, 1952; Brock, 1952; Eads *et al.*, 1953; Wheeler, 1952; Borgman 1953) but it has not been used generally in Gt. Britain, though favourably reported on by Crawshaw. Thiamylal sodium has also been used successfully in pigs (Dunne *et al.*, 1954).

The anæsthetic should be given intravenously in the same way as thiopentone sodium; intraperitoneal administration gives irregular results. It has a potency about 50 per cent. greater than thiopentone, has a slightly less depressant effect on the respiratory centre, but seems to cause greater salivation and requires atropine or hyoscine premedication. Excitement during induction or recovery is less common than with thiopentone sodium.

Toxicity is not great, up to 2·25 times the anæsthetic dose being tolerated in the majority of dogs. The heart is usually unaffected by doses which cause apnœa.

Dosage depends on the method of administration, the more rapid the injection the smaller the dose and the shorter the duration of anæsthesia.

Dog and Cat:	1/8–1/6 gr. per lb. (8·1–11·0 mg./lb., or 17·8–23·2 mg. per kg.)
Pig:	approximately $\frac{1}{8}$ gr. per lb. (8·3 mg. per lb. or 18·26 mg. per kg.) by slow intravenous injection.

Where medium anæsthesia is induced, the duration is approximately 10 minutes, but by continuing to deep anæsthesia duration may be extended to about 20 minutes. Morphine, atropine, hyoscine and tubocurarine have all been used safely in conjunction with thiamylal sodium, and ether is satisfactory for continuing anæsthesia induced by this barbiturate. Where morphine is used as a basal narcotic the dose of barbiturate is reduced by approximately 50 per cent., whilst the duration of anæsthesia is prolonged.

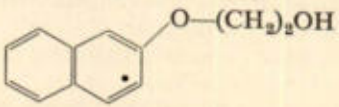
Miscellaneous Non-Volatile Anæsthetics

Apart from the barbiturates, the only non-volatile substance with anæsthetic properties to be discovered in the last two decades is beta-naphthoxyethanol.

Betanaphthoxyethanol, B.Vet.C.

This white crystalline powder with little odour but a characteristic taste is insoluble in water but soluble in organic solvents. It is represented graphically as in (x), and empirically as $C_{12}H_{12}O_2$.

(x) Betanaphthoxyethanol



The compound is officially available as Injection of Betanaphthoxyethanol with Thialbarbitone, known commercially as Anavenol K. This injection consists of a suspension containing 10% of the betanaphthoxyethanol and 2·5 per cent. of the barbiturate. Recently the commercial formula has

been changed and the preparation is now a double strength solution (20 per cent. and 5 per cent.); this makes injection far easier.

Actions and Uses. Considerable controversy has existed since beta-naphthoxyethanol was first introduced in 1949. Its action is peculiar in that it produces an ascending reflex paralysis in which leg and trunk reflexes disappear before head and neck reflexes (Parry, 1950); this process aligns the compound with the muscle relaxants, although Parry (1951b) states categorically that the pharmacological action is not the same as that of curare and related relaxants. Hall (1957) is careful to refer to the action of betanaphthoxyethanol as 'anæsthetic-like'. The problem is not satisfactorily resolved.

Because of the difficulty of obtaining control of the head and neck the mixture of the naphthol and barbituric acid derivatives was produced with the object of combining the ascending action of the naphthol compound with the descending action of the thiobarbiturate. It would seem that this mixture is of little greater value than the naphthol compound alone (Bolton, 1951; Kirkwood, 1952; Watson, 1953.) The apparently good report on its effect in sheep (Harmer *et al.*, 1951) does not bear close examination—it would appear, from the method of administration, dosage, and the type of anæsthesia achieved, that the effects were due almost entirely to the thialbarbitone content. The mixture produces a longer recovery period, the danger of respiratory collapse is greater, and with doses of the barbiturate in excess of 15·0 mg. per kg. there is a danger of barbiturate excitement during the recovery stage.

Wright (1957) and Hall (1957) stress the controversial nature and unreliability of the naphthol compound and barbiturate combination, whilst Hall definitely states that it is unsatisfactory in all species other than the horse.

Toxicity. It has been stressed (Parry, 1950, 1951a & b; Gold *et al.*, 1951, a, b, c) that the compound is toxic to the heart and the British Veterinary Codex indicates that the compound must not be used in species other than horses, pigs, and ruminants, that it is not to be used in old or sick animals, or when heart and lung diseases are present. These conditions considerably restrict its application and usefulness. Too rapid an injection may result in apnœa, and artificial respiration should be applied. Extravascular injection may cause local, but transient, swelling.

Dosage. In all species: 10·0–15·0 ml. per cwt. (50·0 kg.). The smaller the animal the larger the dose rate and *vice versa*. Speed of injection is important: below 5 cwt. (250·0 kg.) the speed should be reduced, whilst above 10 cwt. (500·0 kg.) the speed must be increased: between these limits a speed of injection of 1·0 ml. per second is optimal. A total time of 1½–2 minutes is the average period for injection.

Injections should be continued until the animal goes down. Repeat

injections of about half the induction doses may be given at the same speed to prolong the effect; a dose given five minutes after induction may be expected to extend the effective period from the normal 10–15 minutes to 20–30 minutes.

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CHAPTER 14

NERVOUS SYSTEM DEPRESSANTS

(iii) THE VOLATILE AND GASEOUS ANÆSTHETICS

Volatile Anæsthetics. The members of this group of anæsthetics are fluids with low boiling points which volatilize freely at normal temperature and pressure, the gases produced having anæsthetic effects when inhaled. They are:

1. Ether and vinyl ether.
2. Chloroform
3. Trichloroethylene
4. Bromochlorotrifluoroethane.

Volatile anæsthetics may be used to anæsthetize any species of animal: chloroform is widely used in farm animals and was used in the dog but because of toxicity considerations pure chloroform is not used in the cat: ether is valuable in small animals but is not used to anæsthetize large animals in Gt. Britain, although by using special apparatus it has proved successful in anæsthetizing horses on the Continent; vinyl ether is not used commonly but has been recommended for dogs and cats: trichloroethylene has not made its mark as a veterinary anæsthetic in this country and the fluoroethane compound is only recently available.

Induction. The volatile anæsthetics are administered, using various types of mask or apparatus utilising intra-tracheal tubes, in one of two ways:

1. By auto-inhalation in which air is inhaled through or over the anæsthetic, or through a pad soaked in the anæsthetic, thereby volatilizing the liquid or,

2. By positive feed methods whereby air, oxygen, or oxygen combined with 5 per cent. carbon dioxide, is bubbled through or passed over the anæsthetic and carries with it into the mask or intra-tracheal tube a quantity of anæsthetic vapour. The first way is commonly used for farm animal anæsthesia whilst the second way is more common in small animal anæsthesia.

The anæsthetic circuit may be 'open' or 'semi-closed', exhaled gases being lost into the atmosphere and not used again. Using apparatus with non-return inlet and outlet valves the waste gases pass directly into the atmosphere, but when the more simple auto-inhalation type of mask is used these waste gases are breathed out through the anæsthetic pad causing a high wastage of anæsthetic.

Both auto-inhalation and positive feed methods are widely used in veterinary practice and are adequately described in Wright's *Veterinary Anæsthesia* (Edit. 1, 2, 3 and 4, Baillière, Tindall & Cox, 1947–1957).

The *stages of induction* are common to all inhalation anæsthetics. They are well defined and it is essential that they should be known and recognized. They are:

Stage 1: Voluntary struggling and excitement due to fear.
Stage 2: Involuntary struggling with narcosis.
Stage 3: Anæsthesia.

A fourth stage, that of bulbar paralysis and death, is frequently added to this list.

The indications vary slightly between the species, but in general they follow the same pattern.

In the *horse* stage one is typified by all the signs of fear—spasmodic struggling, rapid deep respirations, dilated pupils and a frequent, strong pulse. Voluntary holding of the breath may occur. Struggling is more violent if the air supply is so low as to verge on suffocation and the anæsthetic concentration high.

As stage one passes to stage two the periods between struggling get longer and movements become less concerted and sluggish, although occasionally relatively continuous but less powerful leg movements may occur. The eyelids open, the pupils remain dilated, nystagmus occurs and breath-holding of an involuntary nature may be noticed. The third stage follows with a general relaxation of muscles and loss of limb and trunk reflexes, the tail is relaxed, respiration becomes shallower, slower and abdominal in type. The pulse should be regular and normal. In light anæsthesia the eyelids should be open and the corneal reflex brisk, but as anæsthesia deepens to medium anæsthesia the eyelids close and the corneal reflex becomes sluggish but is always present; the pupil is constricted; breathing and the pulse are normal. In deep anæsthesia the breathing becomes much slower and shallow, the pulse is normal in rate but less powerful than in the previous stages, the anal and bladder sphincters relax, occasionally allowing involuntary defæcation and urination, the corneal reflex is inconsistent, but the pupil should always be constricted.

Should anæsthesia be taken further, respiratory and circulatory depression arises and the fourth stage, in which C.N.S. paralysis with cessation of breathing and, later, heart failure, supervenes. The onset of this stage is indicated by progressive, or sometimes sudden, dilatation of the pupil and irregular breathing.

Unless euthanasia is intended, anæsthesia should not be allowed to progress beyond the depth of medium anæsthesia, with closure of the eyelids and the development of a sluggish corneal reflex.

In *cattle* the use of volatile anæsthetics is less common than in horses, mainly because of their more phlegmatic disposition and suitability for local and regional anæsthetic techniques. The tendency of all ruminants

to develop tympany when cast and the danger of respiratory failure due to the pressure exerted on the diaphragm, as well as the possibility of regurgitation of ruminal contents, allied with the profuse salivation caused by the anæsthetics, combine to make general anæsthesia relatively hazardous. Nevertheless the induction of narcosis and light anæsthesia using chloroform has been frequently and successfully practised, often combined with local anæsthesia. In general, the stages of induction follow a course similar to that in horses, but the struggling, so typical of inhalation anæsthesia in other species, is relatively mild and insignificant.

The pig is not a good subject for the induction of general anæsthesia by volatile anæsthetics, partly because of the short neck and the possibility of occlusion of the air passage, but also because of the susceptibility of the species to chloroform poisoning—ether and other volatile anæsthetics are not suitable for normal auto-inhalation methods. Induction stages are the same as for the horse, stages one and two being accompanied by struggling and squealing but induction is rapid and the stages therefore short.

In the *dog and cat* small variations occur in the signs indicating the various stages of induction.

Stage one is accompanied by the normal signs of fright—convulsive struggling, growling and biting, defæcation and urination. Vomition is not common. Salivation usually occurs, due more to the irritant effect of the anæsthetic than the response of the animal to anæsthesia. The pupil is widely dilated. Both species will hold their breath voluntarily for as long as ten seconds, after which they inhale deeply: this may occasionally be responsible for high anæsthetic concentrations in the blood followed by respiratory and cardiac paralysis so that great care should be taken to dilute the anæsthetic during these periods either by lifting the mask or by opening air inlets etc.

Stage two arrives imperceptibly, the character of the struggling and the noise changing; movements are less convulsive and less co-ordinated, whilst growling and angry noises change to whining and whimpering during the expiratory phase. The pupil is still dilated and nystagmus is usually marked in cats but not in dogs.

As stage three commences all movements and noises cease and muscular relaxation occurs, breathing becomes regular and slower, nystagmus ceases and all reflexes are lost, the corneal being the last reflex to go. At this stage blood pressure falls and temperature control is diminished; body temperature may fall as much as 5°, making it essential to keep animals warm during anæsthesia. Anæsthesia should normally not be required to go beyond the stage of a sluggish corneal reflex, but its absence has not the significance that it has in the horse and cow.

The imminence of stage four can only be determined by watching the breathing and mucous membranes. The former becomes irregular and shallow, whilst the latter become progressively cyanosed, with a sluggish pressure reaction, and engorged vessels.

Excretion and Recovery. The volatile and gaseous anæsthetics are mainly excreted through the lungs. Only a minor part (8–20 per cent. of ether) is lost in the urine and other secretions. Excretion begins immediately the mask is removed and about half is lost from the body within five minutes but the remaining percentage is lost only gradually, ether taking up to four hours and chloroform almost double this period.

The stages of recovery are similar to those of induction but more rapid and in reverse. Struggling is, however, not so marked but can still be dangerous and with the horse restraint should continue until the animal is able to rise and stay on its feet; this restraint usually consists of keeping the head down only. With cattle and small animals, if they are propped on their brisket (sternum) and left free in a box, kennel, or basket, recovery quickly follows without undue excitement.

The greatest danger period during inhalation anæsthesia is the stage of light narcosis, both in the induction and the recovery phases. In both phases death is usually due to cardiac fibrillation and syncope (heart failure). Death occurs following excessive anæsthetic concentrations allied with reflex respiratory stimulation of the heart and adrenaline outpouring during the struggling and excitement. Of the two periods, struggling during recovery is probably more dangerous, for the venous anæsthetic concentrations are high and there is no means of reducing them rapidly, whereas during induction the intake of anæsthetic can be controlled with care. The only two cats lost out of a series of about 2,000 anæsthetized by volatile anæsthetics (ether-chloroform mixtures) died from heart failure during the recovery narcotic stage following violent attacks of sneezing. This type of accident is more likely with chloroform or chloroform mixtures than if ether alone is used.

Contra-Indications. Inhalation anæsthesia is contra-indicated in patients with respiratory diseases, and in the case of chloroform anæsthesia, hepatic and renal diseases.

Balanced Anæsthesia. Inhalation anæsthesia is now frequently used following premedication with narcotic doses of chloral hydrate, a barbiturate, pethidine or an opium derivative. Belladonna derivatives are very valuable in controlling the excessive salivary and bronchial secretions which follow the irritant action of chloroform and ether. In small animals it is now common practice in the teaching schools, if an operation is likely to be prolonged, to induce anæsthesia with an ultra-short acting barbiturate, insert an endotracheal tube and continue anæsthesia with a volatile or gaseous anæsthetic.

Chloroform, B.Vet.C.

This important volatile anæsthetic is a heavy, clear, volatile liquid with a characteristic odour and burning taste. It is non-inflammable but when exposed to air and light, oxidation produces the poison gases, phosgene

and free chlorine. To reduce this process, all anæsthetic chloroform contains 1–2 per cent. ethyl alcohol as a stabilizer. Chloroform is slightly soluble in water (0·5 per cent.) but miscible with most organic solvents.

Chemically, chloroform is trichloromethane ($CHCl_3$) and is therefore a close relative of carbon tetrachloride (CCl_4) which is used as an anthelmintic. This relationship accounts for the anæsthetic properties of carbon tetrachloride.

Actions. Chloroform has actions when administered externally, by mouth, and when inhaled.

The *external* actions are those of a skin cleanser due to its fat solvent effect, and of a coolant and sedative due to evaporation. Alcohol and ether are preferred for these last effects. Should evaporation be restricted, or a preparation including chloroform be applied with friction, a rubefacient action results because of its irritant and penetrating properties.

Internally chloroform may be administered orally or by inhalation. Following oral administration, irritation causes reflex salivation (sialagogue action), though mixing with demulcents will reduce this effect. On reaching the stomach, carminative, antizymotic and antispasmodic effects are are exerted (see Alimentary System). It is rarely used alone for these purposes, but is a constituent of many gastro-intestinal sedative mixtures, of which chlorodyne (Tincture of Chloroform and Morphine, B.Vet.C.) is probably the best known. In many of these mixtures the chloroform serves the additional purposes of a bacteriostatic. Absorption is rapid but rarely are concentrations great enough to exert any central sedative action. By inhalation, chloroform exerts a powerful C.N.S. depressant effect and it is used in this way as a general anæsthetic for horses, cattle, and occasionally pigs. Its use for dogs is decreasing, and it should never be used alone for anæsthetizing cats.

Chloroform Anæsthesia

The method by which chloroform exerts its anæsthetic action is not known precisely, but the most acceptable theory, the 'lipoid theory', classifies chloroform, ether and other fat soluble anæsthetics together, suggesting that the compounds have an affinity for lipoid tissue and that they are therefore taken up by the brain in relatively large quantities because of the high fat content of the brain. This theory was postulated before the new era of pharmacological investigation and accounts only for the distribution of the anæsthetics. The intracellular effects are as yet unknown but are presumed to be related to the reversible blockage of enzymes. It is probable that these lipophilic anæsthetics interfere with intracellular oxidation processes and that the different groups of anæsthetics do not differ in their pharmacological actions as much as was once thought.

The *local* irritant action of chloroform on the respiratory and naso-pharyngeal mucosæ is responsible for increased salivation and bronchial

secretions in all species, but especially in ruminants. This increase of secretions, allied with the decrease in activity of tracheal and bronchiolar cilia and depression of the cough reflex, increases the danger of post-anæsthetic pneumonia. It is advisable to ensure that if operations are to be at all protracted, the animal lies with its head below the general body level so that secretions will drain towards the mouth.

The *circulatory system* effects of chloroform are important and dangerous. In general, chloroform causes circulatory depression with a progressive fall in blood pressure as the stage of anæsthesia is reached, due mainly to depression of the vasomotor centre, but splanchnic dilation also occurs. Circulatory reflexes are also affected, the inhibitory ones being intensified whilst the pressor reflexes are depressed: this includes the carotid sinus reflexes and the vagal centre reflex reaction to respiratory mucosa irritation. The *heart* muscle is directly poisoned by high concentrations of chloroform and becomes very sensitive, particularly in cats, to a high blood pressure, which may result from adrenaline production during the excitement of the induction and recovery stages of anæsthesia. Heart failure, which has long been acknowledged as the most frequent cause of death during chloroform anæsthesia, is therefore probably due to three major factors: 1. Direct muscle toxicity due to high blood concentrations following erratic inhalation, and 2. Ventricular fibrillation caused by excessive adrenaline production during a period when the heart is particularly sensitive to its action. 3. Vagal arrest. The last two actions are probably intensified by the muscular weakness following the direct toxic action. It follows that anæsthesia must be conducted as quietly and smoothly as possible and that premedication with vagal paralytics (e.g. atropine) and sedatives (e.g. pethidine) should decrease the likelihood of cardiac collapse.

The effects of chloroform on the *respiratory system* are mainly those of depression but in the early induction and late recovery stages they are masked by the effects of fear and narcotic excitement. Strong concentrations of chloroform during the induction stages may produce reflex respiratory arrest. The carbon dioxide excitability threshold is elevated so that reinstitution of breathing may not be stimulated until tissue anoxia has reached a fatal stage. This situation may be responsible for death during induction of anæsthesia.

In deep anæsthesia the character of the breathing changes from predominantly thoracic to diaphragmatic or abdominal breathing, and if anæsthesia is continued further becomes irregular, laboured, and finally stops due to respiratory centre paralysis.

Death from respiratory paralysis rarely occurs except following overdosage and forcing anæsthesia to the stage of medullary paralysis.

The alimentary system is not markedly affected by chloroform, but relaxation and cessation of intestinal movement do occur. In the vomiting species—pig, dog and cat, vomition occasionally occurs during the induction but more commonly in the recovery stages: it is more likely to occur

in toxic patients. This can be very troublesome and dangerous, for it necessitates removal of the mask and unstrapping the patient on at least one side so that the animal can be turned on its side, the vomitus removed and the respiratory passages kept clear. Less danger exists if an endotracheal tube is in place, but even so, interruption of the operation even in its later stages may lessen the animals chances and add to the difficulties of the surgeon. Should it occur whilst an abdominal wound is still open, rapid packing with swabs and opposing the lips of the wound with the fingers or towel clips may prevent disastrous extrusion of the intestines. That this does occur is an indication of the difficulty of maintaining an even state of anæsthesia with volatile anæsthetics and unskilled assistance: vomition occurs during a period of lightening of anæsthesia.

Chloroform has a toxic effect on the liver and kidneys but has little effect on the uterus or foetus *in utero* and is therefore useful as an anæsthetic for Cæsarian section.

Muscular relaxation is good during chloroform anæsthesia. *Analgesia* occurs before the onset of anæsthesia and loss of consciousness. As with ether, sensory pathways are paralysed before the motor reflex components.

Toxicity. Sheep and cats are the most susceptible species of the normal domestic animals but poisoning does affect other species. The acute toxicity of chloroform on the heart and respiratory system has been mentioned, but delayed toxicity is probably as great a danger. The fear of causing delayed poisoning probably predisposes to acute toxic effects for there is a tendency to use only light anæsthesia and to cease administration at the earliest opportunity: the maintenance of a level plane of anæsthesia is difficult and lightening into the narcotic stage happens all too easily, with consequent dangers of narcotic excitement and surgical shock.

Delayed chloroform poisoning takes the form of fatty changes in all parenchymatous organs as well as the heart muscle. Toxic patients, pregnant or parturient animals, young and aged patients, are most susceptible. Protracted operations, in which chloroform anæsthesia is maintained for one hour or more may cause delayed chloroform poisoning in normal adults but in the susceptible group shorter periods than this may be dangerous. Generally speaking affected animals are slower to recover from anæsthesia but definite symptoms may not be seen for about 48 hours. Symptoms include depression, 'dirty' mucous membranes with cold extremities, repeated vomiting, and the development of jaundice. Depression increases and develops into a coma which is followed by death within about a week of the anæsthesia.

Treatment of acute poisoning depends on the cause. Adrenaline is contra-indicated in heart failure during the early stages of induction and the later recovery stages, but can be useful in deep anæsthesia. It is wiser in narcotic stage heart failure, to rely on artificial respiration with cardiac massage in small animals and the use of oxygen if available. Analeptics have also been used but rarely can a heart be restarted no matter what

the treatment. Prophylactic treatment includes premedication with atropine or similar vagal paralytics which prevents at least one of the possible contingencies. With respiratory failure, artificial respiration following clearance of the air passages, and the use of oxygen and analeptics usually reinstitutes breathing.

Delayed chloroform poisoning should be prevented, for treatment is rarely successful. As the resistance of the liver and kidneys is related to their glycogen content, the feeding of glycogenic food and the reduction of protein for a few days before a scheduled operation can be useful. Dextrose and calcium injections (*q.v.*) have been given prophylactically before and therapeutically after chloroform anæsthesia. This is analogous to the treatment of poisoning with carbon tetrachloride.

Dosage:

By mouth:	Horse:	60–120 m. (4·0–8·0 ml.)
	Cow:	120–240 m. (8·0–15·0 ml.)
	Sheep and Pig:	15–40 m. (1·0–2·5 ml.)
	Dog:	5–10 m. (0·3–0·6 ml.)

By Inhalation: Anæsthetic doses for the various species will obviously vary according to the depth and duration of anæsthesia, but in addition they will vary according to atmospheric temperature and therefore rate of volatilization. In winter it is frequently difficult to achieve anæsthetic vapour concentrations during inhalation unless the chloroform container is heated with warm water, whilst the warmth of expired air will drive off and waste anæsthetic applied to swabs or sponges used in auto-inhalation masks not fitted with non-return valves. However, for induction, concentrations of 2–3 per cent. are normally required, and for maintenance, 1–2 per cent. of inhaled gases.

Horse: 1–2 fl. oz. (30·0–60·0 ml.) initially, followed by ½–1 fl. oz. (15·0–30·0 ml.), and then 60–120 m. (4·0–8·0 ml.) as and when required. These doses are usual when the horse is standing. If the animal is cast prior to anæsthesia the initial 'knock down' dose and the air restriction commonly applied at the same time should be omitted.

Cow: Up to 1 fl. oz. (30·0 ml.) initially, followed by ½ fl. oz. (15·0 ml.) as required, in conjunction with local or regional anæsthesia.

Pig: ¼–½ fl. oz. (8·0–15·0 ml.) initially, followed by similar doses when required.

Dog: 15–60 m. (1·0–4·0 ml.), repeated as required.

At temperatures of 50–60° F. and in a sheltered atmosphere unaffected by air currents these amounts should give narcosis in about 5 or 10 minutes and anæsthesia in 10–20 minutes, but where temperatures are lower than this and anæsthesia is being induced in the open these times may be greatly extended.

Anæsthetic Ether, B.Vet.C.

This volatile anæsthetic is a light, highly mobile, 'water white' liquid with a characteristic odour and taste. It is soluble in water 1 in 10 and miscible with all organic solvents. Ether is highly inflammable and at certain concentrations in air, oxygen, or nitrous oxide, forms an explosive mixture with a very low flash point. It is therefore unwise to use ether in the vicinity of an exposed flame, but where this is unavoidable the flame or electric fire must be above the patient as ether vapour is heavier than air. In a dry atmosphere, and where operating tables and covers are insulated, antistatic precautions must be observed. Thermocautery should not be used in conjunction with ether anæsthesia.

Actions and Uses. When applied *externally*, ether evaporates rapidly abstracting heat from the skin and therefore acting as a refrigerant and slight local anæsthetic. It is also a defatting and cleansing agent, but if applied with friction it will cause irritation and have a rubefacient action. Ether is rarely used alone for these purposes, though its defatting action is utilized in the use of ether soaps. A less pure form referred to as Solvent Ether, B.Vet.C. is used to make these soaps. It is also used for making ethereal extractions from various plants—Extract of Male Fern, B.Vet.C. is an example—and for preparing collodia, amongst other preparations.

Internally ether may be given orally or by inhalation.

By oral administration, ether acts in a similar manner to chloroform and alcohol. It is irritant and should be given with a demulcent, or well diluted: this irritant action is responsible for its carminative and antispasmodic effects, and also for its reflex cardiac stimulant action which can also be achieved by subcutaneous or intramuscular injection in the form of 'camphor and ether in oil'. This stimulant effect is frequently referred to as a 'diffusible stimulant' action. Ether is also a rapid but transient intoxicant and oral dosage should be computed with due consideration for this fact.

By inhalation, ether is a relatively non-toxic but weak general anæsthetic mainly used in small animals. Although it is no more irritant than chloroform it is less effective and vapour concentrations necessary to achieve anæsthesia are three times greater than for chloroform. Consequently the irritant effect is far greater, resulting in profuse salivation and increased secretions throughout the respiratory tract in all species. As with chloroform anæsthesia, ciliary movement decreases and great care must be taken to see that secretions neither drain back into the lungs nor block the airway.

The *circulatory system* is not adversely affected by normal anæsthetic concentrations. In the early stages of induction and during surgical anæsthesia there is a tendency for decreased vagal control and increased heart action to develop, with possibly a slight rise in blood pressure. Normal heart muscle is never affected but weak and fatty heart muscle

may be weakened. If anæsthesia is taken to the stage of bulbar paralysis there is a gradual vasomotor depression with a slow fall in blood pressure, but the heart usually functions normally even after respiration has ceased. Death is due to respiratory paralysis and asphyxia.

The *respiratory system* is frequently stimulated in the early stages of induction, intensifying the effect of fear. This decreases the carbon dioxide content of the blood, which can be dangerous, causing respiratory arrest and death. In deep anæsthesia there is progressive depression of the respiratory centre with a raising of its reaction threshold and a decrease in carbon dioxide production. Respiratory paralysis causes asphyxia and death.

The *alimentary system* is affected by ether in much the same way as by chloroform, though the degree is less. In man, ether causes more nausea but much of this is of psychological origin, and though vomition does occur in cats, this can be largely avoided by overnight fasting and also by ensuring that large amounts of saliva are not swallowed. Salivation may be decreased by atropine premedication. The gastro-intestinal depression soon passes off and a period of greater activity may occur after recovery from anæsthesia. Defæcation occurs frequently, so that animals closely confined during the recovery period may become covered in fæces and saliva unless examined periodically during the first ½–1 hour after anæsthesia: this applies especially to cats.

The effect of ether on the liver and kidneys is normally slight, and the effect on the fœtus *in utero* is negligible.

Muscular relaxation is usually fairly good though perhaps not as good as with chloroform. Ether is said to have curare-like effects and it is advisable either to avoid using muscle relaxants with ether or to reduce the dosage rates.

Analgesia occurs before loss of consciousness and before the motor component of the reflexes is lost. This is in accord with chloroform anæsthesia.

Toxicity. Ether is the least toxic of all general anæsthetics, its greatest disadvantage in this respect being its local irritant effect. Though damage to the liver and kidney of a type similar to that caused by chloroform may occur, it is only of clinical importance when liver or kidney diseases are present. Cardiac depression does not occur, and though there may be respiratory arrest due to irregular breathing and fluctuating vapour concentrations, artificial respiration is usually successful in reinstituting normal respiration. Delayed poisoning does not occur with ether.

Dosage:

Oral: for carminative and antispasmodic effect:

Horse:	½–2 fl. oz. (15·0–60·0 ml.)
Cow:	1–3 fl. oz. (30·0–90·0 ml.)
Sheep and Pig:	30–120 m. (2·0–8·0 ml.)
Dog:	15–60 m. (1·0–4·0 ml.)

Subcutaneous or intramuscular injection: as a reflex cardiac stimulant: doses of ether are approximately ¼–½ the above doses. When combined with camphor the approximate proportions are 1 part camphor, 2 parts ether and 4 parts bland oil: this solution is given in doses calculated to give 20–40 gr. (1·3–2·6 G.) of camphor for the horse and 1–2 gr. (0·07–0·14 G.) for the dog. Oral and parenteral use is less common than formerly.

By inhalation: it is difficult and unnecessary to give exact doses for ether anæsthesia. Where an open mask is used in cats a commencing dose of about 2 ml. is required: this is supplemented by similar doses as necessary. If semi-closed positive feed apparatus is used there is no exact dosage, but a steady stream of oxygen is bubbled through the anæsthetic, the rate being determined by individual effect. *Dogs* and other species cannot be adequately anæsthetized by open mask methods: by semi-closed methods dosage is varied according to individual effect.

Vapour concentrations necessary to achieve anæsthesia may be as high as 10 per cent. and maintenance levels 4–6 per cent. by volume.

Ether and Balanced Anæsthesia. The lack of toxicity makes ether very suitable as a maintenance anæsthetic following induction by thiopentone sodium, or as a general anæsthetic subsequent to narcosis induced by morphine or pethidine premedication. In both cases hyoscine or atropine should be used to restrict the profuse secretions induced by ether irritation.

Chloroform-Ether Anæsthetic Mixtures

Both ether and chloroform have disadvantages, and for small animals ether and chloroform mixtures are frequently used. Chloroform has an acute and a delayed toxic potentiality but is non-inflammable, relatively non-irritant and a potent anæsthetic: ether is highly inflammable, is highly irritant locally in anæsthetic concentrations, is not a potent anæsthetic, but is almost non-toxic. The mixtures aim at combining the good points of both—the potency, non-inflammable nature, the low irritant effect, and the rapid induction of chloroform, with the low toxicity of ether. Alcohol is sometimes used as a diluent. The commonest mixtures used are A.C.E.: Alcohol–Chloroform–Ether, in the proportions of 1, 2 and 3, and a straight mixture of chloroform and ether in the proportions of 1 to 2. The proportions in A.C.E. are easy to remember but with the other mixture it is most easily remembered that the most toxic component, chloroform, is present in the lower concentration.

With all mixtures of this type two points are of great importance. The first is that ether evaporates more rapidly than chloroform, and that unless the anæsthetic mixture is freshly prepared accidents will happen for the proportion of chloroform increases with keeping. The second is that the mixtures, though less inflammable than ether alone, are much more dangerous if ignited, for the ether burns the chloroform and the poison gas, phosgene, is produced.

These mixtures are used mainly with auto-inhalation open mask methods.

Vinyl Ether, B.P.

This volatile anæsthetic has an empirical formula $(CH_2 : CH)_2O$. It is a light, clear, colourless liquid with a characteristic odour. It contains 4 per cent. absolute alcohol and a small proportion of a stabilizer to prevent its decomposition to formaldehyde and formic acid on exposure to air and light. The stabilizer gives the anæsthetic a purplish fluorescence. Solubility in water is 1 per cent. and it is miscible with organic solvents. Inflammability is similar to diethyl ether.

Because of its rapid decomposition small containers are used and no liquid should be used from a container opened more than 48 hours previously.

Actions and Uses. An indication of the potency of vinyl ether, which is about four times greater than that of diethyl ether, is the rapidity with which anæsthesia can be induced in small animals even without the aid of prenarcotization. Recovery is likewise very rapid, and administration must be continued to the end of any operation. Reflex indications of the depth of C.N.S. depression are reported to be unreliable in man, and the respiratory reactions are used as a gauge. Muscular relaxation is of about the same degree as with ether but it is less reliable. Analgesia is reasonably good.

Toxicity. In short duration anæsthesia toxicity is slight but there is a tendency to cause liver and renal damage if anæsthesia is prolonged; there is no effect on the heart.

Vinyl Ether-Ethyl Ether Mixtures

The use of a mixture of 1 part vinyl ether with 3 parts ethyl ether has been advocated and used (Jordan, 1955) with good and safe effect in dogs and cats. The anæsthetics form an even mixture and a vapour of constant composition which may be administered by open, semi-closed, or closed methods.

The small amount of vinyl ether is sufficient to give the mixture the necessary potency for rapid induction but insufficient to materially affect the safety of ether anæsthesia.

Trichloroethylene, B.Vet.C.

The empirical formula of trichloroethylene is $CHCl : CCl_2$ and its characteristics are similar to those of chloroform, from which it may be distinguished by a blue dye which is included for this purpose. It decomposes in bright light and air, but thymol is usually included to act as a stabilizer. When combined with oxygen at a temperature of 25·5°C and over it becomes inflammable and burns to produce phosgene and

hydrochloric acid in much the same way as chloroform. Interaction with soda-lime prevents its use with closed anæsthesia circuits: dichloroacetylene is produced.

Trichloroethylene is almost insoluble in water but miscible with the organic solvents.

Actions and Uses. This chlorinated ethylene is a volatile anæsthetic used for small animals, available commercially as Trilene. It has a potency below that of ether, which makes it relatively unsuitable for dogs, though following prenarcotization it can prove quite satisfactory. It has also been used in pigs. It is effective in cats (Joshua, 1950) but the known tendency to create narcotic excitement is confirmed. Pharmacologically it is less irritant and less toxic than chloroform but requires high concentrations and needs to be volatilized by bubbling air or oxygen through a warmed solution. It is not commonly used as an anæsthetic, mainly because of its low potency and tendency to cause excitement during induction and recovery.

Other uses include removal of grease and tar from animals or clothing, and it has been used as an oxyurid anthelmintic in man (Wright *et al.*, 1937). Trichloroethylene is also used in soya bean extraction, but the meal left after this extraction has caused poisoning in cattle and poultry, and it should therefore not be used as an animal feedstuff.

Bromochlorotrifluoroethane

This volatile anæsthetic with a formula $CF_3CHBrCl$., first reported in 1956 (Raventós), is a clear, colourless, heavy liquid with a pungent odour. Its vapour is neither inflammable nor explosive.

Actions and Uses. In a comprehensive report on a series of 100 cases, which included horses, cattle, pigs, dogs, and cats, it was pointed out by Hall (1957) that induction and recovery were rapid and uneventful, that blood pressure and heart rate decreased and that respiration was also depressed—sometimes to the stage when artificial respiration was required. The anæsthetic was satisfactorily combined with all types of premedication chlorpromazine, pethidine, atropine, hyoscine, succinylcholine and tubocurarine, though the last drug had been classed as contra-indicated according to a previous report (Johnstone, 1956). The muscle relaxants were used as the ethane derivative did not give satisfactory abdominal relaxation at safe anæsthetic levels. Closed and semi-closed methods of induction were used.

Further information is required before this anæsthetic could be recommended for general use.

Gaseous Anæsthetics. The gaseous anæsthetics that may be used are three in number, (1) Cyclopropane, (2) Nitrous oxide and (3) Ethyl chloride. These anæsthetics have at the moment only a restricted use in

veterinary anæsthesia, for their administration requires relatively expensive and complicated closed and semi-closed circuit positive feed apparatus. The anæsthetics are kept in cylinders under pressure and are relatively expensive unless used in closed circuit with total rebreathing.

Cyclopropane, B.Vet.C.

The cylinders containing cyclopropane are coloured orange *in toto*. They should be stored in a cool room away from inflammable material. The gas is colourless and has a characteristic odour; it is inflammable and when mixed with oxygen or air is explosive. It should therefore not be used in the presence of open flames and static electrical sparks must be avoided—intrapulmonary explosions have occurred during human anæsthesia, with fatal results.

Actions and Uses. Cyclopropane is a safe, powerful, non-irritant gaseous anæsthetic. Induction and recovery are rapid. Normally there is little effect on respiration and the anæsthetic has been preferred for thoracic surgery. Cardiac irregularities occur, and adrenaline or conditions which are conducive to adrenaline production, are contra-indicated. Blood pressure is rarely affected, though occasionally marked systolic falls have occurred. Liver and kidney toxicity is rare.

Cyclopropane is *administered* as a 20 per cent. mixture in oxygen, preferably by way of an endotracheal tube. This entails induction with pentobarbitone or thiopentone sodium salts. The technique has been used in dogs, cats, sheep, goats, ponies and donkeys (Gregory, 1947; Jones *et al.*, 1952; Dyce *et al.*, 1952). Normally a 4 per cent. concentration is sufficient to give analgesia and narcosis; 15–20% will give anæsthesia in about 3 minutes.

Nitrous Oxide, B.P., U.S.P.

'Laughing gas' is supplied under pressure in cylinders coloured completely blue. As with all gas cylinders, those of nitrous oxide should be stored in a cool place away from inflammable material. The gas is colourless, with a characteristic odour and sweet taste, is non-inflammable, but supports combustion.

Actions and Uses. Nitrous oxide is one of the oldest and safest of the general inhalant anæsthetics. Unfortunately its potency is only about 15 per cent. of that of ether, and concentrations necessary to achieve anæsthesia are so high that adequate oxygenation is not possible. The place of nitrous oxide in veterinary anæsthesia is therefore as a maintenance anæsthetic following thiopentene sodium induction or as a diluent for ether-oxygen anæsthesia. The amount of oxygen used with nitrous oxide should never fall below 20 per cent. Analgesia is very good with nitrous oxide but muscular relaxation is not marked and local anæsthetics or muscle relaxants may be used. Recovery is very rapid.

Toxicity is almost non-existent and any difficulties are usually associated with lack of oxygenation rather than anæsthetic reactions. The gas must be administered by semi-closed or closed methods.

Ethyl chloride, B.Vet.C. has been used for anæsthetizing kittens for spaying, and for anæsthetizing birds. The anæsthetic is supplied as a liquid under pressure in glass vials equipped with trigger release valve nozzles: the nozzles are of two types, a coarse one for general anæsthesia and a fine one for local anæsthesia. General anæsthesia can be achieved by confining the patient in a small glass chamber into which the ethyl chloride can be sprayed, or the anæsthetic can be sprayed into the end of a mask, providing no anæsthetic reaches the face in a fluid form. Induction is rapid but muscular relaxation is not good and respiratory depression occurs. It is not commonly used.

For local anæsthesia of short duration the chloride is sprayed on the skin. Evaporation is rapid and freezing occurs with local anæsthesia. This type of anæsthesia is suitable for removing splinters and similar foreign bodies from the skin, for opening abscesses, and for removing broken claws from small animals.

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CHAPTER 15

NERVOUS SYSTEM DEPRESSANTS

(iv) LOCAL ANÆSTHETICS

A LOCAL anæsthetic may be defined as an agent which, when applied to a nerve ending or trunk, blocks the transmission of impulses, causing loss of sensation if sensory trunks are anæsthetized and muscle paralysis if motor nerves are affected. In no case is brain activity influenced directly during normal use. The action is reversible, and with true anæsthetics no tissue damage is caused when they are used correctly.

The number of local anæsthetics is large but a relatively small number of these is in common use. In general, they may be of three types:

1. Substances causing anæsthesia by freezing:
   (a) Carbon dioxide spray
   (b) Ethyl chloride spray
2. Substances causing anæsthesia by chemical action:
   Amethocaine Hydrochloride, B.P., B.P.C. (Tetracaine Hydrochloride, U.S.P., Anethaine, Decicain, Pantocaine.)
   Benzocaine, B.P., B.P.C., B.Vet.C. (Ethyl Aminobenzoate N.F., Anæsthesin)
   Butacaine Sulphate, B.P., B.P.C., B.Vet.C., N.F. (Butyn)
   Butyl Aminobenzoate, B.P., B.P.C., N.F. (Butesin, Planoform.)
   Chlorbutol, B.P., B.P.C., B.Vet.C., (Chlorbutanol, U.S.P., Chloretone)
   Cocaine Hydrochloride, B.P., B.P.C., B.Vet.C., U.S.P.
   Lignocaine Hydrochloride, B.P., B.P.C., B.Vet.C. (Lidocaine Hydrochloride, N.F., Xylocaine Hydrochloride.)
   Orthocaine, B.P., B.P.C., B.Vet.C. (Orthoform).
   Procaine Hydrochloride, B.P., B.P.C., B.Vet.C., U.S.P. (Novocain, Ethocaine, Planocaine).

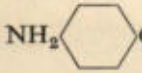
This list gives some idea of the complexity of nomenclature. Many of these substances have been developed by commercial houses and their proprietary trade marks have become widely known. Official recognition and nomenclature has further confused the situation, especially where the official pharmacopœias have adopted different names, as with lignocaine–lidocaine, amethocaine–tetracaine. Mixtures of these and other local anæsthetics are also available commercially and their names add further to the confusion.

3. Substances causing local anæsthesia but not primarily used for this purpose, nor are they normally classified as local anæsthetics. This group includes substances that are generally quite toxic and may, and do, cause necrosis. Phenol, lead salts, belladonna preparations, magnesium sulphate, are all more useful because of their anæsthetic attributes, but their use is restricted.

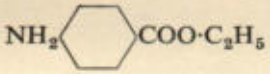
Chemical Classification. The compounds listed in group 2 are only the more useful few of a large number of local anæsthetic compounds which have been developed, initially by modification of the cocaine molecule, and later by manipulation and modification of the procaine molecule.

The majority of the more useful compounds are derivatives of para-aminobenzoic acid (i) which is produced from these compounds during metabolic breakdown, and is responsible for sulphonamide antagonism. They may be:

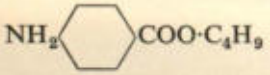
1. Simple alkyl esters such as benzocaine (ii), and butyl-amino-benzoate (iii).



(i) Para-aminobenzoic acid

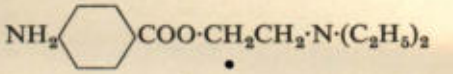


(ii) Para-aminobenzoic ethyl ester. (Benzocaine)

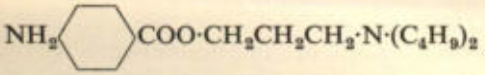


(iii) Para-aminobenzoic butyl ester. (Butyl aminobenzoate)

2. Alkyl amino- simple alkyl esters, such as procaine (iv) and butacaine (v):



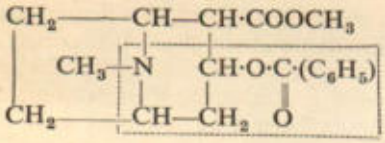
(iv) Para-aminobenzoic ethyl aminodiethyl ester. (Procaine)



(v) Para-aminobenzoic propyl aminodibutyl ester. (Butacaine)

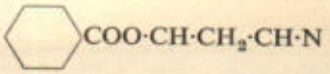
Complex compounds having a basic structure similar to these form the bulk of the local anæsthetics now available, comprehensively grouped as substituted tertiary amino alcohol esters of substituted benzoic acids. Under this heading can be classed amylocaine, amethocaine, piperocaine (U.S.P.), hexylcaine (N.N.R.), and even cocaine (vi), which is perhaps the

most complex of all, and yet contains within its structure the basic grouping (vi *a*)

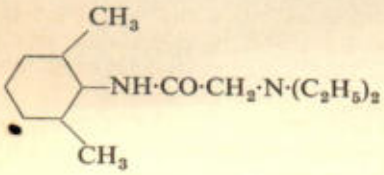


(vi) Cocaine

(vi *a*)



Lignocaine (vii) may be looked upon as conforming to this general pattern but possessing a modified ester linkage with the substitution of an amino-group in place of the hydroxyl group:



(vii) Lignocaine.

A number of local anæsthetics do not fall under this general classification, but they have little veterinary significance.

Pharmacology. The pharmacology of the local anæsthetics is very complex and to a great extent unknown.

Absorption. Local anæsthetics are not absorbed through intact skin, but if the surface is broken or inflamed, certain anæsthetics applied in ointment form or in solution will be absorbed, the rate depending on the degree of damage to the skin and whether adrenaline is included in the formulation. If adrenaline is included the rate of absorption and onset of anæsthesia will be severely curtailed, but the duration of effect will be prolonged. This effect of adrenaline also refers to local anæsthetics applied to mucous membranes through which some local anæsthetics are rapidly absorbed. Following infiltration, the absorption rate depends on the vascularity of the tissues. Inflammation will therefore speed up absorption and reduce the duration of anæsthesia, whilst the inclusion of adrenaline will slow up absorption and increase the duration of effect. Too high a concentration of adrenaline will cause ischæmia, prolonged anæsthesia and, later, a delay in healing, or even necrosis and sloughing: 1 in 50,000 should normally be the maximum concentration to use. *Hyaluronidase* added in concentrations of 150–300 units per 100 ml. anæsthetic will increase the speed of onset, enlarge the area anæsthetized by about 40 per cent. but will shorten the duration owing to an increased absorption rate: it may also for this same reason increase the dangers from toxicity. Inclusion of adrenaline will counteract the increase in absorption rate.

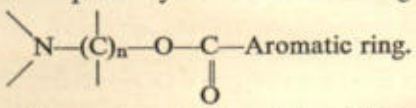
Detoxication and Elimination. The rate of breakdown and elimination varies in the different species and with different anæsthetics. Little is known of the metabolic fate of local anæsthetics other than procaine, but with this and related compounds p.aminobenzoic acid is released and with procaine the side chain becomes diethylaminoethyl alcohol, which is mainly excreted unchanged, but is in part metabolized. The acid is further converted to glycine or conjugated as a glycuronide, though some is excreted unchanged. These changes are achieved by the action of an enzyme possibly identical with cholinesterase. Some non-enzyme breakdown is also said to occur.

Sulphonamide antagonism occurs with all local anæsthetics which produce p.aminobenzoic acid during their metabolic destruction. This will include all the members of the procaine series.

Toxicity. This is similar with all local anæsthetics and is typified by restlessness, excitement, and convulsions, followed by depression, coma and medullary paralysis. Death is due to respiratory failure when the centre is paralysed. Treatment is similar—barbiturate sedatives in the excitement stages and stimulants in the later stages.

It should be remembered that hyaluronidase will increase the possibility of toxic symptoms if near maximal doses of anæsthetic are used.

Action. The relationship between chemical structure and action is still strongly debated but Gray and Geddes (1954), in a very important and comprehensive review of local anæsthetics to which reference should be made for further details on the subject, quoting Charronat, suggest that the anæsthetic action is probably due to the following structure:



This can be seen in the cocaine structure (vi) and the procaine series, but it will be seen that lignocaine makes modifications necessary.

There is no doubt, however, that the addition of an amino (NH_2) group to the aromatic ring in the above 'anæsthophoretic' configuration increases local anæsthetic effect in the benzoic ester series. This amino group must be in the 'para' position to exert maximum effect. Further increase in potency can be gained by alkylation of this group, the increase being greater with each succeeding increase in the length of the chain from methyl up to butyl groups. Unfortunately increase in potency is accompanied by an increase in toxicity.

Quevauviller, also quoted by Gray and Geddes (*loc. cit.*), summarizes the chemical requirements relating to anæsthetic activity. He postulates three basic requirements:

1. A cyclic or heterocyclic ring to give the compound solubility in lipoid tissue, which is essential for local anæsthetic action.
2. An ester or isosteric group as a link.

3. A hydrophilic group to provide water solubility so that administration is easy. This is usually related to an amino-alcohol or an isosteric group.

Should either wing of the compound predominate the resulting substance will be useless, for a too soluble compound will not release the base in the tissues, and a fat soluble compound will be difficult to administer and will not readily diffuse into the tissues.

Whatever the chemical structure of these anæsthetics, they all interfere with the metabolism of nerve fibres, affecting cell metabolism probably by blocking enzyme pathways at the cytochrome C-cytochrome oxidase level (Gray and Geddes, *loc. cit.*). All act by deposition of lipoid soluble bases in the tissues, their salts being used because of their water solubility, which makes manufacture and administration easy. Once deposited in the vicinity of the nerve fibre, they probably diffuse into the lipoid tissue of the fibre competing with the acetylcholine receptors (Thimann quoted by Gray and Geddes, *loc. cit.*), due to structural similarities (viii) thus preventing depolarization of the nerve—at the nodes of Ranvier in myelinated nerves; they therefore prevent the transmission of nerve impulses (See Ionic Theory of Nerve Impulse Transmission). The smaller fibres within a nerve trunk are affected first, but with increase in time or concentration, the larger fibres are affected progressively in order of size. This means that the senses are also progressively affected beginning with vasomotor control (the finest fibres), followed by temperature appreciation and pain, touch, general and special sensation such as joint sensation, taste, deep pressure etc. Motor nerves are affected after the sensory fibres and finally proprioceptor innervation is affected.

(viii)

$$(C_2H_5)_2 \cdot \left| N \cdot (CH_2)_2 \cdot COO \right| \cdot C_6H_4 \cdot NH_2 \quad \text{Procaine}$$

$$(CH_3)_3OH \cdot \left| N \cdot (CH_2)_2 \cdot COO \right| \cdot CH_3 \quad \text{Acetylcholine}$$

Ionic Theory of Nerve Impulse Transmission. It is assumed that a molecular barrier to ionic diffusion exists around the protoplasmic cylinder of nerve fibres. This barrier, called the plasma membrane, is described as being possibly only two molecules in thickness and composed of lipoid and protein. This is surrounded by extra cellular interstitial fluid which in turn is circumscribed by the insulating myelin sheath, broken every millimeter or so by the nodes of Ranvier. This in turn is surrounded by the neurilemma.

In the resting stage, the plasma membrane provides a demarcation between a positive electrical potential on the outside and a negative potential on the inside (ix). These potentials are created by a high concentration of electro-positive sodium ions with a low concentration of electro-positive potassium ions on the outside, and the reverse on the inside with the addition of electro-negative amino-acid, the electro-negative chloride ions remaining more or less static. Following the initiation of an impulse by an outside influence, the plasma membrane becomes

permeable to sodium ions which pass into the cylinder of cytoplasm (by a mechanism not known), whilst potassium ions are static. This therefore reverses the potential for an excess of anions will exist on the inside (x). This change in potential passes along the nerve in a wave motion and is, of course, the nerve impulse. Potassium transmission takes place to the

(ix)	Resting period.	Outside fibre	+ive	K^+ Cl^- Na^{++}
		Inside fibre	−ive	K^{++} Cl^- Na^+ Amino-acid$^-$
(x)	Active period.	Outside fibre	−ive	K^+ Cl^- Na^+
		Inside fibre	+ive	K^+ Cl^- Na^{++} Amino-acid$^-$

outside neutralizing the potential difference and this is later followed by a complete reversal of ion migration and a return to the resting stage. At synapses and motor end-plates, acetylcholine is responsible for the changes in permeability of the plasma membrane, which is followed by the changes in potential.

Local anæsthetics in a way as yet unknown stabilize the ion distribution and prevent the creation of these differences in potential. It is possible that acetylcholine is responsible for the changes in permeability of the plasma membrane and that the local anæsthetics, by their structural similarity, compete for the enzymes by which acetylcholine causes these changes. Most of this is conjecture.

Uses and Application. The method of application and the uses of local anæsthetics are indivisible. They may be applied in several ways:

1. *Topical anæsthesia*, indicating the application of a local anæsthetic to a superficial external surface. This type of anæsthesia is useful for anæsthesia of the mucous membranes of the eye, nose, mouth, ear and perineal region. Topical anæsthesia of the skin is difficult unless abrasions or inflammatory areas exist. Some anæsthetics such as cocaine and amethocaine are very useful in this respect, and others such as procaine are relatively useless.

2. *Infiltration or field anæsthesia* in which a local anæsthetic is injected parenterally around the site of irritation or operation. Cocaine, procaine, and lignocaine, are examples of local anæsthetics suitable for field anæsthesia: the less soluble agents such as amethocaine, butacaine, and benzocaine, are unsuitable for this purpose. Concentrations should be lower than those intended for regional anæsthesia.

3. *Regional anæthesia*, which includes:

(a) Nerve blocking or conduction anæsthesia, in which local anæsthetic solution is injected around, or near and parallel to, a nerve trunk at a superficial point remote from the operation or injured site. By this means the whole region innervated by this nerve trunk is rendered insensitive and, if the trunk incorporates the regional motor fibres, immobile.

Examples of this are the blocking of the plantar and median nerves of the horse, sometimes used in the diagnosis of lameness: paravertebral nerve block in the cow is another type of regional nerve block in which the dorsal and ventral branches of the main spinal nerves are anæsthetized at their point of emergence from the vertebral foramina. The usual nerves that are blocked are the last dorsal (13th), and first three lumbar nerves. Once blocked, the whole flank is completely anæsthetized.

(b) *Epidural* (*spinal*) *nerve block*, by which anæsthetic is introduced into the neural canal but not below the meninges covering the cord. This means that the injection is made into the lower end of the vertebral canal where there is normally space available for the introduction of anæsthetic. Low (posterior), medium, and high (anterior), epidural anæsthesia can be obtained, depending on the volume of fluid used: 'low' anæsthesia is given by the smallest volume (5–15·0 ml. in the cow), as the anæsthetic tends to fill the caudal end of the space first; as the quantity is increased, the space is filled further and further forward giving medium, and with the greatest volume (up to 130·0 ml. for the cow), high, epidural anæsthesia. Low epidurals are useful for tail and perineal operations and for stopping straining in obstetrics. The animal remains standing. Solutions of 1–2·5 per cent. procaine hydrochloride are suitable for this purpose. High epidurals usually cause hind leg paralysis and the animals become cast: they are useful for abdominal operations, surgery of the hind legs and udder, drawing of the penis, and obstetrics. Unilateral epidural anæsthesia can be obtained by injecting the anæsthetic with the animal on its side (Wright, 1942). Epidural injection in cattle between the 1st and 2nd lumbar vertebræ has been developed under the term 'segmental epidural anæsthesia' for rumenotomy in cattle by Magda *et al.* (1952). Its use for Cæsarian section has been reported by Arthur (1956).

Great care must be observed when carrying out high epidural anæsthesia, for bilateral paralysis of the splanchnic nerves containing the vasomotor fibres will produce splanchnic area vasodilatation and an alarming and dangerous fall in blood pressure. These nerves originate at the level of the last seven or eight dorsal, and the first one or two lumbar nerves. This danger is avoided to a great extent by using 1 per cent. solutions only for anterior epidurals, but where it does occur, adrenaline intravenously and the use of cardiac and respiratory stimulants are indicated.

(c) *Intrathecal* (*spinal*) *injection*, which entails the withdrawal of cerebrospinal fluid from the subarachnoid space and its replacement with local anæsthetic, is a technique now rarely if ever used in veterinary anæsthesia.

4. *Intravenous injections* of local anæsthetics have been used for generalized analgesia, but there are few reports and the procedure has not yet been generally accepted.

Topically Applied Anæsthetics. The local anæsthetics can be divided fairly rigidly into those applied topically and those which may be applied

universally. The topically applied may again be divided into those causing anæsthesia by freezing and those which act by biochemical reaction.

Freezing Anæsthetics. There are two of these available: they are of occasional use for superficial and transient anæsthesia. They are carbon dioxide and ethyl chloride. Both are gases stored under pressure. When released, these gases evaporate rapidly drawing heat from the surface upon which they are sprayed; this causes an intense cooling and literally a freezing of the tissues, which results in a loss of sensation. Short duration superficial surgery can be carried out during the period of anæsthesia: this applies to the removal of warts, foreign bodies, the opening of abscesses, the removal of portions of broken claws, and similar operations.

In addition carbon dioxide snow, prepared by releasing the gas rapidly through a nozzle can be moulded and used as a 'pencil' for the removal of warts: repeat applications should only be applied after the inflammation caused by the preceeding application has subsided, and normal skin should always be protected by bland ointments.

Ethyl chloride may also be used as a gaseous general anæsthetic in cats and small animals of the laboratory type.

Biochemically Active Anæsthetics. Of the list given in group 2 of the general classification on p. 292 benzocaine, butacaine sulphate, butylaminobenzoate, chlorbutol, and orthocaine, are primarily intended for topical application although butyl aminobenzoate, for example, is also used combined with other local anæsthetics for parenteral injection. As a group, they are sparingly soluble in water and their action is prolonged when compared with that of the soluble compounds.

Amethocaine Hydrochloride, B.P.

Chemically, this anæsthetic is the hydrochloride of 2-dimethyl-aminoethyl para-butylaminobenzoate. It is a typical local anæsthetic—a white, crystalline, odourless powder with a slightly bitter taste followed by a slight numbness. The hydrochloride is very soluble in water, soluble in alcohol, but insoluble in other organic solvents. Amethocaine hydrochloride is unstable in neutral solutions, but in 0·001 per cent. hydrochloric acid will withstand temperatures up to 115°C.

Actions and Uses. Amethocaine hydrochloride may be used topically or parenterally. When applied topically its action is approximately ten times greater than cocaine, and when used parenterally it is similarly ten times more active than procaine. It has not been used as widely in the veterinary field as in human anæsthesia, and where it is used, it is mainly for surface anæsthesia. Topically, amethocaine has a similar action to cocaine but more prolonged, and 0·25–1 per cent. solutions are very effective in the eye, whilst 1 per cent. ointments are used on the skin. The effect on intact skin is not very great but, when applied to inflamed or

abraded surfaces, anæsthesia is good. Amethocaine is a useful anæsthetic for relieving the irritation caused by otitis in the dog and cat.

Where parenteral administration is intended, strengths of 0·05–0·25 per cent. may be used for infiltration, and for epidural injection, 0·5–1 per cent. In both cases the onset of anæsthesia is slower than with procaine, but more prolonged.

Toxicity. Amethocaine hydrochloride is approximately twelve times more toxic than procaine and though this is largely offset by the greater activity, procaine is still preferred for parenteral use.

Benzocaine, B.Vet.C.

Ethyl para-aminobenzoate is the chemical name for this white, odourless, crystalline powder with a slight bitter taste which is followed by numbing of local sensation. It is almost insoluble in water but soluble in alcohol, ether, and chloroform (1 in 8, 4 & 2 respectively), and to the extent of 2 per cent. in the fixed oils. Benzocaine acid salts such as benzocaine hydrochloride are irritant and of no clinical value. Solutions of benzocaine cannot be sterilized by heat. The base must be sterilized and the anæsthetic incorporated with aseptic techniques.

Actions and Uses. Benzocaine, being relatively insoluble in water and not very soluble in oil unless ether is incorporated, is not suitable for parenteral therapy, and when applied topically does not penetrate deeply. It is therefore indicated only for superficial anæsthesia applied to abraded surfaces and areas of irritation; it is of relatively little value on intact skin or mucous membranes. Though it has been recommended for oral administration in the treatment of emesis in the dog, it is not very effective and occasionally may cause further irritation, following reaction with the hydrochloric acid of the stomach to form the irritant hydrochloride. When applied externally, it is used in the form of 5–20 per cent. ointments, or dusting powders of similar strengths diluted with starch, zinc oxide, calamine, or talc. For oral administration the *dose* in the dog is 2–10 gr.

Toxicity is under one tenth of that of cocaine and is of little significance when used externally.

Butacaine Sulphate, B.Vet.C.

This sulphate of a para-aminobenzoic acid ester is a white, odourless, crystalline powder with a slightly bitter taste and a mild, transient anæsthesia of the mucous membranes. It is slowly but very soluble in water, very soluble in alcohol and acetone: insoluble in ether and almost so in chloroform. Butacaine sulphate solutions may be sterilized by boiling.

Actions and Uses. Butacaine sulphate effectively penetrates mucous membranes and has an action equal to that of cocaine. The onset of anæsthesia is more rapid than that with cocaine and the effect is more

prolonged. With these features, butacaine is particularly suitable for anæsthesia of the eye and does not cause drying, ischæmia, and necrosis of the cornea, all of which result from repeated use of cocaine. Solutions are almost non-irritant and single applications will give superficial corneal anæsthesia in one minute: further applications at 3 minute intervals will give surgical anæsthesia of the cornea and sclera but there is no effect on the iris and pupillary action is maintained.

Solutions of 2 per cent. butacaine sulphate are suitable for anæsthesia of all mucous membranes: it may also be used on the skin.

Toxicity. The toxicity of butacaine sulphate when applied externally lies between that of cocaine and procaine, but parenterally it is more toxic than cocaine and should therefore not be so administered.

Butyl Aminobenzoate, B.P., N.F.

This local anæsthetic is butyl para-aminobenzoate and therefore closely related to benzocaine. Its characteristics are very similar to those of benzocaine although it is slightly more soluble in organic solvents. Solutions for injection may be sterilized by steaming.

Actions and Uses. The action of butyl aminobenzoate is prolonged, injections in oil providing anæsthesia for periods of up to 24 hours. The compound can be used as a dusting powder either undiluted or diluted with talc, boric acid, zinc oxide, and similar diluents, but it must not be used in crystalline form for the crystals will cause mechanical irritation. A concentration of 1 per cent. is usual in ointments. Injections of butyl aminobenzoate alone are uncommon but combinations of 6 per cent. of the aminobenzoate with 5 per cent. benzyl alcohol, as a solvent and adjuvant, often with 1·5 per cent. procaine base, have been widely used for veterinary purposes. Dusting powders and ointments are useful and effective in the treatment of irritant skin lesions, wounds, and burns: solutions in oil have also been used for similar purposes, but these are probably of most value externally in allaying irritation in the ears of small animals. Parenteral injections have been used successfully for prolonged field anæsthesia and for epidural injections to control 'straining' following the return of uterine, vaginal, and rectal prolapses. A similar preparation, but with a base of polyethylene and propylene glycols, and containing procaine hydrochloride also, has been used to achieve epidural and field anæsthesia for periods of a week or more. Reports of tissue necrosis and neuritis have been reported following human therapy, though the damage has been attributed to the vehicle rather than the anæsthetic: this may be so, but it is also probable that the crystals precipitated in the tissues and slowly resorbed cause local irritation and necrosis.

Butamben picrate, N.N.R. 1951 is a combination of butyl aminobenzoate and picric acid. It has been produced commercially as Butesin Picrate. The yellow powder is soluble in water at 1 : 2000 and in oil at

1 : 100. The aqueous solution has anæsthetic effect when applied to the eye but it is most commonly used as a 1 per cent. ointment both for the treatment of burns, scalds, and pruritis of the skin, and also for ocular lesions. All tissues are stained yellow by the picrate.

Toxicity. Butyl aminobenzoate is not significantly toxic, but prolonged use in man has caused dermatitis; this may be severe with the picrate due to the irritant effect of the picric acid.

Chlorbutol, B.Vet.C.

Is most commonly used as a remedy for motion sickness in small animals, but besides its hypnotic central action, chlorbutol is also an effective local anæsthetic for topical application. It is occasionally used for this purpose at a 1–2 per cent. concentration in dusting powders for application to granulating wounds, for which purpose its antiseptic action is also useful. (A saturated solution—0·8 per cent. in water—is completely bacteriostatic and the pure substance has a phenol coefficient of 1·2.) When given orally, the local sedative action on the gastric mucosa is a useful adjunct to the central action: this action is made use of in the oral administration of drugs which tend to cause emesis, particularly anthelmintics. The combination with arecoline hydrobromide in the treatment of tapeworms in the dog is an example.

Orthocaine, B.Vet.C.

The chemical name is methyl, 3 amino, 4 hydroxybenzoate. It is a white, odourless, tasteless, crystalline powder which decomposes on boiling with water, especially alkaline water. Orthocaine is only slightly soluble in water, but is soluble in alcohol and ether to the extent of 1 in 7 and 1 in 50, respectively.

Actions and Uses. Orthocaine is not used very frequently. It may be substituted for benzocaine, as a dusting powder diluted or undiluted, and as ointments in strength of 5–20 per cent., but its action is weaker.

Toxicity. This is of little significance systemically, for its low solubility prevents absorption. Externally it may be responsible for severe irritation and sloughs.

Parenteral Local Anæsthetics

The local anæsthetics which can be classed as parenteral ones are cocaine, procaine, and lignocaine. Cocaine, though no longer recommended for parenteral use, was the first of the true local anæsthetics and was in use (by the late R. Hudson, inventor of the teat spiral) as recently as 1943, for field anæsthesia, in conjunction with morphine sulphate and chloral narcosis. Its efficiency is beyond doubt, but D.D.A. control and the lower toxicity of procaine and lignocaine, as well as other advantages, make it less preferable except for ophthalmic use. Procaine is entirely restricted

to parenteral use but lignocaine, the latest significant discovery, is valuable externally as well as internally.

Cocaine Hydrochloride, B.Vet.C.

Any preparation containing more than 0·1 per cent. of cocaine is subject to control under the Dangerous Drugs Act. *Any* preparation which is merely a dilution of cocaine is controlled in all proportions.

Although many of the oily applications contain the pure alkaloid, it is the hydrochloride which is most widely used. The alkaloid is prepared by extraction of a mixture of alkaloids from the dried leaves of shrubs of the *Erythroxylum* genus. The mixture of alkaloids is usually hydrolysed to ecgonine, from which the cocaine is synthesized. Cocaine hydrochloride is a typical alkaloidal salt: it is a white, crystalline compound with an intensely bitter taste, no odour and a solubility in water of 1 in 0·5, in alcohol and glycerin of 1 in 3, in chloroform of 1 in 20, but it is insoluble in fixed oils. It differs from most other alkaloids in causing temporary anæsthesia of the oral mucosa when tasted. Solutions and ointments cannot be sterilized by heat: vehicles must first be sterilized and the cocaine incorporated aseptically.

Actions. The *local* action of cocaine is one of anæsthesia, first of the nerve endings of touch and pain, and later of pressure. Still later there is a paralysis of motor fibres. Cocaine, by virtue of its antagonism of amine-oxidase, potentiates the action of locally produced adrenaline, which causes a constriction of local capillaries, slows the absorption, and prolongs the action of the cocaine. Anæsthesia takes about five minutes to take effect and lasts for half an hour or more depending on concentration and tissue vascularity. When anæsthesia passes off, overdilation of the capillaries occurs and post-operative bleeding should be anticipated.

When applied to the eye, absorption across the conjunctiva is fairly rapid and deep actions are soon apparent, for the adrenaline potentiation effect causes a dilatation of the pupil, although accommodation is normally unaffected. Intra-ocular pressure reacts irregularly and depends mainly on the degree of iris collapse, closure of the spaces of Fontana and restriction of the drainage. With anæsthesia, the blink reflex is lost and the cornea dries; with the drying arises the danger of conjunctivitis and ulceration. Prolonged treatment with cocaine causes a protoplasmic poisoning and aggravates the drying effect.

The *systemic* effects of cocaine are of little significance in veterinary medicine and surgery, for ocular anæsthesia is now almost its only use and even skin surface applications are rarely in quantities sufficient to cause toxic symptoms on absorption. The action is mainly one of stimulation of the C.N.S., circulatory system, and skeletal muscle. In small quantities mental and physical fatigue are decreased, the heart reacts more powerfully and this, in conjunction with vasoconstriction due to the adrenaline potentiating action, causes a rise in blood pressure. The general

clinical reaction is one of restlessness. Large doses cause convulsions followed by paralysis, coma, and death from respiratory paralysis and asphyxia.

Uses. Cocaine is now almost entirely used for ocular and mucous membrane anæsthesia, and to allay irritation of small wounds in dogs and cats. For surgical anæsthesia, 4–5 per cent. solutions or ophthalmic ointments are satisfactory, but, for repeated use, concentrations should not be greater than 1 per cent. because of the danger of protoplasmic toxicity, and of paralysis of the blink reflex which would result in drying and the adherence of dust.

If anæsthesia of intact skin is required, oily solutions of cocaine base are more easily absorbed and are more likely to give anæsthesia.

Oily eye drops (0·9 per cent.) with and without mercuric chloride are official, and also aqueous eye drops with (1 per cent.), and without (2 per cent.), homatropine (1 per cent.). The B.P.C. eye ointment is of 0·25 per cent. strength.

Toxicity. Cocaine is unsafe to use parenterally and large wounds or abraded surfaces should not be dressed with cocaine, for absorption is more rapid than detoxication and excretion, and toxic levels may be reached rapidly. Treatment is symptomatic. It should be remembered that rabbits are particularly susceptible to cocaine poisoning though ocular anæsthesia with cocaine is not precluded.

Lignocaine Hydrochloride, B.Vet.C.

This valuable local anæsthetic was developed and first used in Sweden. Details were published in 1946. Since then it has gained world-wide recognition in both the human and veterinary fields. It is supplanting procaine for routine veterinary local anæsthesia. Chemically, it is an alkyl amine derivative of meta-xylene (dimethyl benzene).

Lignocaine hydrochloride is a white crystalline powder with a slight but characteristic odour. It is soluble in water, alcohol and chloroform, but insoluble in ether, benzene, and oils. Solutions may be sterilized by heat.

Actions and Uses. Lignocaine is approximately twice as effective as procaine both in potency and area of diffusion, but it is also more toxic in concentrations greater than 0·5 per cent., being approximately 50 per cent. more toxic in 2 per cent. concentrations. The greater potency more than offsets this toxicity. The onset of anæsthesia is more rapid and the duration is more prolonged. Solutions are almost non-irritant. In a series of tests comparing the effects of lignocaine on cattle with those of procaine and other local anæsthetics, Link and Smith (1956) found lignocaine to have the most rapid onset and the best diffusion properties. Lignocaine hydrochloride 2 per cent. with adrenaline 1 : 100,000 was used: for

epidural anæsthesia, 1·25 ml. per cwt. (50·0 kg.) gave anæsthesia of the perineal region in as little as three minutes and a duration of 4·2 hours compared with 1·7 hours for procaine: for *paravertebral* anæsthesia, 7·0 ml. were infiltrated around each nerve; anæsthesia lasted for 4·3 hours and was complete, whilst procaine gave an average of 2 hours of less profound and incomplete anæsthesia with a longer period of induction: for *infiltration* anæsthesia the same solutions were used and though standardization was difficult, lignocaine gave good anæsthesia, rapid diffusion, a shorter latent period and a duration of 2·7 hours compared with procaine, which gave a duration of only 1·6 hours. *Topical* effects were not compared, but whereas procaine is relatively useless, lignocaine is suitable for ophthalmic purposes, anæsthesia of all mucous membranes, and is effective in pruritis and pain from abraded surfaces, wounds, and inflammatory lesions.

Toxicity. No exact figures of maximum doses are available, but if volumes of adrenalinated solutions similar to those used for procaine solutions are used no trouble need be anticipated (B.Vet.C., 1953). The equivalent of approximately 100 ml. of a 2 per cent. solution has been used in cattle without any signs of toxicity. On the basis of 2 per cent. procaine and cocaine solutions, the following volumes would be maximal for 2 per cent. lignocaine solutions given subcutaneously:

Horse and Cow:	400·0 ml.
Sheep and Pig:	80·0 ml.
Dog:	25·0–65·0 ml.
Cat:	8·5 ml.

In practice these volumes will rarely be required.

Availability. Lignocaine hydrochloride is available commercially as sterile injections of 0·5, 1, and 2 per cent. strengths, with adrenaline 1 : 80,000 or 1 : 100,000 in some cases. There are isotonic solutions of 4 per cent. and ointments of 5 per cent. concentrations for topical application, including ophthalmic use, and a 2 per cent. carboxymethylcellulose gel also for topical application.

Procaine Hydrochloride, B.Vet.C.

This was the first of the synthetic true local anæsthetics, and until the advent of lignocaine, was considered the best for routine veterinary use. It is still used very widely.

Chemically, procaine hydrochloride is frequently cited as the typical local anæsthetic of the p. aminobenzoic acid derivatives (see p. 293). It is a white crystalline odourless powder with a bitter taste and causes a slight numbing of the tongue. The hydrochloride is very soluble in water, less soluble in alcohol, slightly in chloroform, and insoluble in ether. Solutions may be sterilized by steaming at 100°C.

Actions and Uses. Procaine hydrochloride is an effective local anæsthetic which has a latent period of 5–10 minutes and a duration of about 1½ hours with a 2 per cent. solution containing adrenaline of 1 : 100,000. *Paravertebral* injections of the same solution in cattle will give anæsthesia for about two hours and *epidural* administration also gives anæsthesia for 2 hours. *Topically*, procaine is about sixteen times less active than cocaine and is considered unsuitable for this purpose.

Procaine is almost non-irritant to tissues; the hydrochloride is therefore used for *field anæsthesia* in strengths of 2 and 5 per cent., but for *regional anæsthesia* it is advisable to use the 5 per cent. concentration. *Epidural* injections of strengths from 1–5 per cent. are used, but where anterior or high epidural is intended 1 per cent. should be used so that disastrous falls in blood pressure may be largely avoided; for cows up to 1200 lbs. 12·0–18·0 ml. will give good epidural anæsthesia for about 2 hours without casting the animals (Roberts, 1950). Inclusion of adrenaline 1 : 50,000 to 1 : 100,000 will prolong anæsthesia to 2·4 hours but an increase in volume or concentration will cause animals to go down. If 2 per cent. strengths are used, posterior or low epidural *doses* will be: heifers: 10·0 ml.; medium sized cows: 12·0 ml.; large cows: 15·0 ml. (Wright's *Veterinary Anæsthesia* Edit. 4, 1957 p. 75, Baillière, Tindall and Cox.) With concentrations of 3–5 per cent. the maximum should be 10·0 ml. Anterior epidurals may require 50·0–130·0 ml. of a 1 per cent. solution.

Toxicity. Procaine is four times less toxic than cocaine when used alone, but with adrenaline it is as much as ten times less toxic. Maximal doses of solutions containing adrenaline are as quoted under lignocaine toxicity (*q.v.*) scaled up or down according to concentration. Symptoms are those of restlessness, excitement and convulsions followed by depression, coma, and death from respiratory paralysis. This is typical of most local anæsthetics. Treatment is symptomatic.

Detailed descriptions of the applications of these local anæsthetics in veterinary surgery may be found in Wright's *Veterinary Anæsthesia*, Editions 1–4, 1947–1957, Baillière, Tindall and Cox.

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CHAPTER 16

NERVOUS SYSTEM STIMULANTS
ANTAGONISTS OF DEPRESSANTS

THE drugs which stimulate the nervous system may be arbitrarily classified according to which part of the system they affect. Two groups result from this type of classification—1. Cerebral and Medullary Stimulants, and 2. Spinal cord stimulants. Division must be arbitrary, for the members of the first group will cause stimulation of the spinal cord if given in large enough doses, and *vice versa*.

The main therapeutic value of the cerebral and medullary stimulants is for counteraction of anæsthetic depression. Certain specific antagonists to nervous system depressants will be included in this chapter, for though some have little or no stimulant effect on the nervous system they all aim at returning the activity of the nervous system to normal.

Group 1 comprises:	Atropine The Xanthines—caffeine, theophylline, theobromine. Picrotoxin, leptazol, and niketha mide, known as analeptics, i.e. convulsants. Amphetamine and methylamphetamine. Camphor.
Group 2 comprises:	Strychnine.
Specific antagonists:	
Morphine antagonist:	Nalorphine.
Barbiturate antagonist:	β-ethyl-β-methylglutarimide (Megimide).
Curare antagonists:	Edrophonium, parasympathetic potentiators.

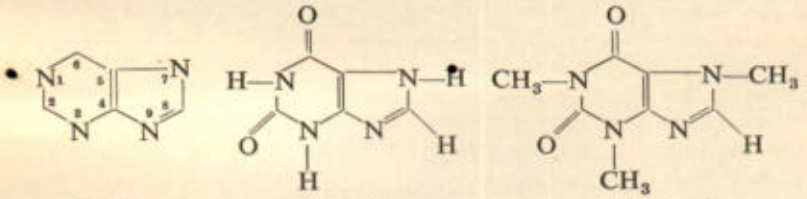
Cerebral and Medullary Stimulants

The action of the analeptics is almost specific to the medulla but the other members of the group cause cerebral as well as medullary stimulation.

Atropine has been referred to in detail in Chapter VII (*q.v.*). Although it is unlikely that atropine will be used for its *central* effects, these effects are of interest from a plant toxicology point of view since atropine is contained in Belladonna—deadly nightshade, Hyoscyamus—henbane, and Datura—thorn apple. In small doses the main result of atropine action on the C.N.S. is one of slight stimulation of respiration: in larger doses

stimulation of the cerebrum occurs causing restlessness and excitement; very large doses may cause convulsions which are followed by depression of both medulla and cerebral cortex; death occurs from respiratory paralysis. When poisoning with any of the plants mentioned occurs, this initial stimulation followed by depression must be remembered and hypnotic doses of chloral hydrate or pentobarbitone sodium may be used to control excitement for repeated periods of perhaps 4–6 hours, depending on the degree of excitement and the dose given. In the depression stage long acting stimulants such as amphetamine or methylamphetamine are required.

Xanthine Derivatives. These compounds consisting of caffeine, theobromine, and theophylline, are also referred to as 'the purine derivatives'. They are methylxanthines, and xanthine is dioxypurine so that both terms are correct though the reference to xanthine is more descriptive:



Purine Xanthine Caffeine

Caffeine is therefore 1 : 3 : 7; trimethylxanthine, theobromine is 3 : 7 dimethylxanthine; and theophylline is 1 : 3 dimethylxanthine. All three may be classified as alkaloids but their activity as bases is very slight, and theophylline forms water soluble compounds with alkalis. They are all white crystalline substances with varying solubilities: caffeine is soluble in water 1 : 50, in alcohol 1 : 75, and 1 : 6 in chloroform: theophylline is soluble in water 1 : 120, alcohol 1 : 80, and only slightly soluble in chloroform: theobromine is the least soluble and therefore the least useful of the three—water 1 : 1800, alcohol 1 : 2,400, and chloroform 1 : 6000.

Actions. The xanthine derivatives are readily and completely absorbed following oral or parenteral administration. Following distribution they have a number of actions which can be divided into central and peripheral effects. Caffeine is preferred for its powerful central stimulation, whereas the other two have more powerful peripheral actions: thus caffeine has the most potent effect on the brain and medulla and theobromine the least; on the circulatory system theophylline is the most powerful and caffeine the least, whilst as diuretics, theophylline is the most powerful but is short acting and theobromine, though less active a diuretic has less central stimulation side actions and can therefore be used in greater quantities than caffeine, thus obtaining a greater effect.

As a *Central Nervous System* stimulant caffeine in particular has powerful effects on the sensory and motor cortex, increasing mental and physical power and diminishing fatigue without causing depression later. The total amount of work done is increased without impairment of accuracy.

The medullary centres are moderately stimulated, the respiratory centre being most markedly affected. The vagus and vasomotor centres are stimulated but peripheral actions usually override these central effects.

In overdosage, the xanthines will produce restlessness, excitement, and convulsions. Increased respirations, vomiting and diarrhœa may also occur. Bromide, chloral hydrate, and morphine or pethidine, are recommended to restrain the nervous excitement: barbiturates are not very successful. Depression subsequent to the excitement does not occur.

Circulatory System effects are complex and vary according to dosage and the individual. In normal therapeutic doses the relaxant effect on smooth muscle causes vasodilatation which over-rides the central vasomotor stimulation, but a direct stimulant action on the heart causes an increase in rate and amplitude and a slightly raised blood pressure. In small doses the heart may be slowed by central vagus stimulation.

The effects on the *urinary system* have been described in the chapter concerned with this system.

Uses. Caffeine itself, as the citrate, and with sodium benzoate, is used as a respiratory and general nervous system stimulant. Occasionally it is combined with digitalis to give cardiac stimulation in the period between administration and the onset of stimulation by the digitalis. It is not of great value in barbiturate depression but may be useful in depression by other narcotics and sedatives. It is also combined with other diuretics.

Theobromine is rarely used, though one or two reports on its combinations with sodium acetate, calcium and sodium salicylate compounds, indicate its value as a diuretic when used intermittently in periods of 4–6 days duration. Oil of theobroma, which is solid at room temperature but liquid at body temperature, is occasionally used as a base for suppositories and pessaries.

Theophylline is rarely used on its own, being combined with mersalyl for its diuretic action, and with ethylene diamine to form aminophylline, which has been recommended for 'broken wind' in horses; with digitalis it has been used for congestion following cardiac decompensation in dogs (See U.S.D. 25th Edit. 1955, quoting Detweiler).

Dosage and Administration:

Caffeine, B.Vet.C.:	Horse and Cow:	15–60 gr. (1·0–4·0 G.)
	Sheep and Pig:	5–25 gr. (0·3–1·5 G.)
	Dog:	¾–4 gr. (50·0–250·0 mg.)

Caffeine and Sodium Benzoate, B.Vet.C.

The dosages are the same as for caffeine but this compound is usually administered by subcutaneous injection. Cats may be given about one third the doses for the dog.

Caffeine Citrate, B.Vet.C.

All species may be given twice the doses of caffeine and sodium benzoate, administered orally.

The relatively larger doses of the last two compounds are related to the caffeine content which is only 50 per cent. of the total weight (caffeine—M.W. 194·2; caffeine citrate M.W. 386·3; caffeine and sodium benzoate consists of approximately equal parts caffeine and sodium benzoate).

Theobromine—Calcium salicylate:	Dog:	5–15 gr. (0·3–1·0 G.)
Sodium acetate and salicylate:	Horse and Cow:	120–240 gr. (8·0–15·0 G.)
	Dog:	5–15 gr. (0·3–1·0 G.)
Aminophylline:	Horse:	30–75 gr. (2·0–5·0 G.) given in food or bolus three times daily for 2–3 weeks.
	Dog:	¾–1½ gr. (50·0–100·0 mg.) three or four times daily orally, intramuscularly or intravenously.

The Analeptics. This term is applied to compounds which if administered to normal animals in therapeutic doses will cause convulsions. This property is used to stimulate and revive patients which are overdepressed by central nervous system depressants, but particularly by anæsthetics. True analeptics have very few actions other than their central nervous system stimulant effects.

The three main analeptics are Leptazol, B.Vet.C.; Nikethamide, B.Vet.C.; and Picrotoxin, B.Vet.C. Although amphetamine and its methyl derivative are used as antisedative drugs they are not so specifically stimulating to the medullary centres as the true analeptics.

Leptazol, B.Vet.C.

Also known as Pentylenetetrazole, U.S.P., the compound is a white crystalline powder with a bitter taste; it is soluble in water, alcohol, ether, and chloroform.

Actions. Leptazol is a central nervous system stimulant. In normal animals its use causes stimulation of the higher centres and results in convulsions. Normal doses affect the medullary centres, but where these centres are depressed, as in narcosis or anæsthesia, the medullary effect

is intensified. The respiratory, vagal, and vasomotor, centres are stimulated indiscriminately so that parasympathetic and sympathetic systems are stimulated equally. Apart from increased rate and depth of respiration, there is an increase in the blood supply to the coronary arteries following vasomotor stimulation, and the heart, and hence the circulation in general, benefit accordingly.

Leptazol is more rapidly absorbed than picrotoxin and has a shorter latent period. It is considered safer to use than the other analeptics.

Uses. Leptazol is mainly used in overdepression due to any anæsthetic or narcotic, but has been reported of most use in barbiturate depression. For this purpose it may be given intravenously until muscle twitchings appear, and repeated every 15 minutes until recovery is assured. In less acute emergencies intramuscular or subcutaneous injections every fifteen minutes should provide adequate stimulation.

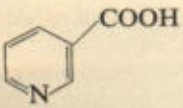
Dosage:

Horse and Cow:	0·5–1·0 G.
Dog:	50·0–100·0 mg.
Cat:	25·0–50·0 mg.

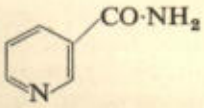
The official injection contains 10 per cent. w/v Leptazol.

Nikethamide, B.Vet.C.

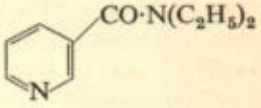
This relative of nicotinic acid and nicotinamide is a yellowish or colourless oily liquid or crystalline solid with a faintly bitter taste. It is miscible with water and is soluble in organic solvents.



Nicotinic acid



Nicotinamide



Nikethamide

Action. Nikethamide is mainly a respiratory stimulant causing an increase in respiratory rate and depth by stimulation of the medullary centres and by action on the chemoreceptors of the carotid body. Some peripheral vasoconstriction is caused but the rise in blood pressure which usually follows is sometimes preceded by a sudden but transient fall. It is not such a potent analeptic as picrotoxin or leptazol.

Uses. Nikethamide is useful in morphine and chloral hydrate depression but is not so effective as the other two in barbiturate depression.

Dosage:

Horse and Cow:	10·0–25·0 ml.
Dog:	1·0–3·0 ml.
Cat:	1·0–2·0 ml.

The official injection is a 25 per cent. w/v solution in water which may be given orally or by any parenteral route. Doses must be repeated every five to ten minutes.

Picrotoxin, B.Vet.C.

Whereas the other two analeptics are synthetic, picrotoxin is the active principle prepared from the seeds of a shrub grown in India and the Malayan Archipelago. It is a white crystalline substance slightly soluble in water, soluble in alcohol and benzene but only slightly in other organic solvents.

Actions. Picrotoxin is a powerful stimulant of the whole central nervous system. The motor cortex, midbrain, and medullary centres, are strongly stimulated by therapeutic doses: larger doses also stimulate the spinal cord. These effects cause a marked increase in respiratory rate and depth, and a rise in blood pressure is also evident. Picrotoxin has been reported of no value in morphine poisoning, but is undoubtedly the most reliable stimulant for barbiturate poisoning: it is not, however, a specific barbiturate antagonist, though this belief has been widely held.

Picrotoxin is slow acting, taking 5–8 minutes to show results following intravenous administration, and 10–30 minutes after oral administration.

Leptazol is often preferred in barbiturate depression because of its more rapid action and the susceptibility of cats to picrotoxin in overdosage. The two may be used in conjunction during anæsthetic collapse.

Dosage:

Horse and Cow:	60·0 mg.
Dog:	1·5–6·0 mg.

If pentobarbitone is the anæsthetic involved, dosage should be calculated at the rate of 2·0–3·0 mg. picrotoxin for each grain (60·0 mg.) of pentobarbitone. If thiopentone is responsible for the depression the ratio is up to 2·0 mg. per grain (60·0 mg.) of thiobarbiturate.

Intravenous or intramuscular doses may be repeated approximately every 15 minutes until recovery is assured.

The usual strength of injections is 3·0 mg. per ml.

With all analeptics, their injection is not intended to take the place of artificial respiration, circulatory stimulants, and the freeing of the airways, etc.

Any overdose of analeptics may be counteracted by a thiobarbiturate or inhalant anæsthetic. Muscle relaxants will also counteract the peripheral effect of the convulsants.

Amphetamine, B.P. and Methylamphetamine, B.P.C.

The basic compounds are mobile liquids with the odour of geranium leaves. The methyl compound, however, is used most commonly as the

hydrochloride and amphetamine as the sulphate or mono- and dibasic-phosphates. Both exist in dextro- and lævo-rotatory forms and are available as racemic mixtures. These salts are water soluble white crystalline substances with a bitter taste but no odour.

Action. Both compounds have powerful vasopressor activity and are classified as sympathomimetic amines which stimulate all structures having an adrenergic nerve supply. They are, additionally, powerful C.N.S. stimulants and, because of strong medullary stimulation, are used as analeptics. The respiratory and vasomotor centres are strongly stimulated and also the cerebral cortex. Clinically, the central and peripheral effects are indicated by a gradual but powerful and sustained rise in blood pressure following myocardial stimulation and peripheral vasoconstriction, increased mental activity, and improved respiration. These effects appear within 2 minutes of parenteral injections of methylamphetamine, and within 30 minutes of oral dosage, but amphetamine salts are slower in taking effect. Both compounds maintain their effects for up to nine hours or more.

Methyl amphetamine is more powerful than amphetamine but the '*l*' form of the methyl compound has a more powerful pressor action than the '*δ*' form, whereas the dextro- form of amphetamine has a more powerful central effect than the '*l*' form. In both cases the racemic mixtures have intermediate potency. Both compounds have a potentiating effect on mental and physical capacity and have been used for this purpose in man, but depression follows their use for this purpose if dosing is protracted. A further action is that of diminishing hunger, doses of amphetamine (*δ* isomer) of 0·5–2·0 mg. subcutaneously have suppressed feeding in fasting dogs for at least one hour (U.S.D. 25th Edit. 1955, p.1940). This property has been used for slimming in humans and has been applied in the treatment of obesity in dogs.

Uses. The amphetamines are mainly used as analeptics, especially in cases of shock with respiratory and circulatory collapse or near collapse. They cause a lightening of anæsthetic depression, with a stimulation of rate and depth of respiration and a rise in blood pressure up to, and possibly beyond, the pre-hypotensive level. With this raised and sustained blood pressure there is an increased danger of post-operative hæmorrhage, and cases where the amphetamines have been used should be closely watched for signs of bleeding during the succeeding 12 hours.

Toxicity. Toxic symptoms are rarely seen but consist of excitement, restlessness, wakefulness, and possibly convulsions. Short acting barbiturates will counteract these effects.

Dosage. Amphetamine, as the dextro-isomer, is mainly used orally in man and the methyl compound for either oral or parenteral administration.

Amphetamine:	Horse and Cow:	100·0–300·0 mg. subcutaneously.
	Dog:	0·5–2·0 mg. per lb. (1·1–4·4 mg./kg.) parenterally.

Oral doses in man rarely exceed 5·0 mg. twice daily.

Methylamphetamine may be given in approximately ¾ of the above doses, on the basis of human dosage, but clinical reports are not available to corroborate this estimate.

For counteracting anæsthetic overdosage single parenteral doses, either by slow intravenous or by intramuscular injection, are usually sufficient, but, if the initial dose does not lighten the depression sufficiently within 15–20 minutes, small supplementary injections may be given.

Injections of amphetamine sulphate usually contain 10·0 mg. per ml., and tablets 5·0 mg. Methylamphetamine injections contain 20·0 mg. per ml. (B.P.C.), and the tablets 5·0 mg. (B.P.C.).

Camphor, B.Vet.C.

Initially obtained from a tree native to Japan and China, the camphor which is used now is mainly synthetic. The natural form is dextrorotatory whereas the synthetic form is a racemic mixture. The substance is white and crystalline, with a powerful and characteristic odour and taste. The compound is relatively volatile and is purified by sublimation: it is classified, along with menthol and similar compounds, as a stearoptene. Like all stearoptenes, camphor is only slightly soluble in water but freely soluble in organic solvents.

Actions. Externally, camphor is irritant but also has a slight analgesic action. It is used in counter-irritant liniments. It is also used as an inhalant for liquefying and loosening bronchial and nasal secretions, either by volatilization from the surface of steaming water, or occasionally by autovaporization following the rubbing of 'camphorated oil' on the chest—this is a greasy unpleasant method of application and should be avoided.

When given orally, camphor acts locally and reflexly. Its local irritant action has a carminative and antispasmodic effect on the stomach and intestines. This same irritant action causes reflex increase and liquefaction of bronchial secretions and, it has been suggested, reflex cardiac and respiratory improvement, but this is unproved and contested. Following intramuscular administration, local irritation occurs and it has been suggested that this may cause reflex heart stimulation. It is now generally considered that camphor has no respiratory or circulatory stimulant action.

Uses. The most frequent uses of camphor are those of counter-irritation in the form of liniments (Liniment of Camphorated Ammonia, B.Vet.C.–see Ammonia), and as an expectorant in cough mixtures, which also

often contain paregoric—Camphorated Tincture of Opium, B.Vet.C. (See Opium).

Its analeptic use is somewhat empirical but solutions of camphor in oil, sometimes along with ether (Curschmans solution—camphor 20 per cent., ether 30 per cent., in sterile olive oil), are still commonly used for their stimulant effects in both large and small animals.

Following rapid absorption from mucous membranes or injection sites, camphor is quickly oxidized to a camphorol and excreted by the urinary system combined with glycuronic acid.

Dosage. Camphor, B.Vet.C.
By intramuscular injection:

Horse and Cow:	15–40 gr. (1·0–2·5 G.)
Dog	1–2 gr. (60·0–120·0 mg.)

Orally:

Horse and Cow:	60–240 gr. (4·0–15·0 G.)
Sheep and Pig:	25–45 gr. (1·5–3·0 G.)
Dog:	1½–10 gr. (0·1–0·6 G.)
Cat:	1–3 gr. (60·0–200·0 mg.)

Liniment of Camphor, B.Vet.C. contains 20 per cent. camphor in arachis oil, but olive or cottonseed oils are also used. Doses may be related to those of camphor.

Spinal Cord Stimulants

Although strychnine and the related alkaloid brucine will stimulate most areas of the brain, their main action is on the spinal cord.

Strychnine, B.Vet.C.

This alkaloid with a complex ring structure is derived from the seeds of a tree, *Strychnos nux vomica*, native to India, Malaya, Indo-China, and Northern Australia, but also from Ignatus beans, the seeds of a climbing shrub native to Indo-China and the Philippines. It is therefore available in the form of the powdered seeds—Prepared Nux Vomica, B.Vet.C., which is a fine light fawn powder—and also as the liquid and dry extracts, and the tincture: the pure alkaloid is usually administered as the hydrochloride or the sulphate, which are typical alkaloidal salts with a bitter taste and about a 2 per cent. water solubility.

Actions. In spite of the use of nux vomica in Europe from the fifteenth or sixteenth centuries and the isolation of strychnine in 1818 (Pelletier and Cavantou), the pharmacological action of strychnine is still imperfectly understood.

Following oral or parenteral administration, strychnine is quickly absorbed and distributed to the tissues in the plasma and blood cells. No specific localization occurs in the nervous system.

After absorption, the main effect of strychnine is on the nervous system. The cerebral cortex may be slightly stimulated by small doses, but the medullary centres are only appreciably affected by near convulsive doses, and the use of strychnine as an analeptic in anæsthetic medullary depression is not recommended.

On the spinal cord, the accepted theory refers to an increase in excitability of the spinal reflexes, resulting in exaggerated muscular responses following slight sensory stimulation. This is evident clinically, but the pharmacological reasons are not clear: there is a definite increase in electrical activity of the nervous tissue with a lowering of the excitation threshold of nerve cells and a slowing of the development of a refractory period. Inhibitory reflexes are eliminated, and 'spreading' of the stimulus up and down the cord causes multiple responses to the stimulation of single reflex arcs if large doses are given. These actions are thought to be due to inhibition of cholinesterase, which results in prolonged acetylcholine activity.

Excretion is via the urine and the majority of a single dose is excreted in 48–72 hours. Should twice daily administration of large doses be given, it can be seen that a *cumulative* effect will result. This is particularly evident in dogs, in which species near maximum doses must be given with care.

Uses. In therapeutic doses, strychnine will act as a general nerve tonic causing improved reflexes and a general speed up in the nervous response. Strychnine is therefore used as a convalescent tonic in horses, cattle, and dogs, Solution of Strychnine Hydrochloride, B.Vet.C. being given as a subcutaneous injection in large animals, and Easton's Syrup (Syrup of Ferrous Phosphate with Quinine and Strychnine, B.Vet.C.) or similar formulæ in tablet or liquid form are given to dogs.

Strychnine in the form of Nux Vomica was at one time used as a treatment for colic (Coulton–Reekes method), but gastro-intestinal stimulation by strychnine is slight and the use of these heroic methods is unjustified. Strychnines bitter taste does, however, improve appetite and digestion when used as a drench, for it then causes reflex salivary and gastric secretion—see Sialagogues.

Strychnine sulphate has been, and still is, used for euthanasia of dogs. This practice is no less reprehensible than prussic acid administration, for death is due to paralysis of the respiratory muscles and asphyxia. Consciousness is unaffected and the muscular paralysis is such that great pain is caused, although the animal is unable to indicate the severity of it or indeed able to show that it exists at all.

Toxicity. The dog is the species which has been most subject to poisoning, because, in addition to the species susceptibility which reputedly exists, the use of strychnine as a rodent and fox bait poison means that the dog may pick up the poison by scavenging. In Great Britain rat poisons no longer contain strychnine but occasional cases of

strychnine poisoning are still seen when hounds and farm dogs gain access to poisoned fox bait. *Symptoms* are unmistakable, consisting mainly of tonic spasms similar to those of tetanus in which the legs and tail are rigidly extended and the head drawn up and back. These spasms increase in severity until the death occurs from asphyxia during a spasm. Also unmistakable is the association of these spasms with any external stimulation, no matter how slight—sudden movements within the animal's sight, or slight noises, are quite sufficient. These symptoms are due to augmented reflexes, loss of the normal inhibitory mechanisms, and indiscriminate tonic contraction of all skeletal muscle: the rigid extension of limbs and appendages is due to the greater strength of extensor muscles which overides the contraction of the flexors. Great pain results from this indiscriminate muscular contraction. Consciousness is unaffected until near the end, when anoxia due to respiratory paralysis during spasms causes cerebral depression. *Treatment* consists of the administration of local emetics only if convulsions have not commenced, followed by the induction of narcosis or anæsthesia, preferably with non-volatile short or medium duration anæsthetics. Pentobarbitone sodium is most suitable for all small species, whereas chloral hydrate would be suitable for large animals, both given intravenously. Dosage should be determined by effect and repeated as soon as muscle twitchings reappear. It will be found in dogs that from three to five times the normal doses are required to achieve anæsthesia, i.e. 3/5–1 gr. (40·0–65·0 mg.) per lb. body weight, or 88·0–143·0 mg. per kg. body weight.

Dosage. The doses of nux vomica powder and tincture have been detailed in the section on Bitters, p. 63.

Nux Vomica.

Dry Extract—Horse and Cow:		5–25 gr. (0·3–1·5 G.)
	Sheep:	1½–5 gr. (0·1–0·3 G.)
	Pig	½–2½ gr. (30·0–150·0 mg.)
	Dog:	1/20–1/3 gr. (3·0–20·0 mg.)

This extract contains 5 per cent. strychnine alkaloid.

The Liquid Extract contains 1·5 per cent. strychnine alkaloid and the doses are therefore approximately three times those of the dry extract, but represented in fluid measures.

Strychnine Salts. Oral or subcutaneous administration.
(Hydrochloride, sulphate, nitrate, and phosphate.)

Horse and Cow:	½–1 gr. (15·0–60·0 mg.)
Sheep:	1/12–¼ gr. (5·0–15·0 mg.)
Pig:	1/30–⅛ gr. (2·0–8·0 mg.)
Dog:	1/200–1/60 gr. (0·3–1·0 mg.)
Cat:	1/600–1/120 (0·1–0·5 mg.)

Solution of strychnine hydrochloride, B.Vet.C. contains 1 per cent. w/v of the hydrochloride—about 1/110th gr. per minim (10·0 mg per ml.)

Easton's Syrup contains 1/360 gr. of strychnine hydrochloride in 10 minims (0·3 mg. per ml.). Doses can be determined by reference to those of strychnine hydrochloride, for the alkaloid content of these compounds determines their dosage.

Morphine Antagonist

In the past the analeptics, caffeine, and strychnine, have all been used in the treatment of morphine overdosage, but with doubtful effect. The discovery of N-allyl morphine has revolutionized the antagonism of the effects of morphine and its relatives.

Nalorphine Hydrobromide, B.P.

This compound is chemically related to morphine having a chemical name of N. allylnormorphine hydrobromide. The hydrochloride is also available and is similar in its details. The compounds are white crystalline powders which darken on exposure to air and light and which are soluble in water but less soluble in alcohol and other organic solvents.

Actions. In spite of, or because of, its relationship to morphine, nalorphine hydrobromide has little or no analgesic or narcotic action, and when administered to patients depressed with morphine or its analgesic and narcotic relatives, nalorphine causes rapid revival. This is not an analeptic effect, for the substance has no convulsant action on normal individuals, nor does it assist in the revival of individuals depressed by barbiturates, chloral hydrate, or the volatile anæsthetics. Nalorphine is thought to act by competitive displacement of morphine and other compounds from the enzyme-coenzyme systems which they block. The effect is thought to be related to the greater affinity which nalorphine has for cholinesterase.

Uses. Nalorphine became prominent as an antagonist to morphine, etc. for veterinary use in Great Britain with the introduction of the narcotic analgesic thiambutene hydrochloride. It has been used extensively in dogs with success. Administration to animals narcotized with thiambutene causes a dramatic recovery in about one minute following intravenous injection, whilst recovery takes up to 20 minutes following subcutaneous administration. In some cases animals relapse into a state of sedation, or occasionally narcosis, but others will show no tendency to relapse. Reports are not available on its use in morphine overdosage but its use is indicated for these cases as well as for overdosage with closer relatives of morphine, such as codeine and diamorphine.

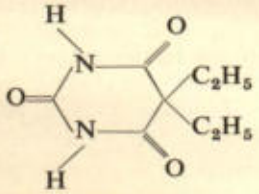
Toxicity in dogs is not reported but overdosage may cause nausea and sedation. The margin of safety is very wide.

Dosage. Dogs: 20·0 mg. by intravenous or subcutaneous injection. Nalorphine hydrobromide is available in Great Britain in 5·0 ml. vials with 20·0 mg. per ml. The U.S.P. injection contains 5·0 mg. per ml.

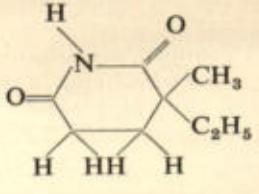
Barbiturate Antagonist

Bemegride, β-ethyl-β-methylglutarimide

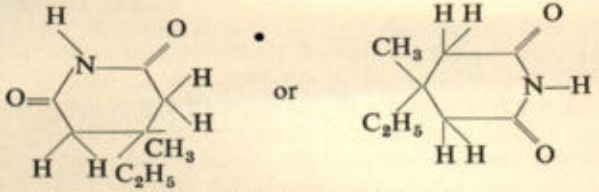
This compound, known also as methetherimide and commercially as Megimide or Mikedimide, is superficially related in structure to the barbiturates.



Barbitone (i)
(Diethyl barbituric acid)



Ethyl methylglutarimide (ii)
(α configuration)



Ethyl methylglutarimide (iii)
(β configuration)

This shows that the main difference consists of the substitution of $(CH_2)_2$ for CO·NH in the barbiturate nucleus. *Glutethimide*, which consists of a phenyl group substituted for the methyl group in the α configuration (ii) above, is related to phenobarbitone in the same way and is actually a sedative and hypnotic drug.

The sodium salt of this glutarimide alkyl derivative is a white crystalline compound which is soluble in water.

Actions and Uses. The pharmacological action of ethyl methylglutarimide is unknown, but it is possible that it acts with barbiturates in a similar manner to that of nalorphine with morphine. The salt, when injected intravenously into individuals anæsthetized with a barbiturate, lightens the depression immediately: in cats it does no more than this, but in dogs, calves, adult cattle, and sheep, an immediate return to consciousness occurs (Shaw *et al.*, 1954, Turner *et al.*, 1956, Jennings, 1958; Sanford, 1958; Toosey, 1958). McFarlane *et al.* (1957) have reported favourably on its use in dogs and cats, and Schwartz (1957) has used the compound in the pig. Hall (1957) reports unfavourably in preliminary work in the dog, and it is obvious that further work is required for a true assessment of its value.

One useful feature reported is that, though 'total sleeping time is not reduced' (McFarlane et al., *loc. cit.*), the animals (dogs and cats) continue in a state of lightening hypnosis, and the stage of narcotic excitement, so dangerous with pentobarbitone anæsthesia, does not occur.

The drug would appear to be indicated mainly as a barbiturate antagonist following overdosage, but additionally can be used to terminate normal barbiturate anæsthesia, especially in poor risk patients.

Toxicity is not reported but is similar to analeptics—shown by muscle twitching with convulsions in severe overdosage—these are controlled by barbiturates. (Recent personal experience indicates that in adult cattle overdosage must be considerable before toxic symptoms are shown—Toosey, 1959).

Dosage. Ethyl methylglutarimide sodium is given as a 2·5 per cent. w/v solution at the rate of 0·2 ml. per lb. (0·44 ml./kg.) by slow intravenous injection in small animals. This is useful in terminating normal anæsthesia but in barbiturate overdosage the doses may be increased up to 0·8 ml. per lb. (1·66 ml./kg.). Up to 5·0 mg. per lb. body weight may be given as a 10% solution in cattle; for the termination of anæsthesia it is are best given rapidly, for this avoids any narcotic excitement (Toosey, 1959).

Muscle Relaxant Antagonists

Of the relaxants used in veterinary surgery, curare, tubocurarine and gallamine triethiodide may be reversed by anticholinesterase drugs such as physostigmine and especially neostigmine, but a substance, related to the quaternary ammonium group of relaxants, *Edrophonium Chloride*, N.N.R., is a specific antagonist. Suxamethonium and suxethonium are potentiated by these antagonists and overdosage cannot be countered by such means.

Edrophonium Chloride, N.N.R.

Dimethylethyl (3-hydroxyphenyl) ammonium chloride is a white, odourless, crystalline powder, readily soluble in water and alcohol, but almost insoluble in other organic solvents.

Actions and Uses. Edrophonium chloride is a competitive antagonist for curariform muscle relaxants which act by preventing acetylcholine depolarizing the motor end-plate. It displaces the relaxants and allows the acetylcholine to resume its normal function. It may therefore be used to terminate the action of a relaxant at the end of an operation, or to eliminate the effects of overdosage. Edrophonium chloride has fewer side actions, but is less persistent than neostigmine.

It should be remembered that circulatory collapse occasioned by overdosage with curariform relaxants is not reversed by edrophonium chloride and must be treated separately.

Toxicity. In excessive doses, edrophonium chloride may itself cause curare-like paralysis, but normally some indication, such as muscle twitching, as well as salivation and other signs of parasympathetic stimulation, should indicate impending overdosage.

Dosage. No veterinary dosage is available. Human dosage is 5·0–10·0 mg. initially by intravenous injection, followed by further injections according to response up to a maximum of 30·0 mg. (±10·0 mg.). Maximum effect is exerted in about 5 minutes and is then quickly dissipated, so that care must be taken, when treating overdosage of relaxants, that the animal does not relapse into its former state. It should also be re-emphasized that edrophonium chloride is not a substitute for artificial respiration and oxygen.

Contra-indications. Edrophonium should not be used as an antagonist to succinylcholine derivatives (suxamethonium), for these relaxants are potentiated and not antagonized by it.

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CHAPTER 17

THE URINARY SYSTEM

THE urinary system provides the most important route by which the body can excrete substances absorbed in excess of current requirements, substances no longer required by the body because of changed circumstances, the products of tissue metabolism that are not required, and any substance for which the body can find no use. These are all filtered out by a complex selective system in the kidney which is influenced by a number of factors. The blood and tissue concentrations of various organic and inorganic compounds are established for a given set of conditions; if these conditions change or if the compounds increase in quantity, the excretory mechanism reacts to eliminate any substance circulating in the blood in excess of requirements. This statement must be qualified, for substances which are essential for continued existence, such as glucose, must reach a very high level in the blood before a normal kidney will eliminate any, whilst others of even more importance, such as proteins, are normally not excreted. The level established for any given set of conditions is known as 'the renal threshold'. An example of such a threshold is that of potassium, with a blood level in a cow of approximately 20·0 mg. per 100·0 ml. of serum (20·0 mg. per cent.). A rigid control of the potassium ion concentration in the blood is essential unless the animal is to suffer from repeated cardiac embarrassment. These thresholds are influenced by a number of hormones, amongst which are an antidiuretic fraction of the posterior pituitary hormone and several adrenal cortex hormones, especially desoxycorticosterone and aldosterone. The hormones would appear to affect resorption rather than initial glomerular filtration, which is influenced more by blood pressure and the volume of blood circulating through the kidney in a given period.

If the kidney function is disturbed either by pathological tissue or hormonal changes, the whole metabolism of the body is jeopardized, and therefore the drugs by which kidney functions can be influenced are of considerable importance. They are grouped into:

(1) Diuretics,
(2) Acidifiers,
(3) Alkalizers,
(4) Antiseptics, and
(5) Sedatives.

Diuretics

These are substances which increase the volume of urine excreted in a given period. By increasing the volume of urine output bacterial infections can be controlled, first by dilution, and secondly by a mechanical 'flushing' whereby bacteria and debris are removed from the kidney and the urinary tract in general.

Where certain types of nephritis (inflammation of the kidney) exist it is desirable to increase the fluid output of the kidney tissue so that metabolites can be excreted, thus preventing a build up of these substances to toxic proportions in the blood and tissues. Diuretics are available which can be used for this purpose.

Diuretics can also be used to reduce the volume of ascitic fluid which accumulates in the body cavities and tissues of animals suffering from cardiac insufficiency.

Fluid excretion in large quantities is a means by which heat generated in febrile conditions can be effectively and safely lost. This is important to remember in such species as the dog which cannot dissipate excessive heat by sweating; heat is lost by fluid excretion far more rapidly than it can be lost via the lungs.

Diuretics can be divided into:

(1) Mechanical,
(2) Saline,
(3) Irritant, and
(4) Cardiovascular diuretics.

In addition, there are a number of compounds which can influence urine output, but this effect is secondary to their main action and use. This miscellaneous group includes cyanides, thyroid extract, synthetic and natural sex hormones, and other steroid compounds.

Mechanical Diuretics. These diuretics act simply by increasing the blood volume and consequently, for a short period, they dilute the plasma, thus lowering viscosity. The normal animal system promptly reacts to excrete the excess fluid, mainly by diuresis. According to Verney (1947), water output is controlled by the antidiuretic hormone of the posterior pituitary gland influenced by nervous impulses from the supra-optic nucleus which in turn reacts to stimulation of 'osmo-receptors'. The osmo-receptors are sensitive to changes in the water content of the blood.

It follows that the injection or oral administration of water and isotonic solutions of saline, with or without dextrose, will result in this mechanism coming into play to return the blood volume and viscosity to normal.

Water so excreted will contain all the normal urine constituents and should the electrolyte content of the body be low, further depletion occurs of sodium, potassium, chloride, and bicarbonate radicles. Normal saline is therefore the mechanical diuretic of choice although it is rarely administered for this purpose.

Saline Diuretics. The action of mechanical diuretics is not very powerful but, by the addition of substances which are not normally required in large quantities by the body and which exert strong osmotic pressures when in solution, this diuretic action can be reinforced.

The substances most frequently used for this purpose are salts of sodium and potassium, but those of ammonium, calcium, and lithium are also used. These salts give the group its name, but other substances such as dextrose and urea will also exert a similar action.

Of the salts which can be used, the potassium ones are of most value, for the renal threshold of the potassium ion is relatively low (potassium extracellular concentration is, in most animals, 15–20 mg. per 100 ml. as against 316–340 mg. per 100 ml. for sodium (man)). Of these potassium salts the nitrate is very widely used in cattle practice and to a lesser extent in other farm animals. The acetate and citrate are used as diuretics in dogs.

Potassium Nitrate, B.Vet.C.

This is a white crystalline, odourless solid with a saline taste. It is very soluble in water and when dissolved with ammonium chloride in a ratio of one part of each in sixteen parts of water it gives a refrigerating solution.

Actions and Uses. Potassium nitrate is rapidly absorbed from the intestines and ionizes in the blood. The potassium ion is excreted, mainly via the kidney, as the bicarbonate and takes water with it. The nitrate usually combines with sodium and is excreted partly as the potassium and partly as the sodium salt, some of which may be converted within the tubule to ammonium nitrate. The sodium ion can then be reabsorbed in order to conserve this essential substance. In excess, the nitrate is irritant and the preparation is contra-indicated where nephritis is present. The urine is strongly alkalized.

Potassium nitrate is widely used in cattle practice as a diuretic and febrifuge. It was frequently used compounded with ammonium carbonate and acetanilide, but this type of drench is not popular since the advent of sulphonamides and antibiotics. The salt is not commonly used in other species, less irritant organic acid radicles being preferred to the nitrate.

Dosage and Administration:

Horse and Cow:	30–180 gr. (2·0–12·0 G.)
Sheep, Pig and Goat:	15–30 gr. (1·0–2·0 G.)

The drug is normally administered to cattle in twice daily 60 gr. (4·0 G.) doses as a drench, sometimes combined with 4 oz. (120·0 G.) magnesium sulphate and ½ oz. (15·0 G.) ammonium carbonate.

Potassium citrate and *acetate* are used in the dog when saline diuretics are required; both ionize to give potassium and organic acid radicles. The potassium ion is excreted as the bicarbonate and takes with it water of solution. The citrate and acetate radicles are partly excreted unchanged while the greater part is metabolized.

The acetate is deliquescent and the relatively stable citrate is a more practicable compound for general use. The citrate is very widely used in human medicine but is not very popular in veterinary practice.

Of the *sodium* salts, the chloride administered orally in small doses will have a diuretic and febrifuge (i.e. antipyretic) action: as such it is used in the horse and cow in 4 oz. (120·0 G.) doses twice daily until the fever subsides. The chloride can also be used in sheep and goats, but care should be taken if pigs and poultry are dosed with salt. These species are susceptible to salt poisoning and access to unlimited drinking water should be available if salt is administered.

In small animals, *sodium acid phosphate* acts as a saline diuretic but its main use is as a urinary acidifier (*q.v.*), when it is usually combined with hexamine, itself a diuretic although primarily used as a urinary antiseptic (*q.v.*).

Ammonium salts can also be used as diuretics. The most popular compound used for this purpose is *Ammonium chloride*, B.Vet.C. which is used in horses and small animals. It acts as a urinary acidifier as well as a diuretic and is used in conjunction with organic mercurial diuretics, with which it seems to be synergistic. Part of the absorbed ammonium chloride is excreted by the lungs, and by thinning and loosening the bronchial mucous secretions it acts as an *expectorant*. This action has not been fully substantiated. It is not used so frequently for this purpose in veterinary medicine but is widely favoured in human expectorant mixtures. Similarly, its diaphoretic (sweating) action is not of great importance. The largest part of the ammonium radicle is converted into urea, mainly by the liver and kidney. This urea is excreted along with its water of solution, which is frequently provided from that released into the blood stream when the alkali reserve (mainly sodium ions) is depleted to neutralize the acid radicle of the ammonium salt.

Urea, B.Vet.C. has been used as a diuretic in doses of 2–8 oz. (60·0–250·0 G.) for the horse, and 15–180 gr. (0·5–12·0 G.) for the dog. In cattle it has been used as a feed supplement for ruminal synthesis of amino-acids. Because of this ruminal utilization it cannot be used as a diuretic in cattle, sheep and goats.

Urea is a metabolite and is therefore not favoured as a systemic drug because of the danger of raising concentrations in the blood to toxic levels. This danger determines the contra-indications of hepatitis and nephritis.

The antiseptic action of urea has been made use of in tooth pastes and wound dressings, where its slight local anæsthetic properties are an advantage. Its modern use is as a neutralizer of sulphonamide antagonists such as para-aminobenzoic acid and methionine. It is used in concentrations of up to 20 per cent. in sulphonamide lotions and ointments, but concentrations of 10–15 per cent. are preferred as they are less irritant.

Irritant Diuretics. All drugs of an irritant nature which are excreted through the kidney will have some diuretic effect, but those which are used primarily for a diuretic effect may be grouped as (1) *Mercurial diuretics* and (2) *Volatile oil* diuretics. There are a few exceptions, such as Black Antimony—antimony sulphide, which was widely used in horse practice, and is still used by some practitioners, in 30–60 gr. doses (2·0–4·0 G.) given twice daily in food.

Mercurial Diuretics. Any compound of mercury, if absorbed, will cause diuresis during excretion through the kidney. This action is attributed to the interference with metabolism in the tubular epithelial cells, a number of enzyme systems being unbalanced. This prevents the cells resorbing from the tubules, chloride, sodium, potassium, and calcium, ions in addition to water. This loss of chloride and base, in turn, releases more water for excretion, and should there be ascitic fluid within the body cavities, large quantities can be mobilized into the blood and excreted by the kidneys. This applies only to cardiac and hepatic œdema, and not nephritic œdema.

In therapeutic concentrations only mild irritation is caused in the kidney, but in high dosage severe nephritis may result with blood and albumin appearing in the urine. Mercurial preparations are consequently contra-indicated where nephritis is already present.

Calomel, administered orally and by intramuscular injection, has on occasions been used to cause diuresis, but the strong irritant action, the purgative effects, and the painful nature of the injections, have made it unpopular for this purpose.

Organic mercurials have replaced calomel for parenteral injections, for they ionize only slightly and are consequently less irritant and safer. They have not found the same favour in veterinary medicine as in human medicine and are used infrequently, and then only in dogs and cats.

The first of these organic preparations to be used was *novasurol*, but this compound was relatively toxic and was soon superseded by *mersalyl*. Other preparations have since been marketed, though mersalyl remains the standard compound in Great Britain.

Mersalyl, B.Vet.C.

This white deliquescent powder containing approximately 40 per cent. metallic mercury is used as an injection or in tablet form. It is normally used in combination with theophylline, a cardiovascular diuretic, which appears to combine with the mercury compounds, making them less toxic and more active. Injection of Mersalyl, B.Vet.C. contains 10 per cent. of mersalyl and 5 per cent. theophylline.

The main use of these diuretics is as a means of resorbing and excreting the œdematous fluid which collects in tissues and body cavities following venous congestion. This congestion may be the result of either cardiac

inefficiency or liver fibrosis. They are of no value in nephritic œdema or in chylous ascites of the cat.

The injection usually causes drowsiness and the animal may sleep for several hours, subsequent to which copious amounts of urine are passed. Excretion reaches a peak in about 6–8 hours but may continue at a decreasing rate for up to 24 hours. Oral medication with an ammonium chloride 5 gr. (0·3 G.) tablet three times daily for the dog, and half this quantity for the cat, will increase the effect.

Dosage and Administration.

Oral: Dog and Cat: 160·0–240·0 mg.
i/v or i/m: Dog 1·0–2·0 ml. Cat: 0·5–1·0 ml.

Small trial doses will help in preventing accidents, for some animals show a sensitivity to these compounds. Where no ill effects result from the test dose normal therapeutic doses can be given 24 hours later. The therapeutic doses can be repeated at intervals of 3–7 days depending on the individual reactions.

Oral dosage, though sometimes more convenient is less effective owing to the low absorption rate of mercurial compounds. Tablets normally contain 80·0 mg. mersalyl and 40·0 mg. theophylline.

Parenteral dosing should be carried out with care. Deep intramuscular injection is the best route, but the intravenous route can be used providing the injection is given slowly, for cardiac damage may follow too rapid an injection rate. The subcutaneous route should not be used as sloughs may result from mercurial irritation.

Volatile Oils. One of the remote local effects of volatile oils and similar compounds is the irritation of the kidney and the rest of the urinary system. Their action is said to be twofold in that capillary dilatation occurs allowing greater filtration, whilst tubular irritation results in less resorption.

Volatile oils still used for this purpose are camphor and turpentine, whilst colophony (resin) and benzoin have a similar effect but are less popular. Chelidonium extracts, which contain alkaloids and an irritant principle are popular in small animal practice and are used occasionally for large animal diuresis.

Most volatile oils also act as urinary antiseptics but their action is relatively slight when compared with hexamine and chemotherapeutic agents. They have the advantage of acting irrespective of urine pH and are less irritant than the mercurial diuretics.

Cardiovascular Diuretics. The members of this section are so classified because their diuretic effect is subsidiary to their main actions on the cardiovascular system.

In general, their effect is indirect and related to increased cardiac output and circulatory pressure. The volume and pressure of blood

passing through the kidney is increased, which results in increased volume and speed of glomerular filtration, with a proportional increase in volume and rate of urine production. In many cases the urine excretion is so markedly increased that tissue œdema and fluid within body cavities is resorbed into the blood stream and then excreted by the kidney. Some compounds can therefore be used in renal œdema, as well as cardiac and hepatic œdema.

In some cases these cardiovascular diuretics also have a direct action on the kidney itself.

There are two main groups of cardiovascular diuretics:

(1) The *cardiac glycosides* of digitalis, strophanthus, and squills.

(2) The *xanthine derivatives*, caffeine, theobromine and theophylline.

1. The *cardiac glycosides* used are mainly those from species of fox-glove, *Digitalis purpurea*, the common purple foxglove, and *Digitalis lanata*. Other cardiac glycosides, such as those obtained from strophanthus and squills, are not frequently used although Strophanthin K., B.Vet.C., a mixture of glycosides, has a more active diuretic effect than digitalis glycosides. This is probably due to the more rapid absorption rate.

The use of cardiac glycosides is mainly restricted to the treatment of dogs. They have very little diuretic effect in normal animals, but where cardiac œdema is present they are strongly indicated. These compounds achieve diuresis by a combination of cardiac and peripheral vascular effects, which are dealt with more fully in the section dealing with the heart and circulatory system. Briefly, cardiac output and arterial pressure is increased and venous pressure decreased; the peripheral effect results in capillary constriction in the splanchnic area and a tendency for vaso-dilatation in the kidney. The total effect is to resorb œdematous fluid which is then filtered out by the glomerulæ as the increased volume of blood circulates through the kidney at a higher pressure. Mercurial diuretics are said to increase the effect, mainly by decreasing tubular resorption.

These drugs, often in conjunction with nitrites, are usually given orally in dogs and also in species other than ruminants. Cattle and sheep should be given digitalis glycosides by injection, as ruminal fermentation is believed to destroy the compounds when administered orally. Other details of glycoside administration, such as the possibility of gastro-intestinal irritation and cumulation are mentioned more fully in Chapter 10.

2. *The xanthine derivatives* are rarely used as diuretics in veterinary medicine.

Caffeine is more important for its central nervous system stimulant action and, through this stimulation, its effect on respiration and heart action. In addition, arteriolar dilatation occurs by peripheral action which counteracts any effect due to stimulation of the vasomotor centre in the medulla. The presence of very few constrictor fibres in the kidney means that here, as well as in other areas such as the brain, the dilator effect

predominates, and the circulatory volume of the kidney increases. As a result, increased filtration occurs. Increase in urine output is not entirely accounted for by increased blood throughput; some workers believe that caffeine is responsible for mobilizing dormant glomeruli and also for decreasing fluid resorption, for the urine produced has a relatively high water content and therefore a lower specific gravity.

Theobromine is suggested as the best xanthine diuretic as it has less tendency to cause gastric irritation and a more prolonged action than theophylline. It has been claimed that theobromine has a more powerful diuretic effect than caffeine or theophylline, but Eddy and Downs (1928) showed that 1 part caffeine was equivalent to 1·2 and 0·4 parts of theobromine and theophylline respectively. The apparent superiority of theobromine is therefore related to its inferior nervous system stimulant effect, which allows doses four times greater than those of caffeine to be used.

Theophylline is not used on its own. Though more powerful as a diuretic than its two relatives, its action is short lived and it is therefore combined with other drugs such as mercurial diuretics.

It must be remembered that theobromine reaches its peak effect within 24 hours of the first dose being given, whereas caffeine must be administered regularly for three–four days before maximum effect is achieved.

All xanthine derivatives are administered by oral or parenteral routes as double salts with organic sodium compounds such as sodium benzoate, salicylate or acetate. These salts increase solubility, and so improve intestinal absorption and make solution for injection much easier. Dosages are given in pages 152, 309 and 310.

Urinary Acidifiers

The substances causing acidification of the urine are salts which will release into the urine an excess of acid radicles. They are all saline diuretics.

In general, they are combinations of acid radicles with basic radicles which will either be metabolized releasing an excess of acid radicles, or will be absorbed into the alkaline reserve allowing the acid radicle to be excreted. Examples of the first group are the salts of ammonia such as ammonium acid phosphate, ammonium mandelate, or ammonium chloride. The second group include sodium acid phosphate. Salts of sulphuric acid are not used as the sulphate radicle is only slowly absorbed, and though the nitrates are used, they tend to be more irritant than the weaker acid radicles.

Ammonium salts ionize to release ammonium and acid radicles. The ammonium is changed into urea and the excess chloride or the acid phosphate radicles are excreted, causing an acidification of the urine.

Sodium acid phosphate ionizes and the sodium ion is normally accepted into the alkali reserve whilst the acid phosphate is excreted giving an acid pH to the urine.

Urinary acidifiers are used in cats, dogs, and pigs. The urine of herbivores

is normally alkaline and can be rendered acid only with large doses of ammonium chloride (Nicoletti *et al.*, 1956). These workers gave 225·0 G. of the salt to each of two cows in three equal doses; an acid urine with a pH of between pH5 and pH6 was achieved without any serious side effects within 12 hours, and was maintained for 48 hours with the addition of a further 150·0 G. Tabangui (1949) reported using as much as 2 lb. sodium phosphate without achieving an acid urine in cows.

It is generally found that bacterial growth is favoured by alkaline urine and, frequently, acidification will rapidly clear up an infection. This applies particularly to cystitis in dogs and cats.

The *dosage* of ammonium chloride for horses and cattle is from 60 gr.–½ oz. (4·0–15·0 G.), and for dogs and cats about ¼ grain (0·025 G.) per lb. body weight per day in divided doses: 5 gr. (0·3 G.) given three times daily is a common dose. The administration in large animals mainly achieves a saline diuresis with a slight shift in pH towards acidity.

Sodium acid phosphate is used extensively in small animals as a urinary acidifier in doses of 2½–5 gr. (0·15–0·3 G.) given orally three times daily. It is valuable in neuter cats which are prone to urine retention; this retention, either from laziness or imprisonment, results in the urine becoming alkaline, which allows bacterial growth and cystitis, (inflammation of the bladder) and also increases the incidence of the soft cream-white deposits in the urethra which are the common cause of urethral obstruction in the cat. Once this obstruction has occurred and been cleared, the animal should be dosed with acid phosphate tablets—2½ gr. (0·15 G.) tablets once or twice daily are usually sufficient to prevent further obstruction. The acid phosphate is most frequently used as a urinary acidifier in conjunction with hexamine, either combined in tablet form, or as two separate solutions, when the hexamine dose is given 15–20 minutes after the acid phosphate dose. Ammonium chloride is also used occasionally for this purpose.

Urinary Alkalizers

These also are saline diuretics. The salts are combinations of strong basic radicles and weak acid radicles and the best therefore are sodium bicarbonate, acetate, and citrate. Potassium salts are equally effective, but the acetate and citrate are deliquescent and are consequently of less practical value.

The acetate and citrate radicles are metabolized, and the base released is excreted as bicarbonate which gives a strong alkaline reaction to the urine.

The main value of urinary alkalizers is during the administration of sulphonamides whenever there is the danger of crystalluria and damage to the kidneys. The sulphonamides themselves are more soluble in alkaline media, and the formation of the less soluble acetyl derivatives is decreased. Bicarbonates are also said to increase both the absorption and excretion of salicylates.

The alkalizers are not very often required for the urine of herbivores is normally alkaline and the incidence of crystalluria in carnivores is not very great.

Urinary Antiseptics

The historical urinary antiseptics were mainly volatile oils and oleoresins such as the oils of sandalwood, cubebs, and buchu. Of these, only buchu is now used in veterinary medicine. In doses of 5–60 m. (0·3–4·0 ml.), *Tincture of Buchu*, B.P.C., 1949, has been combined with similar doses of *Tincture of Hyoscyamus*, B.Vet.C. in urinary antiseptic and sedative mixtures for the dog.

These urinary antiseptics have very little antibacterial action compared with *Hexamine*, B.Vet.C. which is still very widely used as urinary antiseptic, though superseded to a large extent by the sulphonamides and antibiotics, which are the most efficient of all urinary antiseptics.

Hexamine, B.Vet.C.

This drug is known by a number of different names; hexamethylenetetramine, urotropine and methenamine. An odourless, colourless crystal or white crystalline powder, hexamine has a characteristic warm, sweet taste, which becomes bitter. It burns with a blue non-luminous flame and is the main constituent of many proprietary fire lighters. It is very soluble in water and alcohol.

Actions and Uses. The action of hexamine is firstly one of diuresis and secondly of urinary antisepsis, provided the pH of the urine is acid. This is achieved in small animals by the administration of sodium acid phosphate at least twenty minutes before the first dose, but subsequently at the same time as the hexamine. Combined tablets with 5 gr. (0·3 G.) hexamine and 2½ gr. (0·15 G.) sodium acid phosphate are available. In acid urine, hexamine slowly decomposes releasing ammonia and formaldehyde; the latter exerts an antibacterial action: the effect in no way compares with that of more modern treatments.

Hexamine has been used as an intravenous injection in the form of hexamine camphorate, or by mouth as hexamine, in the treatment of tetanus in the horse and other species, and also in the treatment of 'hard-pad' or infectious canine encephalitis.

In the former disease, the hexamine in the blood stream is reputed to break down the 'blood-brain barrier' and allow free access of antitoxin into the cerebrospinal fluid. In the latter disease no scientific justification has been found, though many clinical reports seem to indicate some beneficial effect.

(Hexamine camphorate releases camphoric acid in the blood stream along with hexamine. Both are excreted simultaneously and the presence of camphoric acid in the urine obviates the need for concurrent administration of urinary acidifiers.)

Dosage and Administration.

Hexamine:	Horse and Cow:	60–120 gr. (4·8–8·0 G.)
	Sheep and Pig:	20–40 gr. (1·3–2·6 G.)
	Dog:	5–10 gr. (0·3–1·0 G.)
	Cat:	2–5 gr. (0·15–0·3 G.)

Hexamine Camphorate (administered intravenously):

Horse and Cow:	50·0–300·0 ml.
Sheep and Pig:	2·0–10·0 ml.
Dog and Cat:	1·0–5·0 ml.

Hexamine is administered orally as a drench in large and small animals, but, provided adequate water is available, tablets provide the easiest way of giving the drug. Subcutaneous and intravenous injections are permissible if the solutions are neutral or alkaline.

Toxicity. Hexamine is non-irritant, but even slight acid concentrations release formalin which is highly irritant and will cause marked tissue reactions.

If large quantities are administered to small animals, the toxic effects will vary according to the urine pH. Thus, animals with strongly acid urine will rapidly develop nephritis with large quantities of albumin rendering the urine milky in appearance. In very severe cases urine may be stained with blood, indicating severe tissue damage and the ulceration of blood vessels. In animals with alkaline or neutral urine similar doses will cause relatively little damage and few symptoms.

This effect of urine pH is no doubt responsible for the conflicting reports on the use of hexamine camphorate in the severe 'hard-pad' epizootic in dogs throughout Great Britain between 1947 and 1952. In some cases nephritis resulted from injections of 5·0 ml., whereas as much as 15·0 ml. were given to others with little apparent effect. Urinary alkalizers and diuretics are useful in combating this nephritis.

Mandelic acid has been used in human medicine in cases of urinary infections which do not respond to sulphonamide therapy. In veterinary medicine, urinary infections in dogs and cats have occasionally been treated with the drug although the newer antibiotics are safer and more effective. The acid itself is a deliquescent crystalline solid, and *ammonium mandelate* or *Calcium Mandelate*, B.Vet.C. are preferred for their greater stability. The calcium salt is particularly stable being insoluble in water and has only a slight saline taste; it must be used with a wetting and suspending agent.

Actions and Uses. Mandelic acid is absorbed following its release from the salts in the stomach. It circulates and is excreted unchanged through

the kidney. In the urine, it exerts a bacteriostatic effect in acid urine but relatively little in alkaline and neutral urine. The optimum effect is exerted in urine at a pH below 5·5, and should methyl red indicator not confirm this, ammonium chloride or acid sodium phosphate should be given. The ammonium and calcium salts act as self-acidifying compounds and are all the more favoured because of this. Further intensification of the action can be achieved by restricting water intake to a minimum. This is an exception to the rule that patients with urinary infections should be encouraged to drink as much fluid as possible.

Dosage and Administration.

Calcium Mandelate B.Vet.C.	Dog:	7½–45 gr. (0·5–3·0 G.)
	Cat:	5–25 gr. (0·3–1·5 G.)

Salts other than the calcium one may be given in solutions which, however, are strongly saline in taste and not readily accepted. Calcium mandelate is available as a dispersible powder for oral administration 3–4 times daily.

Toxicity. Mandelic acid is irritant, mainly because of the extreme acidity required for optimum effect. It should therefore be administered for a maximum of fourteen days, and if further treatment seems indicated, mandelic acid must not be used until 12–14 days have elapsed after the end of the 14 day course. In the majority of indicated cases bacteriological cure is achieved in 6–7 days.

Urinary Sedatives.

These drugs are used mainly to relieve irritation in the bladder, but are also of value in depressing the irritability of the whole urinary tract.

The sedation may be achieved by (a) removing the cause of the irritation, and (b) anæsthetizing the mucous membrane.

The first group includes antibacterial agents such as sulphonamides and antibiotics, particularly streptomycin and the 'broad spectrum' compounds. Occasionally urinary acidifiers and alkalizers may relieve irritation by changing the pH, and may also arrest bacterial growth. This first group should be used in conjunction with the members of the second group if the most satisfactory results are to be obtained.

The second group consists of preparations of belladonna and hyoscyamus, but especially the latter. Most compounds containing atropine will have a peripheral sedative action, but preparations of Hyoscyamus, B.Vet.C. contain a high proportion of hyoscyamine which has a stronger anæsthetic effect on the mucous membrane. The hyoscine also contained assists in countering the central nervous system stimulant action of the small quantity of atropine and the hyoscyamine.

The preparation of hyoscyamus most frequently used is the tincture, but the liquid and dry extracts are also used.

Dosage and Administration.

Tincture of Hyoscyamus, B.Vet.C.

Horse and Cow:	½–2 fl. oz. (15·0–60·0 ml.)
Sheep and Goat:	60–180 m. (4·0–12·0 ml.)
Pig:	30–90 m. (2·0–6·0 ml.)
Dog:	15–60 m. (1·0–4·0 ml.)

Liquid Extract of Hyoscyamus, B.Vet.C.

Horse and Cow:	60–120 m. (4·0–8·0 ml.)
Sheep and Goat:	5–15 m. (0·3–1·0 ml.)
Pig:	3–10 m. (0·2–0·6 ml.)
Dog:	3–6 m. (0·2–0·4)

The Dry Extract of Hyoscyamus, B.Vet.C. contains six times more alkaloids than the liquid extract, that is 0·3 per cent. total alkaloids as against 0·05 per cent. in the liquid preparation. Doses are proportionately smaller. All doses are oral.

Toxicity is similar to atropine poisoning and the treatment is therefore the same. Hyperexcitability in the earlier stages requires short acting sedatives, and the later depression should be countered by medullary stimulants such as picrotoxin, leptazol and nikethamide. Unabsorbed alkaloid can be removed either by emesis if treatment commences before excitability is shown, otherwise tannic acid and potassium permanganate may be used to precipitate the alkaloids. The precipitated alkaloids can then be expelled by laxatives.

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CHAPTER 18

THE REPRODUCTIVE SYSTEM

THE drugs which affect the reproductive system more or less selectively can be divided into three groups for ease in discussion:

1. Aphrodisiacs and Anaphrodisiacs.
2. Ecbolics.
3. Hormones.

Groups two and three, whilst not identical, will include drugs which may be logically classified under either heading. This refers particularly to oxytocin, which is a hormone with very powerful ecbolic effects.

Aphrodisiacs and Anaphrodisiacs

The aphrodisiacs are drugs which increase sexual desire and libido. Conversely, the anaphrodisiacs are drugs which decrease sexual desire and libido. In veterinary medicine there is little need for the use of aphrodisiacs providing the hygiene and husbandry of animals is correct.

In the past, aphrodisiacs were resorted to if a stud male was slow in serving any of the females presented to him in œstrus. Little cognizance was taken of the fact that perhaps he was overweight from the lack of exercise, that his feet were overgrown and service exerted a strain on tendons and joints which caused pain, that perhaps he was deficient in vitamins due to bad housing and feeding, or merely that he was overworked. The female was not considered.

To-day there is little indication for the use of the old type of aphrodisiac, the general opinion being that if animals refuse to mate there must be some physiological, and perhaps pathological, cause. Before any drug is resorted to, therefore, a full investigation of the feeding, hygiene, and husbandry should be carried out. Following this, and if no possible cause has been found, a thorough physical examination and observation of mating behaviour is the second stage of investigation. If no pathological features such as arthritis, either of the limb joints, but more important, of the thoraco-lumbar vertebral joints, are found then, and only then, may stimulants be considered. Such stimulants may be of a general type such as strychnine therapy, but, particularly in the old male, modern therapy inclines toward the use of androgens or stimulators of androgen production (chorionic gonadotrophin). It should be remembered, however, that while

such hormones may increase libido they tend to depress spermatozoa production and should not be used indiscriminately as a treatment for reproductive derangements.

In the female, suboestrus—blind bulling in the cow or silent heat, can similarly be treated with hormones.

Anaphrodisiacs have a small but definite part to play. Their use is restricted almost entirely to suppressing excessive libido in puppies at puberty, when sexual excitement and masturbation may become a problem. They may be used empirically in nymphomania in large animals. Nerve sedatives are used to control these symptoms: potassium, sodium, or ammonium bromides or mixtures of these, phenobarbitone and other barbiturates, chloral hydrate, hyoscyamus, chlorbutol, and primidone are all used; the bromides are quite efficient and economic, especially if combined with hard and frequent exercise.

Old Type Aphrodisiacs. The non-hormonal aphrodisiacs are of two types, (1) those which exert their action through their effects on the nervous system and (2) those which irritate the urinogenital system during excretion. Strychnine, alcohol, and possibly yohimbine, are examples of group one, whereas cantharides and damiana are representative of group two.

Strychnine is only aphrodisiac by virtue of general toning up of spinal reflexes. Nevertheless it can be of use in the lazy, sluggish male when lack of inclination to serve is due to overweight and need of exercise. Without adjustment of management and feeding strychnine is not very effective.

Alcohol in humans has been considered as an aphrodisiac and is reputed to act by the removal of social and sexual inhibitions during intoxication. It has no application in the veterinary field.

Yohimbine has been used in man and animals to stimulate 'sex drive', though it is reported to be ineffective in creating sexual desire and certainly ineffective in therapeutic doses. It is reputed to act in one of two ways or possibly both: (a) by stimulation of the lower spinal centres and (b) by general vasodilatation in the skin and mucous membranes, but particularly in the genital organs, which results in erection. The vasodilatation is due to the adrenaline reversal effect which yohimbine has in common with ergotoxine. Oral *doses* used have been ½–1½ gr. (30·0–90·0 mg.) for horses and cattle, and 1/100–1/20 gr. (0·6–3·0 mg.) for the dog.

Cantharides B.P.C. (1949) has also been used as an aphrodisiac but is now rarely used for this purpose. Its effects, however, may occasionally be observed following the injudicious use of a cantharides blister in the vicinity of the prepuce, when preputial contamination causes irritation and penile erection, or when a large area has been dressed and sufficient drug has been absorbed through the skin to cause irritation during excretion: trouble may also result from animals licking an area blistered

with cantharides. Most of the cantharidin absorbed is excreted via the kidneys and, during excretion, irritation of the urethra occurs. This results in penile erection. Copious fluid intake and hyoscyamus will help to counteract renal and sexual symptoms of poisoning, the remaining symptoms being treated symptomatically.

Damiana is another irritant aphrodisiac that is now disappearing from official and semi-official references.

Ecbolics

An ecbolic is an agent which stimulates muscle contraction in the uterus and is frequently referred to as an oxytocic agent. The use of ecbolics in the pregnant animal may cause abortion, but though they are often referred to as abortificients, this is not their constant therapeutic effect nor their indicated use in animals, indeed their use is contra-indicated in the pregnant animal.

The use of ecbolics is indicated:

(a) In parturition where position and presentation are normal and where the cervix is adequately dilated. They should not be used unless parturition is prolonged.

(b) In a flaccid post-parturient uterus which is not contracting (involuting.)

(c) In post-parturient hæmorrhage.

In all cases of uterine inertia or slow delivery, doses should be small and repeated.

Many substances have an ecbolic action, including all types of purgatives but particularly the 'drastics', the anthracenes, and the neuromuscular purgatives: some poisons such as the salts of lead and some volatile oils including those of ragwort are also ecbolics and abortifacients. Despite the number of substances with ecbolic actions, those used therapeutically number only two—ergot and its preparations, and extracts of the posterior pituitary gland.

Ergot, B.Vet.C. and Its Preparations

Ergot is a stage in the life cycle of a fungus, *Claviceps purpurea*. It consists of a spur-like body or sclerotium derived from the ovary of rye, and is black on the outside but has a cream interior which shows dark veining when the sclerotium is fractured tranversely. At one time almost unknown in Great Britain it is, since the inundations by the sea in 1952, fairly widespread as an infection of rye grass in East Anglia and has been reported in Leicestershire (Dring, 1955) and Berkshire. Ergot poisoning is therefore no longer an academic abstract condition occurring on the continent, but must definitely be included in British toxicological classifications.

Prepared Ergot, B.Vet.C. has a standard alkaloid content (0·2 per cent. calculated as ergotoxine: 15 per cent. of this is the minimum proportion of

water soluble alkaloids calculated in terms of ergometrine). It is a purplish-brown powder prepared by grinding ergot of rye and defatting to a maximum fat content of 5 per cent.

Liquid Extract of Ergot, B.P.C. is also used. This extract is prepared by maceration and percolation of the powdered ergot and is standardized to contain 0·06 per cent. total alkaloids when fresh, but a minimum of 0·04 per cent. after keeping. Calculations are in terms of ergotoxine. This liquid extract loses its activity rapidly on dilution but less rapidly if concentrated and kept in completely full, light-tight containers. It should be dispensed undiluted with instructions to dilute immediately prior to administration.

The main active constituents of ergot are six pairs of stereoisomeric alkaloids. The naturally occurring lævorotatory alkaloids are the most important and active, whilst the dextrorotatory stereoisomers are relatively inactive. These alkaloids have been classed chemically into three groups:

	Lævorotatory	Dextrorotatory
1. The Ergotamine groups:	Ergotamine	Ergotaminine
	Ergosine	Ergosinine
2. The Ergotoxine group:	Ergocrystine	Ergocrystinine
	Ergocryptine	Ergocryptinine
	Ergocornine	Ergocorninine
3. The Ergometrine group:	Ergometrine	Ergometrinine.

The discovery of these alkaloids has occurred piecemeal and of the alkaloids listed above a number are still referred to by other names both officially and unofficially. Thus ergocrystinine is also known as ergotinine, ergocorninine as ergotinine, and ergometrine as Ergonovine, U.S.P., ergobasine, ergostetrine and ergotocine. Ergotoxine is now recognized as being not a single compound but a mixture of the three lævorotatory alkaloids listed above.

Besides these and other alkaloids, ergot also contains various amino-acids, amines, organic carboxylic acids, and vitamin D, as well as about 40 per cent. fixed oil, sugars, and glycosides. These do not materially affect the action of ergot.

Action. Although, chemically, the main alkaloids are classified under three heads, the polypeptides (groups one and two above) are grouped together therapeutically, whilst the less complex ergometrine makes a second therapeutic class.

Both groups of alkaloids stimulate smooth muscle though ergometrine has very little effect on smooth muscle other than that of the uterus.

The *ergotamine–'ergotoxine' group* is slowly and poorly absorbed from the intestines following oral administration or intramuscular injection (15–30 minutes). Following absorption, small doses affect mainly the uterine muscle by direct stimulation, causing an increase in power and extent of the rhythmic contractions of the non-pregnant, and especially the parturient and immediately post-parturient, uterus. Larger doses will stimulate the bladder, intestine, and blood vessels when there may be a rise in blood pressure due to arteriolar constriction, though a slowing of the heart tends to mask this effect. In very large, super-therapeutic, doses, the group causes the 'adrenaline reversal' action whereby the blood pressure falls if adrenaline is injected after a large dose of 'ergotoxine' or to a lesser degree, ergotamine. This action is due to paralysis of the motor sympathetic nerve endings but not the sympathetic inhibitor or relaxing terminations.

Ergometrine (ergonovine) is readily soluble in water and is rapidly absorbed and rapidly effective (5–8 minutes after oral dosing, 2 minutes and 1 minute after intramuscular and intravenous injections respectively). The action persists maximally for about one hour and gradually lessens over a period of several hours. It affects the uterus fairly selectively and is the ergot derivative most preferred for this action.

Uses. Ergot, as the prepared powder or the liquid extract, and ergometrine are useful for causing expulsion of the placenta and involution of the post-parturient uterus. They are also useful in stopping hæmorrhage from the uterus after parturition, the effect being achieved mainly by rapid and considerable reduction in uterine size which exerts pressure on the vessels as the tissues become compacted. The cruder preparations are used more in the large animals whereas ergometrine, in the form of a solution of the maleate, is preferred in small animals. 'Ergotoxine' and ergotamine are rarely used. (Ergotoxine in human medicine is used mainly for the treatment of migraine).

Note. Great care is required in the administration of ergot alkaloids, for large doses, or use during fœtal expulsion, may cause tonic 'band' contractions in the uterus and imprisonment of the young, with considerable danger to both mother and offspring. These effects are also very painful.

Dosage. Owing to the extended duration of effect, and the catastrophic results of overdosage, it is better to err on the side of underdosage if any doubt exists and rely on repetition to achieve the desired effect.

Prepared Ergot, B.Vet.C.

Horse and Cow:	½–1 oz. (15·0–30·0 G.)
Sheep and Pig:	30–90 gr. (2·0–6·0 G.)
Dog:	8–30 gr. (0·5–2·0 G.)
Cat:	1½–15 gr. (0·1–1·0 G.)

Liquid Extract of Ergot, B.P.C.

Horse and Cow:	120–360 m. (8·0–23·0 ml.)
Sheep and Pig:	10–40 m. (0·6–2·6 ml.)
Dog:	5–10 m. (0·3–0·6 ml.)

Ergometrine Maleate, B.Vet.C. (as tablets or injection).

Horse and Cow:	10·0–20·0 mg.
Sheep and Pig:	0·5–1·0 mg.
Dog:	0·2–1·0 mg.
Cat:	0·2–0·5 mg.

Toxicology. Two types of poisoning occur. The acute type takes the form of hyperexcitability, muscular inco-ordination, and tremors, with blindness, and possibly convulsions. The pupils of the eyes are often tightly constricted as in morphine poisoning. The chronic form follows from the arteriolar constrictor effect of the polypeptide alkaloids and takes the form of end-artery infarction with necrosis and sloughing, particularly of areas on the legs (Dring, 1955). These symptoms are usually associated with a drop in milk yield, dullness, lethargy, inappetance, and wasting. Treatment is symptomatic, the main benefit being derived from removal of the source of poisoning. In man, the treatment consists in keeping the limbs cool and the body warm: Methacholine Chloride, B.P. (acetyl-b-methylcholine), and glyceryl trinitrate (nitroglycerin) have been used to counteract the arteriolar constriction effects of the ergot alkaloids.

Injection of Pituitary (Posterior Lobe), B.Vet.C.

This injection is a sterile aqueous extract of the posterior lobe of pigs' and cattle pituitary glands. It is standardized to contain 10 oxytocic units per ml. When subjected to fractionation, almost pure preparations of the two main therapeutic constituents, oxytocin and vasopressin, can be obtained. These fractions are official as *Injection of Oxytocin*, B.P., which contains 10 oxytocic units and 0·5 units of pressor activity; and *Injection of Vasopressin*, B.P., which contains 20 units vasopressor activity and not more than 1 oxytocic unit per ml. It is now suggested that the single oxytocic unit of activity is an inherent activity of vasopressin (du Vigneaud *et al.*, 1953). The antidiuretic activity of this latter fraction is not assayed.

Actions. The active principles of this injection are hormones. These hormones have three main actions of therapeutic significance and a fourth of no clinical importance, but so far it has not been possible to isolate more than two hormones, the main effects of which are oxytocic or uterine stimulant effects, and vasoconstrictor actions; these actions are due to the oxytocin and vasopressin principles respectively. Some

authorities also recognize the presence of a third principle which has an antidiuretic effect, and a fourth principle which causes the dilatation of melanophores: the antidiuretic hormone is said to be related to, if not identical with, vasopressin.

Oxytocin, a complex polypeptide, acts specifically on the uterine musculature but is only completely effective when the uterus is sensitized to, or under the influence of, œstrogens. It is therefore strongly active on the non-pregnant and late pregnant uterus: in the latter case, pituitary secretions are suggested to be responsible for the induction of parturition when ovarian œstrogen production reaches a 'trigger' level in the tissues. Pituitary injections have little effect on the early pregnant uterus which is under the protection of luteal and, later, placental hormones. Oxytocin is also said to be involved to a major extent in artificial 'letting down' of milk by pituitary extract injections although the vasopressin is also implicated. This action is said to result from stimulation and contraction of the smooth muscle fibres located around the mammary alveoli. This contraction is thought to expel the milk mechanically as it does not increase the daily output of milk.

Vasopressin, probably a polypeptide similar to oxytocin, is a general stimulant of smooth muscle with strong vasopressor activity and an antidiuretic effect. The pressor effects produce a rise in blood pressure; this is caused by the direct action of the hormone on heart and arteriolar muscle. The constriction of the blood vessels and increased heart beat maintain the rise in blood-pressure for about half an hour. Vasopressin also affects the intestines but the effects vary from one species to another; there is usually an increase in motility and propulsive effort. Stimulation of urinary bladder contractions also results from vasopressin activity.

The antidiuretic factor causes an increase in tubular resorption of glomerular filtrate, therapy causing a decrease in the urine output of the kidney.

Uses. Injections of pituitary extracts and of oxytocin are primarily used for speeding expulsion of the fœtus or fœtuses when uterine inertia is diagnosed. They should not be used for this purpose unless position and presentation are normal. They are occasionally useful in obtaining the expulsion of the last puppy, piglet, or kitten, and are probably of more use in these multi-fœtal species than those producing only one offspring at a time. After parturition, pituitary extract will aid the expulsion of placental debris and involution of the uterus, and it is especially useful in cattle to inject 3·0 ml. or more directly into the uterine muscle after the removal of the fœtus during Cæsarian section: this also controls uterine bleeding. Following uterine prolapse the administration of injection of pituitary extracts at several places in the organ will reduce engorgement and contract the everted uterus, which can then be replaced more easily.

Agalactia in sows responds well to the injection of 2–3 ml. of the injection, and occasionally milk will spurt from the teats within a few

minutes of administration. It is not indicated in mastitis or in inability to suckle a litter due to other causes. In examination of milk during investigation of 'baby pig disease' due to hæmolytic antibodies in milk related to rhesus factor differences between offspring and sow, the collection of milk samples has been facilitated by the intravenous injection of about 1·0 ml. of pituitary extract. The milk is vigorously expressed from the teats and saves the laborious task of manual expression.

Oxytocin intravenously in doses of 10–40 units has been used in the treatment of mastitis in cattle, as an aid to expressing all infected milk from the quarters prior to introducing chemotherapeutics, but in controlled experiments on goats and cows, Smith and Pattison (1954a & b.) were unable to find any benefit from its use.

Pituitary extract has been suggested for the treatment of cæcal and colonic impaction in animals and for atony of the bladder but it is not very reliable when used for these purposes. It is also suggested as an agent for shortening post-anæsthetic recovery periods in cattle and horses if given intravenously, and has been suggested for the treatment of low blood pressure resulting from surgical shock.

Diabetes insipidus in dogs, characterized by continuous elimination of large quantities of urine with no abnormal constituents but a very low specific gravity (1006) can be controlled by the administration of relatively small doses of vasopressin: 3–5 units is sufficient in man, given every thirty-six to forty-eight hours.

Dosage and Administration.

Horse and Cow:	5·0–10·0 ml. (50—100 units)
Sheep and Pig:	1·0–5·0 ml. (30–50 units)
Dog:	0·25–1·5 ml. (2½–15 units)
Cat:	0·25–0·5 ml. (2½–5 units).

Vasopressin is not commonly used, but the dosage should be in accordance with the higher unitage of the official injection, i.e. half the above dosage in millilitres.

The injections should be given by deep intramuscular injection. Subcutaneous injection can cause very severe 'bruising', with discoloration of the area around the site of injection up to a diameter of six inches or so, depending on the dose; the centre of the area may slough out. Intravenous injection can be used, but care should be taken in small animals. Injections should be about ⅓ of the intramuscular doses and should preferably be diluted to 1 : 10 with sterile Water for Injection, B.Vet.C. In large animals this is not so important but even these precautions may not be adequate in dogs and cats—3·0 ml. of a 1 : 10 dilution given to a Great Dane bitch intravenously was followed by immediate collapse; recovery took place slowly over the succeeding 24 hours and was not followed by any untoward sequelæ.

It must be emphasized, as with ergot preparations, that parturition

cases are consistently overdosed in small animal practice, and that it is far better to give repeated small doses rather than one single large dose. A large dose, besides causing uterine spasm, also increases the danger of sloughs and causes the animal unnecessary pain and discomfort.

Hormones Affecting Reproductive Physiology

Included under this heading are the hormones produced by the ovary and testis, and also those produced elsewhere which influence the production of these hormones by the gonads. There are thus three main groups of naturally produced reproductive hormones:

1. Ovarian hormones:	(a) Œstrogens:	Œstrone Œstradiol Œstriol.
	(b) Progesterone	
2. Testicular hormones:	Androgens:	Testosterone Androsterone.
3. Gonadotrophins:	(a) Chorionic gonadotrophin (luteinizing hormone)	
	(b) Serum gonadotrophin (Follicle-stimulating hormone)	

There are, in addition to these, subsidiary hormones such as that possibly produced by the prostrate gland in the male and that by the allantois in the pregnant female. These are, however, little more than postulates at the moment and are of no therapeutic significance.

We may add to these naturally produced hormones a number of synthetic hormones and hormone-like substances:

Synthetic hormones.

Œstrogenic:	Ethinylœstradiol
	Hexœstrol
	Dienœstrol
	Stilbœstrol
Luteal:	Ethinyltestosterone (ethisterone)
Androgenic:	Methyltestosterone

The Gonadal or Sex Hormones. All the *naturally* produced sex hormones are classified chemically as steroids, that is, compounds related to the organic alcohols known as sterols. Both steroids and sterols have been grouped under the heading of sterids (Sobotka).

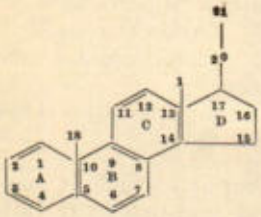
The *sterols* are saturated and unsaturated alcohols which occur in fixed oils of both animal (zoosterols), higher plant (phytosterols), and fungal (mycosterols), origin. They may occur free, or combined as esters and glycosides. The principle zoosterol is *cholesterol* and the principle

phytosterol is *stigmasterol*, both of which are widely used as starting points in the manufacture of the sex hormones.

The *steroids* are very similar in structure to the sterols and occur widely throughout the plant and animal kingdom. They are very active, and frequently highly poisonous, substances; consequently, as a group, they are of considerable physiological and therapeutic importance. Included in the group are bile acids, calciferol and related vitamin D steroids, the sex hormones, many of the adrenal hormones and the genins, or aglycones, of many glycosides, including the cardiac glycosides and the saponins of digitalis.

Chemistry. All these naturally occurring sterols and steroids may be considered as derivatives of cyclopentenophenanthrene (1), an unsaturated cyclic hydrocarbon. (The phenanthrene nucleus is common to many other compounds, including morphine).

(i)



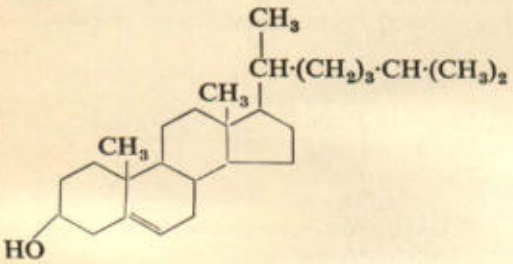
cyclopentenophenanthrene

(ia)



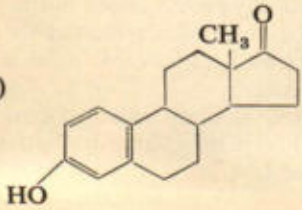
phenanthrene

(ii)

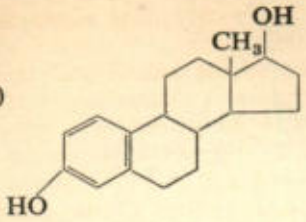


cholesterol

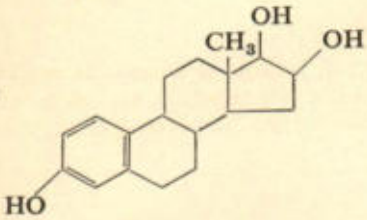
(iii)



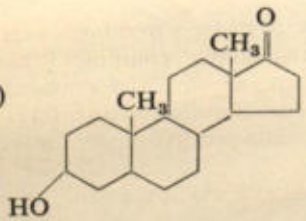
œstrone (the single oxygen at carbon 17, giving it the '-one' structure and distinguishing it from the di-alcohol ('-diol') structure of œstradiol.)

(iv) 

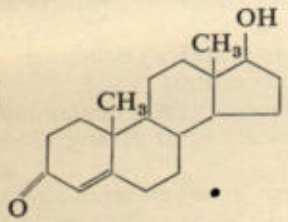
œstradiol

(v) 

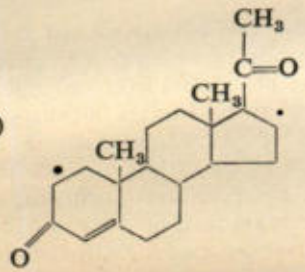
œstriol ('-triol' instead of '-one')

(vi) 

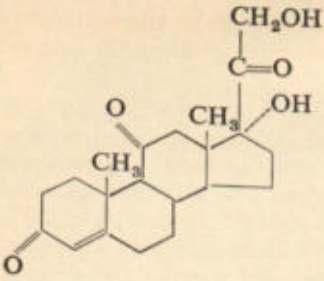
Androsterone

(vii) 

Testosterone

(viii) 

Progesterone (pregn-4-ene-3:20dione)

(ix) 

Cortisone (17:21 dihydroxy-pregn-4-ene-3:11:20trione)

Note: '-ene' indicates a double bond and is related to the first carbon atom in the link, e.g.  is 1-ene,  is 3-ene,  is 4-ene, and  is 5(10)-ene.

The nomenclature is related to the reduction of hydrogen atoms attached to the carbons and the formation of an unsaturated compound in the same manner that cyclohex*ane* becomes benz*ene* with the removal of hydrogen atoms and the creation of double bonds. Similarly with saturation cyclopent*eno*phenanthrene become cyclopent*ano*perhydrophenanthrene and vice versa.

'-one' indicates an oxygen linked by a double bond; thus two, '-dione' and three, '-trione'.

'-ol' indicates a hydroxyl group and from this '-diol' with two and '-triol' compounds with three hydroxyl groups.

'Œstri-' indicates a steroid with œstrogenic properties containing only one methyl group attached at carbon 13 in the nucleus.

'Androst-' indicates a steroid with androgenic properties containing two methyl groups—one attached to carbon 10 and one at carbon 13 in the nucleus.

'Pregn-' indicates a further stage, in which a methyl-ketone group is added to the androgen formation at carbon 17 (carbons 20 and 21).

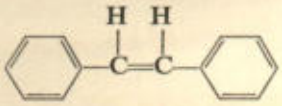
A comparison of these formulæ will show how closely related are the androgens, œstrogens, and the adrenocorticoids, of which group cortisone (ix) is a member. Androsterone (vi) for example, differs from œstrone (iii) by the addition of one methyl group only, at carbon 10. It is not surprising therefore that the androgens and œstrogens have very similar actions and, in some cases, can be substituted for each other in either sex without causing significantly different effects. It is, however, very surprising that the substitution in the progesterone molecule (viii) of an oxygen for two hydrogen atoms at carbon 11, and of hydroxyl groups for hydrogen atoms

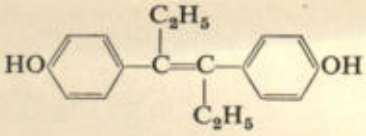
on carbons 17 and 21, should create the vast pharmacological and physiological differences that exist between that compound and the cortisone (ix) which is formed by these changes.

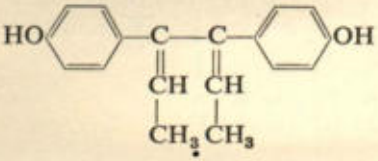
The *physical characters* of the œstrogens, androgens and progesterone are very similar. In general, they are white to creamy white crystalline powders which are odourless and tasteless, and are almost insoluble in water but soluble in alcohol and other organic solvents, including fixed oils. Œstrone is only slightly soluble in these solvents. Œstradiol and testosterone form salts with organic acids, of which those of propionic and benzoic acids are the most frequently used.

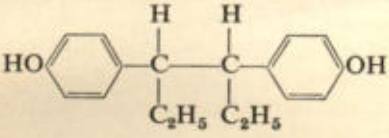
Synthetic œstrogens, androgens and progestins are now frequently used orally, mainly because their activity is maintained when given by this route, but also because continuous maintenance dosing is, apart from implantation, most convenient by this route.

The *synthetic œstrogens* are of two types—those which may be looked upon as having a stilbene nucleus (x) and those derived from natural œstrogens. The former are stilbœstrol (xi), dienœstrol (xii), and hexœstrol (xiii), whilst the latter are represented by ethinylœstradiol (xiv). The likeness of the stilbene derivatives is even more apparent if the ethyl groups of stilbœstrol and hexœstrol are written as $—CH_2·CH_3$.

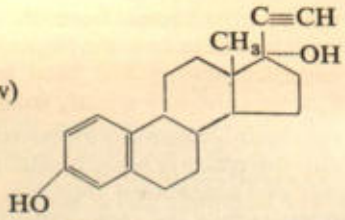
(x)  Stilbene nucleus

(xi)  Stilbœstrol

(xii)  Dienœstrol

(xiii)  Hexœstrol

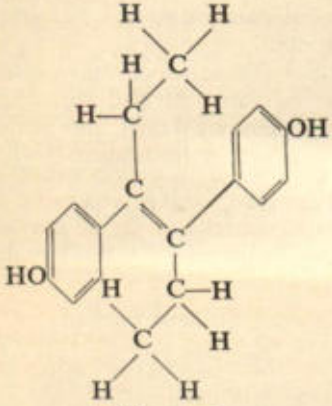
(xiv)



Ethinylœstradiol.

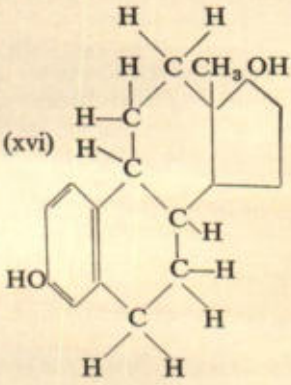
It is not at first apparent why a compound chemically unrelated to the natural œstrogens should have œstrogenic effects but if the stilbœstrol formula is rewritten as in (xv) and compared with the graphic formula of œstradiol (xvi) the problem becomes less abstruse. Even so these synthetic compounds are not steroids and cannot be considered as true hormones.

(xv)



Stilbœstrol

(xvi)

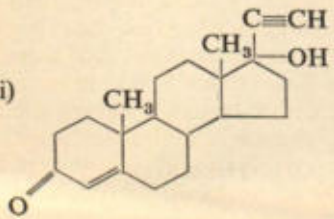


Œstradiol.

Synthetic androgens are represented by methyl testosterone in which a hydrogen atom at carbon 17 of testosterone (vii) is replaced by a methyl group.

Synthetic progestins are represented by ethisterone which is ethinyltestosterone (xvii) and therefore has a formula analogous to ethinylœstradiol (xiv).

(xvii)



Ethisterone (ethinyltestosterone).

The *physical characters* are similar to those of the natural hormones in that most are white crystalline substances without odour or taste, insoluble, or almost so, in water but soluble in organic solvents and fixed oils. Exceptions are dienœstrol and ethisterone, which are only slightly soluble in organic solvents including fixed oils.

Assay. The *natural* œstrogens may be assayed biologically using ovariectomized adult rats as an indicator. The technique makes use of the cornification of the vaginal epithelium, which occurs following the administration of œstrogens and is shown by vaginal smears. Two œstrogen units are recognized, an œstrone unit and a benzoate (œstradiol) unit. Now that these hormones are produced synthetically in pure form, chemical assay methods are used, but where hormones are of natural origin biological methods are still required and used.

Testosterone is usually assayed chemically. *Progesterone* assay may be biological using rabbits and guinea pigs, but normally the chemical and physical analyses are sufficient.

Action. The *œstrogens* in the female are entirely comparable in effect with the *androgens* in the male. These sex hormones are responsible for both the growth and correct functioning of the primary and secondary sex characters, though in the female they work in collaboration with progesterone in the functional control of the uterus and other reproductive structures. They antagonize any tendency to sex reversal which may occur due to simultaneous production of either androgenic (in the female) or œstrogenic (in the male) substances elsewhere, as for example, in the adrenal cortex: this antagonism of œstrogens and androgens by each other in respect of masculinization and feminization is now used extensively in the agricultural industry for chemical caponization, and the improvement in fattening rates and carcase quality that this brings.

Both œstrogens and androgens increase the blood supply to certain tissues, increasing nutrition and oxygen supply and improving tone and activity. The most important tissues are smooth and striated muscles, the tone and power of action being most strongly affected by androgens: this is accounted for largely by the improved circulation. The effect on muscles is made use of in the œstrogen and androgen therapy of urinary incontinence. Besides the muscles, the sex organs, brain, heart, middle and inner ear, and the kidneys, are all affected.

Androgens and œstrogens also affect mammary gland development and function in both male and female. These hormones increase duct development, but inhibit the breakdown of acinar epithelium and therefore decrease milk production, although this latter effect is counteracted by continued suckling or milking. Suppression of lactation during pseudopregnancy in the bitch is best achieved by the use of androgens, which do not induce œstrus as do the œstrogens if similarly used. This anti-lactation action is probably related to depression of prolactin secretion by the anterior pituitary gland.

Perhaps one of the most important actions of these androgens and œstrogens is their suppressive effect on some of the gonadotrophic hormones of the anterior pituitary glands. In this context the androgens are less powerful than the œstrogens, but their relative lack of toxicity and fewer side actions in the female allows them to be used more freely for anterior pituitary suppression. That these hormones should exert this suppressive action is only logical, for if excess œstrogen is circulating in the female the anterior pituitary gland must produce less follicle-stimulating hormone; the œstrogen is the logical substance to do this. In the same way in the male, if too much testosterone is circulating, the circulating luteinizing fraction of the anterior pituitary must be reduced to produce less stimulation, and it is the excess testosterone which causes this reduction. Because of this depression of the anterior pituitary activity, androgens and œstrogens must be used with extreme care in the treatment of infertility, for there will be a tendency to suppress both follicle and spermatozoa production.

The œstrogens have suppressive effects on certain benign tumours and some carcinomata, hence their use in prostatic hypertrophy and ulcerating anal adenomata. On repeated topical application, however, they have some carcinogenic effect though this is unlikely to be of veterinary clinical significance.

Of more importance is the sensitizing effect to pituitary extracts (posterior lobe) which œstrogens have.

Progesterone, produced by the corpus luteum formed after ovulation, supplements and continues the action of the œstrogens in the female. It will only affect tissues 'activated' by œstrogens. The main effects of progesterone, as its name implies, are therefore preparation of the uterus for nidation and, after implantation has taken place, to maintain the uterine insensitivity towards oxytocin throughout pregnancy, or until placental hormones are produced in sufficient quantity to take over this function, depending on the species involved. In continuation of the œstrogen development of the duct system of the mammary gland, progesterone completes the duct development and also develops glandular tissue to the stage of milk production.

Progesterone depresses œstrogen production, possibly by suppressing production of the follicular stimulating fraction of the anterior pituitary gland. It is itself antagonized by large doses of œstrogens as evinced by the use in mesalliance in bitches of 10–15 mg. stilbœstrol, which maintains the state of œstrus despite the ovulation and, presumably, corpus luteum formation.

Progesterone, as might be expected from its close chemical resemblance to androgens and adrenocortical hormones, has slight activity in both these directions.

Absorption. The natural œstrogens and androgens are all absorbed in varying degrees from the intestinal tract but, either because they are

absorbed slowly, metabolized, or excreted rapidly, they are not very active by this route. These œstrogens and androgens are therefore mainly given by parenteral injection. The synthetic œstrogens and androgens are, however, effective by mouth.

Progesterone is not absorbed in a physiologically active form and must be given parenterally, but the synthetic ethisterone is active by mouth though in relatively large doses.

Excretion. Œstrogens, androgens, and progesterone, are converted, possibly in the liver, into derivatives which have little physiological activity. These are usually sulphates, glycuronates, or less active steroids. They are excreted in the urine and possibly in the bile.

Relative Activity. The *œstrogens* are very difficult to compare, for each has activities greater in one respect than another and one hormone may therefore be more efficient for, say, suppressing lactation and yet relatively inefficient in initiating œstrus. A second hormone may have exactly the reverse potency. However, their relative activities when given orally in women have been generally assessed as: ethinylœstradiol 0·4, stilbœstrol 3·0, œstradiol 13·4, and œstrone 31·5; œstriol is not sufficiently active for therapeutic purposes by any route. Relative efficacies by the intramuscular routes were: œstradiol dipropionate 0·86, monobenzoate 1·06 and œstrone 3·0. When given orally, 1·0 mg. stilbœstrol is approximately equivalent in œstrogenic activity to 0·5 mg. œstradiol monobenzoate given by intramuscular injection. By injection, stilbœstrol dipropionate is slightly more active than œstrone given by the same route.

Of the *androgens*, only testosterone or its esters and derivatives are sufficiently active for clinical use. The androgen unit is equivalent to the activity of 0·1 mg. androsterone, and pure testosterone has a potency of 67 units per mg.: it is thus nearly seven times more active than androsterone, which is one of its excretory products. Testosterone propionate has 50 units activity per mg. Methyl testosterone when given orally requires doses 3 to 5 times greater than those of testosterone propionate given intramuscularly.

When *progesterone* is given parenterally (the hormone is almost inactive when given orally) it is from five to ten times more active than ethisterone administered orally.

Uses, Dosage and Administration. Though our knowledge of the physiology of hormones grows slowly, owing to the complex interplay and interdependence of hormones within the body, the use of hormones is increasing rapidly and the indications are being augmented annually. The sex hormones are no exception, as evinced by the introduction in 1957 of synthetic œstrogens for fattening steers in Great Britain. This practice, within one year, became very widespread.

Œstrogens

Œstradiol monobenzoate, stilbœstrol, and stilbœstrol dipropionate, are the most commonly used œstrogens in veterinary medicine, although dienœstrol is increasingly used. Hexœstrol is also used, but caponization of poultry and fattening of cattle are the only purposes for which it has found popularity.

In the *mare*, œstrogens have been little used. No doubt the danger of causing nymphomania (Arthur, 1957) has been responsible. Nevertheless, where follicular activity is present but the signs of œstrus are slight or absent, œstradiol monobenzoate in single doses of 5·0–10·0 mg. for maiden mares, and 10·0–15·0 mg. for barren mares, given intramuscularly as the follicle increases to its maximum size, may induce ovulation and œstrus. The subsequent œstrus period is more likely to result in ovulation. Dienœstrol has been used in single 5·0 mg. doses subcutaneously, and stilbœstrol, as its dipropionate ester, has also been used. Service should follow within 12 hours of the injection and should be repeated in 24 hours if possible. In general, mares respond more effectively to the administration of follicular stimulating and luteinizing hormones, and warm, boiled water flushing of the uterus is effective (Day, 1957), causing œstrus with ovulation in 3–5 days.

Day (1957) has used 2 × 0·5 G. or 1·0 G. implants of stilbœstrol in the treatment of vaginal discharges associated with 'bunch of grape ovaries' and, usually, irregular cycles. The implants have been left *in situ* for 2 to 2½ months. The same sized implants have also been used by him to reduce enlarged ovaries to a size convenient for removal *per vaginam*.

In *cattle*, œstrogens have been far more widely used. Anœstrus or subœstrus may be treated with œstrogens in the same way as described for the mare, but, as with the mare, the hormones which stimulate the ovary to increased function are far superior and are less likely to result in cystic ovaries and nymphomania.

The relaxing effect on the cervix and the sensitizing of the uterus to the ecbolic effects of posterior pituitary extracts has led to the use of œstrogens as an aid in removing retained placentæ and for mummified fœtus expulsion. It has similarly been used in metritis and pyometra. Doses in these cases have been 15·0–25·0 mg. of œstradiol monobenzoate given intramuscularly, once in the first two conditions, but repeated weekly for two or three weeks in the last condition. Stilbœstrol has been used in similar doses. Controversy still exists with regard to the use of œstrogens in these conditions and their use for these purposes is far less frequent than formerly.

In *fattening steers*, stilbœstrol has become very popular and widely used since the spring of 1957. Hexœstrol is similarly active in about the same dosage. If a 50·0–60·0 mg. implant of either of these compounds is inserted subcutaneously at the base of the ear using aseptic precautions some three months before the anticipated slaughter date, up to 25 per cent. increase in

killing-out weight can be achieved without impairment of quality. Because of the public health danger, implants should not be inserted in any place other than the ear, for they are normally discarded with the ear at the time of slaughter. Implantation of heifers and cows is not recommended because of side actions, particularly related to nymphomania, vaginal prolapse, faulty calcium metabolism, which, with the nymphomania—and sometimes without—results in pelvic and vertebral fractures. The doses recommended in the British Veterinary Codex and elsewhere (1·0 G.) are decidedly dangerous and should not be used. In the United States, stilbœstrol is used as a feed supplement for fattening beef cattle. Assessment is continuing, but it is unlikely that the residual quantities of œstrogens in the meat will be sufficiently high to have a public health significance.

In *sheep*, perhaps the most important use of œstrogens is the induction of early œstrus, with lambing antedated by as much as two months. By this means, and by inducing œstrus in the post-lambing anœstrus period, two crops of lambs per year have been obtained. Work is continuing and it is too early to assess the commercial value of this treatment. The doses used for this purpose have been 1·0 mg. of œstradiol monobenzoate, preferably given as four daily 0·25 mg. intramuscular doses, and no doubt dienœstrol would be similarly effective. Note: work being carried out by Dr. Ian Gordon indicates that progesterone in 25·0 mg. doses on alternate days for three to five doses followed by up to 1000 units serum gonadotrophin (P.M.S.) on the ninth day after the first injection and again three days later has been giving good results without any deleterious side actions (Review, Vet. Rec., 1957; Report, F. & S., 1959; Report, Vet. Rec., 1959).

Œstrogens have also been used for fattening sheep, but have so far proved less successful than in poultry and steers. Further work is required before œstrogens could be recommended for this purpose. The implant has been of 12·0–15·0 mg. size.

Goats may be given œstrogens for the same purposes and in the same dosages as for sheep. Œstrus induced by œstrogens is not usually fertile, but œstrus subsequent to the artificially induced heat should be fertile.

In *sows*, œstrus induced by 5·0–10·0 mg. œstradiol monobenzoate or similar doses of stilbœstrol dipropionate, both given intramuscularly, is usually fertile and the animal should be served as soon as she comes into season. Double service with an interval of 24 hours between the two is advisable.

In the *bitch*, the main indication for œstrogens is in the treatment of 'mesalliance'—unintentional mating. For this purpose, stilbœstrol dipropionate or œstradiol monobenzoate, given subcutaneously or intramuscularly in doses of 10·0–15·0 mg., will prevent pregnancy. The maximum interval after mating frequently stated is 4 days, but experience indicates that a delay of up to ten days is not detrimental to the effect. A great disadvantage is that bitches may remain in œstrus for up to six weeks, and pregnancy has been known to follow service late on in this

period. It may be that injected androgens can be used instead, as with the suppression of pseudo-pregnancy. This would be of great value in small animal practice. Orally administered œstrogens are of no value in averting pregnancy, even in 30·0 mg. doses (stilbœstrol).

Œstrogens—preferably stilbœstrol in doses of 1·0–3·0 mg. daily by mouth—can be used in fat bitches where the fat is laid down due to hypogonadism. It is also of value for urinary incontinence in old or spayed bitches. Œstradiol monobenzoate implants can be used.

In the *dog*, œstrogens are of value for the treatment of anal adenomata, especially where ulceration has occurred, and for causing a regression of hypertrophied prostate glands. For anal adenomata 5·0–10·0 mg. stilbœstrol dipropionate subcutaneously once a week is effective, but causes some increase in thirst and urination: frequently an injection is used initially and is followed by 1·0–5·0 mg. daily by mouth. This latter course is better in the frail old terrier, where overdosing can cause rapid collapse, and death within 24–48 hours. For hypertrophied prostate glands, 3·0–5·0 mg. stilbœstrol by mouth daily is usually adequate. This treatment can be successfully replaced by the use of 15·0 mg. stilbœstrol implants or preferably 20·0–50·0 mg. of implanted œstradiol.

Lactation in bitches and cats can be diminished by the use of œstrogens—10·0 mg. twice with a twelve hour interval in the bitch, and 3·0–5·0 mg. similarly in the cat. Androgens are to be preferred.

Poultry are now frequently caponized (young and old cockerels) by implantation of 15·0 mg. stilbœstrol or combinations of 7·5 mg. each of stilbœstrol and hexœstrol. The implants are introduced at 8 weeks or later, subcutaneously in the neck just below the head so that at slaughter any remaining portion of the implant may be discarded with the head.

Androgens

It is only within the last ten years that synthetic manufacture has enabled the androgens to become economically usable in veterinary medicine. Because of the high doses of methyl testosterone required orally, testosterone itself as an implant, is the most commonly used androgen.

In the *horse*, testosterone is mainly indicated for treating premature ageing of geldings and deficiency of sex drive in stallions. The dosage in both cases is from 3–500 mg. implanted subcutaneously, but it must be stressed that in the stallion testosterone may reduce the production of spermatozoa due to its suppression of the anterior pituitary (F.S.H.) hormone, and it should therefore not be used where sperm production or fertility are suspect.

In the *bull*, the indications are the same as for the stallion and doses are identical.

With these large doses given by implantation adequate activity is only gained by the use of multiple implants, for the surface area of a single implant is not sufficient to provide adequate daily absorption levels. There is also less tendency to wall off a group of implants than a single one,

though this will occur even with a group. Large implants also offer greater manufacturing difficulties.

For the *ram*, *billy goat*, and *boar*, testosterone in 50–100 mg. doses can be used in the same circumstances.

In the *bitch*, testosterone implants of 25·0–100·0 mg. size can be used to eliminate pseudo-pregnancy, especially when this is associated with excessive lactation. It is far superior to œstrogens for this purpose. Similar doses may be used to suppress œstrus indefinitely.

In the *dog*, testosterone implants are ideal for treating senile alopecia with feminization: if associated with testicular tumours, testosterone is still indicated. Other indications are hypogonadal obesity and slow healing fractures. The dosage in all cases is 25·0–100·0 mg. in 1, 2 or 4 individual implants (25·0, 50·0 and 100·0 mg. sizes).

For *cats*, testosterone is successful in treating the majority of so-called fish eczema cases in females and castrate males. It may be used to suppress œstrus in the female and to prevent urine retention with the formation of wax-like material which obstructs the urethra. Doses are 25·0 mg. as an implant in all cases except œstrus-suppression, where the dose needs to be 50·0–100·0 mg.

Progesterone

The main indication for the use of progesterone is for the maintenance of pregnancy where abortion has occurred habitually. Abortion of hormonal origin may occur early in pregnancy due to failure of the corpus luteum to secrete sufficient progesterone to allow implantation and maintenance of the embryo *in utero*, or later in pregnancy when the chorion fails to maintain an adequate level of protecting hormones in those species where the corpus luteum regresses before pregnancy is complete. In these cases progesterone implants are ideal. Doses for this purpose are: mare, cow and heifer: 300–400 mg. in the first third of pregnancy, or 200–300 mg. in the second two-thirds of pregnancy; bitches: 25·0–100·0 mg. implanted at the time of service. Day (1957) reports good results in a small number of mares following implantation of 150–300 mg. progesterone between the 130th to 150th days of pregnancy. The implants were removed about two weeks before the expected date of parturition.

Progesterone injected intramuscularly at the daily rate of 100·0 mg. in cattle, 50·0 mg. in the sow, 10·0 mg. in the ewe, 1·0–1·5 mg./lb. (2·2–3·3 mg./kg.) in the bitch, and in the cat 2·5–5·0 mg. every three days, will delay œstrus so that a group of females can be served within a short period. Œstrus will begin within a few days of stopping the injections. This same treatment has been used in racing greyhounds, in which œstrus means a long enforced rest from racing. Progesterone implants are more satisfactory if prolonged suppression is required and may be used as an alternative to testosterone implants in the bitch and queen cat. The dosage for both bitches and cats is 50·0–100·0 mg.

Implants of 50 mg. have been used in cattle for the treatment of cystic ovaries where luteinizing hormone has failed.

Toxicity. It should be remembered that œstrogens in the female, if injudiciously used, will cause the development of cystic ovaries and if continued, ovarian hypoplasia. The former condition will result in nymphomania with all its difficulties and dangers. In the male, œstrogens in repeated doses will cause feminization and in large doses an imbalance in water metabolism, with acute thirst and polyuria, pruritis, and eczema (in the dog), and larger doses still may cause collapse and death.

Androgens have masculinizing actions in the female but their toxic effects are not known. Progesterone in the female will cause excessive luteinization and the formation of luteinized follicles which may be extremely difficult to eliminate.

The Gonadotrophins. The anterior pituitary gland in the normal female is responsible for the cyclic changes of the ovary from follicular phase to luteal phase and back again. In the male the cyclic changes are not apparent but specific effects on androgen production and on sperm formation are exerted by analogous hormones. The two hormones involved are the *follicle-stimulating hormone*, which stimulates follicular development in the female and sperm development in the male, and the *luteinizing hormone* (female) or *interstitial cell stimulating hormone* (male), which is responsible for ovulation and development of the corpus luteum in the female and the production of testosterone by the interstitial cells of the testes in the male.

These two hormones have been isolated from pig and sheep pituitary glands, but this source is not economically feasible. However, it has been found that similar hormones are produced by the chorion and excreted in the urine of pregnant women (luteinizing hormone or chorionic gonadotrophin) and by the mare, possibly by special areas in the endometrium, and obtained in the serum between the 60th and 75th days of pregnancy (follicle-stimulating hormone, pregnant mare's serum, or serum gonadotrophin). Each of the preparations from these sources contains small quantities of the other.

Both these gonadotrophins are white, though the chorionic one may be fawn, amorphous powders, which are soluble in water. They are kept in sealed ampoules as powders for solution in water immediately before use. The powders are assayed biologically: Serum Gonadotrophin, B.Vet.C. should contain not less than 100 units of follicle-stimulating activity per mg., while the Chorionic Gonadotrophin, B.Vet.C. should contain not less than 400 units luteinizing activity per mg.

Uses. In *horses*, the gonadotrophins are used mainly for achieving ovulation in the female, for the treatment of cryptorchidism in the foal and yearling, and for deficiencies in sperm production and sex drive in the stallion.

In *mares* which fail to come into œstrus and yet on examination have follicles present in one ovary, œstrogens, in the form of stilbœstrol, œstradiol monobenzoate, or dienœstrol, in doses up to 15·0 mg. intramuscularly, can be used and sometimes cause spontaneous ovulation with an œstrus period of 24–48 hours. This cannot be relied upon (Day, 1957) and chorionic gonadotrophin in doses of 1500 i.u. given subcutaneously or intramuscularly, repeated if necessary two or three days later, is a more reliable treatment; œstrus usually follows, with ovulation about 24 hours after the second injection. An alternative is to give serum gonadotrophin in doses of 2000 i.u. intramuscularly daily for four days, repeating the treatment 14 days later if necessary. Day (*loc. cit.*) indicates that ovulation may not be accompanied by œstrus if the intravenous route is used for the administration of chorionic gonadotrophin, but follows after a normal inter-œstrous period of 16–21 days.

In prolonged œstrus, usually met in the early part of the season, and in mares where early ovulation is required to give the best chance of conception, chorionic gonadotrophin may be given intravenously on the day of service, but it is essential to ensure that a follicle of not less than 3·0 cm. in diameter is present in the ovary (Day, *loc. cit.*). Doses may be varied from a minimum of 1500 i.units, but where a number of follicles are present making a grape-like ovary, Day has recommended from 3000 to 5000 units. Ovulation should follow within 40 hours.

Nymphomania in mares may be treated with chorionic gonadotrophin given intravenously in doses of 2000–3000 i.units and repeated one month later. The rationale of this treatment is not apparent, for it has been pointed out that nymphomania in the mare is not associated with cystic ovaries (Arthur, *loc. cit.*).

Where lactation has failed after parturition, luteinizing hormone in doses of 2000–3000 units may be given and repeated 24 hours later when necessary.

In the *male*, cryptorchidism in the foal or yearling can be treated with luteinizing hormone given intramuscularly twice weekly for 4–6 weeks, and where this is associated with genital hypoplasia 200 mg. of testosterone implanted subcutaneously should be of help. It is important to make sure that there is no mechanical obstruction to testicular descent before commencing treatment. There are, of course, ethical and genetic reasons why treatment of any description, short of castration, should be avoided.

In the stallion which is 'slow', luteinizing hormone may be used to stimulate testosterone production by the interstitial cells of the testicle. By using this hormone there is less likelihood of injuring spermatogenesis, for the small contaminating amounts of follicle-stimulating hormone should likewise stimulate spermatogenesis. Day (*loc. cit.*) has postulated the use of testosterone implants in this context and it is probable that small implants would be satisfactory. A 100 mg. implant, for example, should provide a daily intake of 1·1 mg. testosterone over a period of

about 90 days. These figures will vary with the individual and site of implantation, but they may be taken as an approximate guide. Up to 500 mg. have been suggested as a dose. The possible effect on sperm production is not exactly known, but it has been stated (B.P.C., 1954) that small amounts of testosterone will stimulate sperm production. Too much reliance should not be placed on this statement, for it is definitely known that reasonable doses have reduced sperm production.

Impaired spermatogenesis can be treated with serum gonadotrophin in doses of up to 1500 units twice weekly by intramuscular injection over a period of 3–6 weeks.

In the gelding, where premature ageing can be troublesome, testosterone implants in doses up to 400 mg. will prove adequate for periods of about three months.

In *cattle*, the indications for the use of gonadotrophins are similar to those in the horse.

Luteinizing hormone (chorionic gonadotrophin) may be used in sub-œstrus—blind bulling or silent heat—by intramuscular injection, in ovulatory failure or to ensure ovulation given by intravenous injection during œstrus, and in place of progesterone in early non-specific abortion, when weekly intramuscular injections are required for the first month or so after service. Doses of 1000 to 1500 i.units are required in these cases. In nymphomania, associated as it usually is with cystic ovaries, 1500 to 3000 units given intramuscularly and repeated after a month may help, especially if assisted by expressing or puncturing the larger cysts. Chorionic gonadotrophin may also prove effective in the treatment of metritis subsequent to parturition and complicated by failure to involute. Intramuscular injections daily, or on alternate days, of 1000–1500 units should be continued until the discharge clears. In the bull chorionic gonadotrophin in doses of 500 i.units given by intramuscular injection twice weekly will promote the descent of the testicles. Treatment should continue for 4–6 weeks, when a short period of a few weeks should be allowed before repeating the treatment. This is necessary for observation of results and to allow the stimulatory effects on the rest of the hormonal system to be dissipated. In genital hypoplasia, up to 200 mg. testosterone in the form of implants can be used. In lazy bulls, where other causes have been eliminated, chorionic gonadotrophin in doses of up to 1000 i.units can be given, or up to 500 mg. of testosterone may be implanted, but the possible effects on spermatogenesis must be considered, especially in the latter case. Where infertility is related to the quantity and quality of spermatozoa produced, up to 1500 units of serum gonadotrophin may be given twice weekly by intramuscular injection for up to six weeks.

In *sheep*, where twinning and triplets are, apart from the possibility of pregnancy toxæmia, less dangerous and sometimes even desired by the farmer, the use of serum gonadotrophin will increase the production of follicles and improve the conception rate. Single doses of 500 to 1000 i.units should be given intramuscularly between the 12th and 15th days

of a three week cycle. Cryptorchidism may be treated as in other species, using doses of 500 i.units chorionic gonadotrophin, whilst deficient sex drive requires similar doses of the same compound given in the same way. Testosterone implants used for this latter purpose should not exceed 100 mg. in size. *Billy goats* may be similarly treated. In the *nanny* out of season, induced œstrus will follow the injection of two intramuscular doses of 1000 i.units serum gonadotrophin given with an interval of 24 hours—œstrogens have also been mentioned in this context. Where non-ovulation is suspected as the cause of returning to service, up to 500 i.units of chorionic gonadotrophin may be given on the day of service.

In *pigs* the details are similar to those for sheep and goats. Anœstrus in the sow may be terminated with 1000 units of serum gonadotrophin intramuscularly (or œstrogens); non-ovulation can be treated with 500 i.units on the day of service, and failure of lactation after farrowing may be countered by two 500 i.unit subcutaneous doses of chorionic gonadotrophin given with a 24 hour interval: pituitary injection (posterior lobe) will give more rapid response but the effect may not be so sustained. In the boar, chorionic gonadotrophin is suitable for treating cryptorchidism and deficiency in sex drive, using the doses given for the ram, whilst spermatogenesis may be stimulated by using alternate 500 i.unit doses of chorionic and serum gonadotrophins at weekly intervals.

In the *bitch*, ovulation may be induced by two intramuscular doses of chorionic gonadotrophin given with an interval of two days between doses. The usual maximum dose is 500 i.units. Œstrus may be induced by the injection of up to 200 i.units of serum gonadotrophin daily for three weeks, followed by up to 300 i.units of the chorionic gonadotrophin on the day of service. Failure of lactation after parturition may be treated with up to 500 i.units of chorionic gonadotrophin given intramuscularly and repeated 24 hours later if necessary. Chorionic gonadotrophin may also be used in pyometra, but the effects are not sufficient to merit an unreserved recommendation: doses used have not exceeded 500 i.units daily. Chorionic gonadotrophin can be used to terminate or suppress œstrus, using up to 250 i.units intramuscularly: progesterone implants are probably superior.

In the *dog*, cryptorchidism responds very well to chorionic gonadotrophin in doses up to 500 i.units twice weekly for up to six weeks, but not infrequently spectacular results have occurred after the first two or three injections. If genital hypoplasia also exists, testosterone propionate in 5·0 mg. doses intramuscularly twice a week will be beneficial. Stud dogs which are sluggish and when non-hormonal causes have been eliminated may, as in other species, benefit from chorionic gonadotrophin in 200 i.unit doses twice weekly for up to six weeks; testosterone implants of from 25·0 to 100·0 mg. sizes may also be used, but it is likely that implants of 100·0 mg. will be too large and 50·0 mg. should normally not be exceeded.

CHAPTER 19

AGENTS AFFECTING THE SKIN

(i) INTRODUCTION

COMPOUNDS which have an action on the skin can be applied in various forms, as powders, aqueous solutions and suspensions, alcoholic solutions and suspensions, mineral oil and fat solutions and suspensions, and vegetable and animal oil or fat solutions and suspensions.

In general, their degree of action is related to their position in this scale, for drugs applied as powders have only a superficial action unless applied to wounds, whereas the same compounds incorporated in animal fats could have a deep penetrating action and might be absorbed in sufficient quantities to have a systemic and even a toxic effect.

Iodine compounds provide an illustration. Iodine is not normally applied to the skin in powder form but Aqueous Solution of Iodine, B.Vet.C., Lugol's iodine, which contains 5 per cent. of iodine is of very little use externally. The Weak Solution of Iodine, B.Vet.C. and the Strong Solution of Iodine, B.Vet.C., which are 2½ per cent. and 10 per cent. alcoholic solutions respectively, are sufficiently active to be used as counter-irritants. The strong solution is frequently used as a penetrating counter-irritant in both human and veterinary medicine in the treatment of chronic inflammations of structures below the skin. Swollen lymph glands and chronic, suppressed abscesses, which may occur in strangles in the horse, bursitis, and synovitis, have all benefited from such treatment. Iodine dissolved in mineral oil, and ointments with bases incorporating animal fats, have a stronger effect still. The mineral oil solutions, if applied to large areas or too frequently, will produce iodism—iodine poisoning—within a few days.

It follows from this that the form and method of applying drugs externally must be carefully chosen according to the degree and type of action required.

The effect of concentration is, of course, additional to these two factors. In most cases, higher concentrations will produce actions differing from those of lower concentrations in degree only, but in some cases the clinical results may appear totally different. The application of mercuric iodide in a mineral fat base at a concentration of 1 : 64 will cause a slight reddening of the skin (rubefacient action) and will also have a fungicidal effect. The same drug in a concentration of 1 in 4 in the same base, or an animal fat base, will produce severe blisters and, in certain circumstances,

sloughing of the skin and scar formation. Pathologically, however, this vesication is only an advanced stage of an action, the early stage of which is dilatation of the superficial blood vessels and congestion—a rubefacient action. Another example of actions apparently varying according to concentration is that of mercuric chloride or corrosive sublimate. In concentrations of 1 : 10,000 mercuric chloride acts as an antiseptic and bactericide; in concentrations higher than 1 : 500 the compound destroys tissues and will act as a deeply penetrating caustic. These two effects, however, are different degrees of a single action of mercuric chloride, namely, that of poisoning cell protoplasm.

There are exceptions to this rule of concentrations, but most of them concern those substances the actions of which are due more to physical attributes than to chemotherapeutic effect. Thus glycerin in dilute concentrations exerts an emollient or softening and soothing action on tissue, whereas in strong concentrations it exerts a high osmotic pressure and will have a 'lymph lavage' effect, particularly in wounds and on abraded surfaces. This 'lymph lavage' action consists of a withdrawal of serous fluid from the tissues immediately around the area of application in an attempt to neutralize intracellular and extracellular pressures. The phenomenon is typical of all substances exerting high osmotic pressures, such as sodium chloride, other salts, and sugars.

Caustics

These are agents which destroy tissue. They may be used to destroy excessive granulation, to destroy indolent granulation with the aim of stimulating normal growth, to destroy minor superficial tumours—warts, and to destroy horn buds in calves. They were once extensively used in conjunction with wooden clams for castration of cattle and horses, but this practice is almost entirely discontinued in favour of surgical methods.

Silver nitrate, phenol, and antimony trichloride, are in frequent use, whilst podophyllin resin and glacial acetic acid are also occasionally used for the removal of warts (carbon dioxide is rarely used for this purpose in veterinary medicine.)

Nitric acid has been used for acid firing, but though there are modern advocates, this method of counter-irritation is not liked because of the difficulty of limiting the action. The possibility of a severe caustic effect with sloughing and scarring is always present.

Caustic soda and *caustic potash* are used for their caustic effect only for the destruction of horn buds of calves. The caustic is often made into a paste, of which Vienna Paste is an example; this usually consists of equal parts of potassium hydroxide and quicklime, but other pastes are also used in which the quicklime is replaced by chalk and similar diluents.

Mercuric chloride, though a caustic, is not used as such because of its dangerous corrosive action. (A corrosive action is one where cell protein is destroyed but either remains in solution or is redissolved in an excess

of the agent, thus allowing penetration of the corrosive substances to the underlying tissue. Penetration of the corrosive will continue almost indefinitely).

Phenol is used occasionally for cautery of corneal ulcers, but the difficulty of restraining the action has limited its popularity in the veterinary field, where silver nitrate is normally the drug of choice. *Liquefied Phenol*, B.Vet.C., consisting of 80 per cent. phenol in distilled water, is applied by touching the ulcer with a swab moistened in the solution. Applied to the skin, phenol has some corrosive action, forming a white eschar which turns red and then brown. Anæsthesia of nerve endings occurs which can disguise the fact that necrosis of the tissue is taking place. The dead tissue sloughs without pus formation. Phenol burns are best treated with glycerin which considerably reduces the caustic effect.

Antimony Trichloride, B.Vet.C. is a very deliquescent, colourless crystalline substance which is incompatible with water, giving an insoluble white powder, the oxychloride. It is soluble in dilute hydrochloric acid, absolute alcohol, chloroform, and ether.

The compound is an ingredient of disbudding preparations for calves. It is combined usually with salicyclic acid to soften the keratin layers of the skin in concentrations of about 28 per cent. chloride with 5–7 per cent. acid. Solutions in oil are available, but these fluid preparations are difficult to control and the more suitable collodion vehicle is most frequently used. Collodion of Antimony Trichloride, B.Vet.C. is the official example. The volatile components of the collodion evaporate following application, leaving the active agents applied to the area with a thin film of nitrated cellulose (pyroxylin) covering and ensuring adherence of the caustic. Three things are important to remember with these caustic collodia: (1) The material will not adhere to wet or greasy surfaces. It is therefore necessary, before applying the collodion, to clip, clean and defat the horn bud area with ether or chloroform. Application is best achieved by a short stiff bristled brush of the type used for stencil painting. (2) Normal skin surrounding the horn bud should be protected by the application of a protective greasy ointment such as zinc oxide ointment, and (3) Disbudding, to achieve the best results, should be carried out within 48 hours of birth, and treatment should be thorough.

Podophyllum Resin, B.Vet.C. is obsolete as a drastic purgative but it is occasionally used in an oily vehicle as a paint for warts. Most formulæ are similar to *Paint of Podophyllum*, B.Vet.C. which consists of 25 per cent. w/v of the resin dissolved in liquid paraffin. Care should be taken, (1) to see that the material is not applied to normal skin of either the operator or patient, (2) to prevent licking of the area dressed and (3) to prevent contact with the eyes.

Silver Preparations

The preparations of silver used in veterinary practice consist of Silver Nitrate, B.Vet.C. and various proteinates which depend for their activity

on the ionization of the compounds. There are two proteinates in the Codex—Silver Protein, B.Vet.C. and Mild Silver Protein, B.Vet.C., the former contains 8 per cent. w/v and the latter about 20 per cent. w/v metallic silver. 'Lunar caustic' is a caustic pencil formed by fusing silver nitrate with a proportion of potassium nitrate.

These silver compounds are mostly used for the treatment of ocular conditions. The nitrate is used for cauterization of wounds and ulcers, including those of the cornea, as well as for conjunctivitis and keratitis, although these last conditions require less drastic treatment and the organic compounds are preferred.

Silver Nitrate, B.Vet.C.

Consisting of colourless sheet crystals with no odour and a bitter metallic taste, silver nitrate is very soluble in distilled water but less soluble in the organic solvents. It is incompatible particularly with halogens, proteins, and tannic acid.

Actions and Uses. The action of silver nitrate is related to its incompatibilities, in that it precipitates protein as silver proteinate. When applied to tissue not protected by keratin it will therefore precipitate the protein in all the superficial cells. These superficial cells will be destroyed, but those cells in the deeper layers will be protected by this film of almost insoluble proteinate. Some of the proteinate will slowly redissolve and ionize to release minute amounts of silver ions, which cause a certain amount of counter-irritation and stimulate healing. At the same time these slowly released silver ions have an antibacterial or antiseptic effect. Any silver compound thus has an effect which is proportional to the concentrations of the dissociated silver ions.

Strong silver nitrate, usually in crystal or 'lunar caustic' form, is used to cauterize corneal ulcers and small superficial wounds; also to remove small warts, although occasionally the nitrate appears to stimulate the return of the wart. In concentrations of 1 per cent. in distilled, chloride-free water, sometimes combined with about ½ per cent. zinc sulphate, silver nitrate has an astringent effect and is used as an eye lotion or eye drops for the treatment of general keratoconjunctivitis. This condition is met with as 'distemper eye' in dogs and in the rickettsial condition of cattle—'New Forest disease'.

Silver Protein Compounds

In many cases silver nitrate is too irritant and caustic. Following the realization that silver nitrate when combined with protein became less caustic and corrosive, compounds of protein and silver were prepared.

These protein salts of silver are all relatively non-irritant brown powders which are slowly soluble in water, but insoluble in the organic solvents. They contain various quantities of silver—the concentrations of the official preparations have already been mentioned—and their activity is

whereas the same salt at a strength of 1 in 4 in lard will have an effect only just short of pustulation. A change in concentration alone will not achieve such a wide variation.

When volatile drugs are in use bandaging will, by preventing evaporation, intensify the effect of the counter-irritant. This can be demonstrated by bandaging an area immediately after the application of *White Liniment*, B.Vet.C. which is a commonly used stimulating embrocation. The ammonia and turpentine cannot evaporate and blistering of the area can result.

Further factors involved in the use of this group of compounds are the amount of friction used and the duration of application. Apart from an increased circulation which normally follows, vigorous rubbing will massage the dressing into the skin. This penetration will increase proportionally to the vigour and duration of massage, and the degree of effect will similarly increase.

Iodine

Iodine and its preparations have been used as rubefacients for many years by both the medical and veterinary professions, but more recently the popularity of these compounds with the veterinary profession has declined. Iodine possesses some advantages, for its action is persistent due to its take up by the cornified layers of skin and its slow release. Its action is also mild and vesication only follows repeated applications of strong alcoholic solutions.

For strong counter-irritation the accepted method is to paint the area with Strong Solution of Iodine, B.Vet.C. (a 10 per cent. alcoholic solution) or Churchill's iodine (a 6·5 per cent. alcoholic solution) on alternate days until signs of desquamation appear.

For weak counter-irritation the Weak Solution of Iodine, B.Vet.C. containing 2·5 per cent. iodine in alcoholic solution can be painted on daily or on alternate days, but Non-staining Iodine Ointment, B.Vet.C. is less irritating. This ointment is an organic iodine complex prepared by dissolving 5 per cent. iodine in arachis oil and making up to 100 per cent. with yellow soft paraffin. A similar ointment containing 5 per cent. methyl salicylate is described in the Veterinary Codex. This will be slightly more active as a counter-irritant. The ointments are less irritant than the alcoholic solutions and should be applied at least once daily.

The tinctures are usually used for painting areas of skin overlying swollen glands or chronically inflamed soft tissues, and though the ointments may also be used for this purpose they are of more value for massaging into affected joints, bone lesions, and tendon or ligament lesions.

On occasions, Aqueous Solution of Iodine, B.Vet.C., known as Lugol's iodine, which is a 5 per cent. iodine solution in water with potassium iodide to assist solution, has occasionally been injected, following drainage, as a counter-irritant into the lesion in cattle known as 'hygroma'. This is a chronic bursitis of the carpus due to repeated knocking on the manger

during rising and lying down. No doubt counter-irritation plays some part when this preparation after dilution is injected into the uterus or vagina in the treatment of infertility in the cow, and also when injected into peritoneal cavity in the obsolete treatment of peritonitis. In neither of these cases is the treatment wholly accepted as rational.

Ammonia

Ammonia and its preparations are probably the compounds most frequently used for achieving a rubefacient effect. They are non-corrosive and non-persistent, but nevertheless are strongly irritant and if bandaged on can cause severe blistering. The compounds, however, are rarely bandaged on but are applied in an emulsified form as a liniment—for external application with friction. Ammonium hydroxide, in the form of Strong Solution of Ammonia B.Vet.C., ammonium carbonate, and ammonium chloride, are all used, sometimes together, frequently with other drugs. Volatile oils such as camphor, methyl salicylate (oil of wintergreen), and turpentine, are commonly used with ammonium compounds.

The following are representative of the many formulæ in common use:

℞

Ammonium carbonate	120 gr.	8·0 G.
Oil of turpentine	1 fl. oz.	30·0 ml.
Soft soap	½ oz.	15·0 G.
Water	to 8 fl. oz.	to 0·25 L.

or,

℞

Strong solution of ammonia	1 fl. oz.	30·0 ml.
Rape oil	to 8 fl. oz.	to 0·25 L.

To this latter prescription may be added ½ fl. oz. of turpentine should a stronger action be required.

A camphorated liniment, containing 12·5 per cent. w/v of camphor with 25 per cent. v/v of strong solution of ammonia in 90 per cent. industrial methylated spirits, is also frequently used.

These liniments are best applied to areas clipped of hair, but clipping is not essential.

Other details and actions of ammonia and its preparations are as follows:

Strong Solution of Ammonia, B.Vet.C. is a 33⅓ per cent. solution of ammonia gas in water. It is colourless, with a pungent, characteristic odour and taste, and is strongly irritant.

Actions and Uses. Apart from the external actions and uses already mentioned, this compound has only two other uses. The first is as a stimulant in threatened respiratory collapse, when the stopper of an ammonia bottle is held under the animal's nose. The small amounts

inhaled are sufficient to cause marked irritation of the nasal and respiratory mucosæ. This irritation initiates reflexes which result in increased respiration and also affects the blood pressure acting via the respiratory and vasomotor centres respectively. Other stimulants such as the analeptics leptazol, nikethamide, picrotoxin, and amphetamine, are most active and more dependable. No ammonia solution should contact the mucous membranes otherwise tissue may be damaged and sloughing might follow.

The other use is to prepare *Dilute Solution of Ammonia*, B.Vet.C. which contains only 10 per cent. of ammonia gas. It is prepared by adding two parts of distilled water to one of the strong ammonia solution. It has all the characteristics of the strong solution, but to a lesser degree.

Actions and Uses. The dilute solution is of relatively little use externally but can be used internally as an alternative to ammonium carbonate. These two compounds act internally as 'diffusible stimulants'. The term is now unfashionable but was used to describe a drug of a volatile nature which was rapidly absorbed and which caused an irritation of the gastric mucosa during absorption; this irritation initiated transient reflex stimulation of the respiratory and vasomotor centres and systems. Aromatic spirits of ammonia is a combination of these same two compounds with 70 per cent. alcohol and volatile oils in water. It is used for the same stimulatory purpose. Ammonia has a strong antacid action and is widely used in preparing drenches for cattle. It has been claimed to promote gastric, ruminal, and intestinal activity, but this effect has not so far been proved experimentally; nevertheless, the compound is widely used for this purpose. Some carminative effect is also attributed to the compound. Following absorption, the major part of all ammonium compounds is converted into urea and acts as a diuretic during excretion. Small amounts are excreted into the lungs and have a slight expectorant and diaphoretic effect.

Dosage and Administration.

Horse:	120–240 m. (8·0–16·0 ml.)
Cow:	240–480 m. (16·0–30·0 ml.)
Sheep and Pig:	10–60 m. (0·6–4·0 ml.)
Dog:	5–15 m. (0·3–1·0 ml.)

The compound is resented by dogs and therefore rarely used in this species. It is administered as a drench diluted about twenty times in water or starch gruel and similar demulcents.

Toxicity. Where overdosage has occurred, treatment consists of administration of organic acids—citric or lactic acid, or borax initially, followed by demulcents. Honey and borax electuaries are suitable. (Ammonia has been used to separate fighting dogs. It should not be used for this purpose because of the danger both to combatants and to human attendants. A strong inhalation of ammonia can cause an acute paralysis

of respiration with at least a temporary black-out, partial asphyxia and, subsequently, pneumonia.)

Ammonium Carbonate, B.Vet.C. 1934 consists of a mixture of ammonium bicarbonate and ammonium carbamate. It is a white crystalline powder with a very strong smell of ammonia which decreases with exposure. It has a pungent taste and is slowly soluble in water. *Ammonium bicarbonate*, B.Vet.C. is preferred pharmaceutically because of its greater stability and relatively slight ammoniacal odour which remains constant. The carbonate, however, is preferred by clinicians and is very widely used in practice.

Actions and Uses. The carbonate and bicarbonate have all the external actions of the official ammonia solutions but the former are more persistent and have a more prolonged effect. Internally, the actions of these four compounds are similar. The carbonates are thus antacids, alkaline stomachics, possibly carminatives, and expectorants. They stimulate the gastro-intestinal mucosa and this results in increased respiratory and cardiac activity—they are diffusible stimulants. They are reputed also to increase intestinal tonus and to stimulate intestinal activity whilst exerting an antispasmodic effect. As with ammonia solutions these last details have not yet been proved experimentally.

Dosage and Administration.

Horse and Cow:	60–240 gr. (4·0–16·0 G.)
Sheep and Pig:	10–30 gr. (0·6–2·0 G.)
Dog:	2–10 gr. (0·12–0·6 G.)

Both carbonates are given orally as drenches and should be well diluted.

Ammonium chloride, B.Vet.C. is a white crystalline solid with a saline taste and no smell of ammonia. It is well known as sal ammoniac and as such is used in the making of simple electric batteries.

Actions and Uses. Externally, ammonium chloride has been included in liniments, partly for its irritant properties and partly for its stabilizing action on the emulsions. Internally, this salt has already been mentioned as a diuretic and urinary acidifier (Chapter 17), but it also has a weak expectorant action and some diaphoretic effect.

Dosage and Administration are similar to those of the carbonates.

The *Strong* and *Dilute Solutions of Ammonium Acetate*, B.Vet.C. are used internally because of actions similar to those of ammonium chloride. The actions, however, are very mild and the solutions are used with similar or more active drugs, a common one being Spirit of Nitrous Ether, B.Vet.C. (Sp. Æther Nit.) which has similar actions—mild diuretic,

diaphoretic, febrifuge and, additionally, carminative, antispasmodic, and stimulant actions. (Both these products are falling into disuse.) Most of the ammonium radicle is converted into urea and excreted as such, whilst the acetate radicle is usually metabolized.

Volatile Oils

Most volatile oils will cause a dilation of cutaneous blood vessels due to local irritation, and also will cause a slight local anæsthesia which gives them an anodyne (pain killing) effect. Not all volatile oils are suitable rubefacients but camphor, turpentine, and mustard oil are frequently used with good effect.

Camphor, B.Vet.C.

This stearoptene is a white crystalline substance obtained from a Sino-Japanese tree and purified by sublimation. It is also prepared synthetically. It has all the properties of volatile oils and is slightly soluble in water but freely soluble in normal organic solvents and fixed oils. The odour is characteristic and the taste is pungent followed by a cool feeling due to slight anæsthesia.

Actions and Uses. Externally, camphor is a mild rubefacient and anodyne. It is applied to the skin as:

(1) *Liniment of Camphor*, B.Vet.C., commonly known as 'camphorated oil', which is a 20 per cent. solution of camphor in arachis oil.
(2) *Ammoniated Camphor Liniment*, B.Vet.C., already mentioned as containing 12½ per cent. camphor, and
(3) *Liniment of Soap*, B.Vet.C. (Lin.Saponis) which contains 4 per cent. of camphor with 8 per cent. soft soap in alcohol and water.

These liniments should be applied only to chronic conditions, with vigorous friction.

Internally, the actions of camphor are subject to doubt. Following *oral* administration, camphor causes mild gastro-intestinal irritation. This causes;

(1) Reflex expectorant effects.
(2) Reflex cardiac stimulation.
(3) Carminative and antispasmodic effects.

The reflex expectorant action is supported by the slight local effect of the small quantities which are excreted by the lungs in the form of *camphorol* following absorption and oxidation. A more effective way of achieving this action is by inhalation of the volatilized compound: volatilization is achieved either by floating camphor on hot water, or more easily by applying camphorated oil to the animal's chest and forelegs, when the body heat is utilized.

Camphor is frequently administered orally in the form of *paregoric* or *Camphorated Tincture of Opium*, B.Vet.C.

Following *intramuscular injection*, camphor has been reputed to have an analeptic action, and the substance has therefore been used to treat shock and collapse, mainly in large animals. Solutions of 10–20 per cent. camphor in ether and oil have been injected intramuscularly for this purpose, but experimental work has not established that non-toxic doses will cause anything but a very slight heart and respiratory stimulation which is possibly due to reflex action following local irritation. Analeptics such as *Dexamphetamine Sulphate*, B.P.C. are preferred for these purposes.

Excretion. Camphor is oxidized in the body to camphorol and then conjugated with glycuronic acid. Irritation during excretion results in slight expectorant and diuretic effects.

Dosage and Administration.

Camphor, B.Vet.C.

Horse and Cow:	60–240 gr. (4·0–16·0 G.)
Sheep and Pig:	5–45 gr. (0·3–3·0 G.)
Dog and Cat:	1–10 gr. (0·06–0·6 G.)

Camphorated Tincture of Opium, B.Vet.C.

Horse and Cow:	1–4 fl. oz. (30·0–120·0 ml.)
Sheep and Pig:	60–120 m. (4·0–8·0 ml.)
Dog:	30–60 m. (2·0–4·0 ml.)

Liniment of Camphor, B.Vet.C. by intramuscular injection.

Horse and Cow:	120–240 m. (8·0–16·0 ml.)
Dog:	5–10 m. (0·3–0·6 ml.)

Camphor, when administered orally, should be well diluted and preferably mixed with a demulcent.

Toxicity. The symptoms following oral overdosage of camphor are mainly those of gastro-intestinal irritation, hyperexcitability, convulsions, and nephritis with a low urine output. These, with the exception of the nervous system symptoms, are what would be expected from any volatile oil. Treatment is symptomatic. Toxicity is most likely to be seen in the dog but is rare even in that species.

Methyl Salicylate, B.Vet.C.

This salicylate is a colourless or pale yellow liquid with a characteristic odour and taste. It has the solubilities of a volatile oil.

Methyl salicylate forms the greater part of oil of wintergreen or gaultheria and is dispensed wherever this oil is prescribed.

Actions and Uses. Though methyl salicylate possesses most of the properties of salicylates, it is not normally given by mouth. Externally, it has a mild rubefacient and anodyne action and has been used as such in ointments at a concentration of up to 10 per cent. The Veterinary Codex

details a liniment which contains 25 per cent. methyl salicylate in a bland oil, a 5 per cent. methyl salicylate ointment and a compound ointment of 5 per cent. methyl salicylate in non-staining iodine ointment. Kaolin Poultice, B.Vet.C. contains 0·2 per cent. methyl salicylate, more to give the preparation an odour than to exert any pharmacological action; it is more for this purpose that methyl salicylate is now used.

The compound was used widely as a fly repellant but better preparations are now available (e.g. dimethylphthallate). It has also been used in an attempt to make bitches in season less attractive to dogs, but is even less effective than it is as a fly repellant. Note: recent reports indicate that aerosol preparations are more successful than other presentations (Hopson, 1959).

Capsicum or Cayenne pepper has also been used as a counter-irritant, but the irritant principle capsicin causes pain and severe prolonged irritation. The compound is now rarely used.

Black Mustard, B.Vet.C. (Sinapis Nigra)

This, when ground, is used in varying proportions with white mustard to make mustard flour.

Actions and Uses. If made into a paste with luke-warm water (NOT HOT, or the enzyme may be inactivated), an enzyme *myrosin* reacts with a glycoside *sinigrin* to form a volatile oil, allyl isothiocyanate, *Volatile Mustard Oil*, B.Vet.C. This oil is a very rapidly acting irritant and should not be left in contact with the skin for longer than 1 hour, otherwise vesicles and pustules may be produced. If the paste is applied to skin between two layers of gauze the application may be removed after each 15 minutes or so to examine the degree of reddening. Blisters produced by mustard are slow in healing and mustard should therefore only be used as a rubefacient. It has been used in pneumonic conditions, but its use in this context is obsolete.

Black mustard has also been used as an emetic in dogs at the rate of one tablespoonful in a cup of warm water. Vomition does not always occur and concentrated salt solution is preferable where only household agents are available.

The rubefacient action of *Turpentine*, B.Vet.C. has already been briefly described on p. 75. This volatile oil is usually incorporated with other volatile rubefacients, particularly ammonium compounds, to give the preparations greater effect. It is usually applied in liniment form, White Liniment (Linimentum Alba), B.Vet.C. being a typical example.

Cantharides

Widely known as 'Spanish fly', these dried beetles are crushed to prepare a brown powder with iridescent green particles. This powder contains an

irritant active principle which is chemically a lactone of cantharidic acid, and is officially recognized under the name of *Cantharidin*, B.Vet.C. This compound is a colourless, odourless, crystalline substance.

Cantharides ointments are standardized by their cantharidin content and commercially available samples contain from 0·01 per cent. to 0·16 per cent. of cantharidin. Liquor Epispasticus or Blistering Liquid, B.Vet.C. contains 0·4 per cent. cantharidin in oil, acetone, and resin, but the concentration and difficulty of controlling fluid blisters makes this preparation unpopular.

Actions and Uses. Widely known as an aphrodisiac, its action as such is not very efficient and though it causes engorgement of erectile tissue in the male and female, there is no increase in sexual desire. There is therefore no excuse for its internal administration.

Externally, cantharides preparations cause intense irritation, with a rubefacient action when dilute, and blistering effect in stronger concentrations. The blisters formed are large in area but penetration is relatively slight and inflammatory reaction is therefore not very deep. Cantharides and its derivatives are often combined with Red Mercuric Iodide, B.Vet.C. to make use of the diffuse superficial effect of the former with the more circumscribed but penetrating effect of the latter. These combined blisters are very powerful and should be used circumspectly.

Administration. As with the application of all blisters, the affected area should be clipped and a protecting and limiting application of a bland zinc ointment smeared around the area. Special attention should be shown to protecting the inner angles of joints where misapplication may cause severe damage in the creased skin areas. The blistering ointment should be rubbed in for five or ten minutes, depending on the degree of action required, and then any excess of ointment removed by rubbing with cotton wool or a cloth. Blistering will occur after a minimum of three hours and will appear more rapidly in thin skinned animals and those where strong concentrations are applied with vigour. Animals should be prevented from licking and biting the blistered area. Cantharides blisters should not be applied to sites where direct contamination of mucous membranes, particularly of the urogenital system, can occur.

Toxicity. Cantharidin can be absorbed through the skin in sufficient quantities to cause trouble if large areas are dressed or if the animal can lick and bite the area. Should this happen, symptoms of acute gastro-intestinal enteritis and nephritis will be seen, possibly with penile erection in the male and difficulty in urination. Treatment consists of washing off the local application and the oral administration of demulcents of a non-oleaginous character. Hyoscyamus tincture may help in counteracting the urinary system irritation.

Mercury, B.Vet.C. and Its Compounds

The pharmacology and usage of this metal and its derivatives are governed mainly by their individual solubilities and the ionization of each compound. Those which are soluble and highly ionized will be the most active, whilst the least soluble and un-ionized compounds will be relatively inactive. This principle, of course, is not confined to mercury compounds alone but applies to all simple inorganic salts. As mercury ions, but particularly mercuric ions, are protoplasmic poisons, it follows that soluble and ionized compounds will be highly toxic and therefore only used externally, if at all. The less soluble forms will be safer and available for internal use.

The mercury compounds in veterinary use, arranged according to activity in descending order, are:

Mercuric chloride,
Mercuric iodide,
Ammoniated mercury,
Mercuric oxide,
Mercurous chloride,
Metallic mercury,
Organic mercurials.

It should be remembered, however, that metallic mercury if vaporized or very finely divided as in Mercury Ointment, B.Vet.C., is relatively easily absorbed, and toxic effects can result from its administration in these forms, whether accidental or otherwise.

Of these compounds only mercurous chloride and metallic mercury are used internally. All have external actions and uses, although mercuric chloride is so dangerous that it should not appear on the shelves of any veterinary pharmacy.

Mercuric Chloride, B.Vet.C. (Corrosive Sublimate, Hydrarg. *Perchlor.*)

This is a white crystalline solid with no odour; it is soluble in water and very soluble in alcohol, giving water-white solutions; solutions should be coloured with methylene blue or crystal violet to protect against accidental drinking. Metal instruments should not be used in contact with the salt because of its strong corrosive action.

Actions and Uses. Mercuric chloride precipitates protein and poisons protoplasm. In tissues, the mercury-protein compound is soluble in excess protein and precipitation does not occur, thus no protective proteinate pellicle is formed and the mercury can affect successive tissue layers until all the free mercuric ions are taken up. This may take a considerable time, requiring a large amount of tissue, and very deep penetration can occur; this is a corrosive action. A penetrating action would not be so dangerous but for the protoplasmic poisoning action. Every cell is destroyed in which the mercuric ion reacts with the protein.

These corrosive and protoplasmic poisoning actions have been utilized when mercuric chloride solutions were used for antiseptic and disinfectant purposes. There is now no justification for its use in this way.

The corrosive effect was made use of when the salt was incorporated in caustic pastes; counter-irritant solutions containing mercuric chloride have been recommended for the treatment of traumatic arthritis. These uses are also unjustifiable.

Toxicity. Mercuric chloride poisoning is usually very acute and severe. The *acute toxicity*, which follows mistaken or accidental administration, is typified by acute and extremely severe gastro-enteritis. If the animal revives from these conditions there follows stomatitis and, from the chloride absorbed, acute hepatitis but more especially nephritis, within 24–48 hours. Death results from cardiac and circulatory collapse subsequent to renal failure and concomitant uræmia with convulsions.

Treatment consists of gastric lavage where possible and the administration of sodium phosphite or hypophosphite (10·0 G. per cwt.) by mouth. Raw white of egg has been used as a very temporary measure to bind the mercury with the protein, even though in a soluble form; charcoal is also very useful. These and other treatments are aimed at preventing absorption; if they are to be effective, they must be administered immediately and the gastric contents extracted within ten minutes. Unless these measures are applied quickly recovery from toxic doses is unlikely. Once absorption has taken place treatment is problematical. It is possible that the chelation compounds such as Calcium Edetate, B.P.C., calcium disodium ethylenediamine-tetracetate (Calcium Versenate), would be of value and should be tried.

Chronic toxicity follows repeated applications of skin dressings, repeated dosings with calomel, grey powder etc., and vapour inhalation. Mercuric chloride is rarely responsible for this type of poisoning now that it is no longer used for dressing wounds. The chronic toxicity is called *mercurism* and results from cumulation. The symptoms are those of stomatitis and nephritis which regress when the source of the poison is eliminated and symptomatic treatment applied.

Mercuric Iodide, B.Vet.C. (Bioniodide of Mercury, Hydrarg. Iod. Rub.) This is the most important inorganic mercury salt in veterinary use. It is a bright vermilion heavy powder, amorphous, odourless, and tasteless. Almost insoluble in water, mercuric iodide can be dissolved with the aid of an equal weight of potassium iodide. It is slightly soluble in alcohol and ether.

Actions and Uses. The external actions of mercuric iodide are counter-irritant, fungicide, and antiseptic. The iodide of mercury is not markedly corrosive but it is strongly irritant to the tissues, particularly if applied in alcoholic solution. In a soft paraffin or animal fat base mercuric iodide

has been and is widely used both as a mild and a strong counter-irritant. Concentrations of 1 : 40 or 1 : 50 have a mild rubefacient action, but at strengths of 1 : 8 a strong vesicant effect is given. Exceptionally, concentrations of 1 : 4 in lard have been rubbed in vigorously for 5–10 minutes, to be followed after several hours by severe blistering. There is always a danger at this strength of causing pustulation.

The biniodide blister penetrates deeply, producing many small blisters which, after a period, will coalesce. Alcoholic solutions are even more effective than animal fat ointments but, because of the difficulty of limiting the action of fluid blisters and the danger of pustulation, they are not frequently used.

Strengths of 1 : 40 to 1 : 50 have been effectively used for ringworm dressings. Alcoholic solutions of 1 per cent. of the iodide have also been used.

Mercuric iodide is strongly antiseptic and it has been used as aqueous and alcoholic solutions at strengths of 1 : 500 to 1 : 2000 as a paint for operation sites and as a rinse for surgeons' hands prior to and during operations. Quaternary ammonium and similar antiseptics are preferable, particularly as dermatitis may develop following repeated use of mercurial compounds.

No mercuric iodide preparation should be used near to the eyes because of the danger of permanent damage and blindness, and where mercury is being used for ringworm dressings the yellow oxide ointment should be used for lesions around the eyes.

Internally, mercuric iodide is sometimes used as a supplementary or interim treatment for actinobacillosis when iodism has followed the administration of either sodium or potassium iodide. It seems that the mercuric compound in small doses (5–8 gr. or 0·3–0·5 G.), with an equal quantity of potassium iodide, in water given twice daily will often maintain the disease in equilibrium until the iodism symptoms subside and the potassium or sodium salt can be used again.

Donovan's solution, which contains mercuric and arsenic iodides, was used as a general tonic, but the solution discolours and dissociates forming a very toxic mixture. It is now rarely used.

Any iodide which is absorbed will cause a diuresis by irritation during excretion.

Grey powder, *mercury pill* and *mercurous chloride* (calomel) have all been mentioned as mercurial laxatives and purgatives on p. 86. *Yellow Mercuric Oxide*, B.Vet.C. and *Ammoniated Mercury*, B.Vet.C. are all fungicidal and are mentioned on p. 430.

Phenylmercuric Nitrate, B.Vet.C. and *Phenylmercuric Acetate*, B.Vet.C. are mentioned with other antiseptics on p. 398 and the diuretic *organic mercurials* are dealt with on p. 326 *et seq.*

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CHAPTER 20

AGENTS AFFECTING THE SKIN

(ii) SKIN SEDATIVES

THE depression of skin irritability and the relief of irritation or pruritis may be achieved by the use of a drug or drugs from one or more of the following groups:

1. Emollients.
2. Sedative and protective powders.
3. Astringents.
4. Local and general anæsthetics (analgesics).
5. Antiseptics, including detergents.
6. Antihistaminics.

Emollients

Emollients are agents which soften, soothe, lubricate and, protect a skin surface. By this definition they will therefore be fats, fixed oils, waxes, both natural and synthetic, hydrocarbons, and derivatives of these.

The *oils* used are olive, castor, rape, arachis, almond, theobroma, and cottonseed oils. Linseed oil is not used alone because of its property of oxidizing to produce varnishes when exposed to the atmosphere. Fish oils such as cod-liver oil may also be used. Derivatives include the oleates and stearates of metals such as zinc, magnesium, copper, and aluminium. Glycerol (glycerin) and other polyhydric alcohols such as propylene glycol are also emollient derivatives of oils.

The *fats* in common use are lard (pig-fat), lanolin (wool fat), and wool alcohols derived from lanolin.

The *waxes* used are beeswax, a natural wax, and synthetic ones such as the polyethylene glycols and Emulsifying Wax, B.Vet.C.

The *hydrocarbons* obtained as a by-product in oil refining are all well known—liquid paraffin, soft paraffin and hard paraffin.

Fixed Oils

The fixed plant oils are all colourless to amber liquids depending on their purity, except oil of theobroma which is solid at normal room temperature but fluid at body temperature; some oils, such as olive and arachis oils, partially solidify at winter temperatures. They each have a slight but

characteristic odour and in pure forms, a bland taste—impure forms frequently have a disagreeable taste; fish oils usually have a strong fish odour and taste. On keeping, all oils tend to go rancid, but fish oils are much worse than plant oils which may keep several years without becoming unusable. Physical recognition of fixed oils depends on testing for insolubility in water, lubricant properties, the ability to make a permanent grease stain on brown paper, a black stain with osmic acid, and saponification with alkalis.

Actions and Uses. The plant oils are widely used as vehicles for the external, oral, and parenteral administration of drugs. Externally, rape oil, castor, and cottonseed oils are frequently used for preparing counter-irritant liniments, parasiticidal dressings, and bland emollient ointments such as the well known *Ointment of Zinc Oxide and Castor Oil*, B.Vet.C. (zinc and castor oil ointment). If mixed in equal parts with lime water various liniments are formed which were used extensively at one time for the treatment of burns and scalds: olive oil forms *linimentum calcis* and linseed oil forms *carron oil*. These are still useful for extensive burns in large animals if sodium bicarbonate paste is not available. Arachis oil is rarely used externally, being an 'edible oil' and almond oil, though it has similar external actions to olive oil and rape oil, is not frequently used because of its cost. Oil of theobroma is a solid oil used mainly as a vehicle for pessaries and suppositories, but it is being replaced by glycogelatin which is more stable and of a standard quality. Internally, fixed plant oils are laxative and purgative (*q.v.*), for which actions castor oil and linseed oil are the best, as their respective soaps, ricinoleates and linoleates, are more irritant than those of olive oil and rape oil.

The fish oils can be used externally in the same way as plant oils but their odour is objectionable and restricts their use. The vitamin A and D content is widely believed to impart better healing properties when applied to the skin, and there would appear to be some clinical justification for the belief. Cod-liver oil is very effective as a vehicle in oily eye drops and lotions.

Internally, the fish oils are valuable vitamin feed supplements as well as having nutritional value. These oils are dealt with more fully in the section on vitamins.

Derivatives of Fixed Oils

The *oleates and stearates* are soaps of the fatty acids present in fixed oils and fats. The sodium and potassium soaps are well known as detergents, but the insoluble oleates and stearates have other uses, mainly of skin sedation. The oleates in general penetrate the skin very easily and the attached metallic ion is readily absorbed: mercury oleate was at one time applied to the skin specifically as a means of systemic mercury therapy in syphilis: 5 per cent. copper oleate is still used in parasitic and antifungal dressings. The stearates, which are white or yellowish powders, possess

strong skin sedative properties—zinc stearate is used in concentrations of up to 50 per cent. in ointments and can be applied as a dusting powder in any concentration, occasionally being substituted for talc; it is claimed to have mild astringent and antiseptic properties. Magnesium and aluminium stearates are used pharmaceutically as lubricants, water repellants, and gelling agents. Aluminium stearate is used as a suspending agent for parenteral injections and intramammary injections in strengths of approximately 2 per cent. Lithium stearate is also used in intramammary injections.

Some *polyhydric alcohols* possess strong emollient properties. Glycerol (glycerin) and propylene glycol are used extensively for their emollient and solvent properties.

Glycerin, B.Vet.C.

Sometimes known as glycerol, this compound is a thick, syrupy, colourless, odourless liquid with a sweet taste. It is hygroscopic, water and alcohol miscible, but insoluble in fixed oils, ether, and chloroform. Its main origin is as a by-product of soap manufacture.

Actions and Uses. The majority of the effects of glycerin are due to the high osmotic pressure of the compound and its aqueous or alcoholic solutions. These high osmotic pressures cause slight pain when pure glycerin is applied to abraded skin and to the conjunctiva, but the pain is transient.

Externally, glycerin applied to unbroken skin is a very useful emollient. Applied to wounds, the osmotic pressure results in a lymphagogue or lymph lavage action, which is defined as the bathing of a wound by lymph drawn into it in the process of neutralizing the osmotic pressure exerted by the glycerin or other lavage agents (salines, sugars). Besides mechanical cleansing by passage of the lymph, there is a concentration of the body's defence agents—antibodies, phagocytes etc. which help to overcome infection and aid healing. The combination of these two actions makes glycerin a very useful skin dressing for chapped, dry areas and for wounds; Glycerin of Starch, B.Vet.C. is especially useful for this purpose. A wound dressing, Morison's Paste—*Paste of Magnesium Sulphate*, B.Vet.C., containing approximately equal parts of exciccated magnesium sulphate and glycerin, is a very useful large animal wound dressing, particularly if wounds are dirty and pocketing.

By virtue of its high osmotic pressure, glycerin is also mildly antiseptic and is sometimes used as a preservative for vaccines, enzymes, and pathological specimens, but tends to shrink specimens and does not always control moulds.

Semen diluents frequently contain glycerin up to a concentration of 10 per cent., and Holt (1953) reported an increase in fertility by such a dilution. 10 per cent. glycerin is also reported to enable bull semen to be stored at −79°C. for up to 32 weeks without loss of fertility. (Polge *et al.*, 1952).

Glycerin has been used in industry and pharmacy as a 'humectant'—for maintaining a degree of moisture—and so preventing the drying of ointments, bread etc. More recently it has been replaced by sorbitan derivatives.

Glycerin is also used in conjunction with gelatin to make the glycogelatin bases of pessaries and suppositories, as well as those of lamellæ, capsules, and throat pastilles.

Internally, glycerin is a good *demulcent* and *sweetening* agent. These properties are useful in inflammations of the mouth and pharynx, and various glycerin and drug mixtures have been in human use for many years. The veterinary uses of *Glycerin of Borax*, B.Vet.C., and *Glycerin of Alum*, B.Vet.C. are restricted, but electuaries based on these and perhaps incorporating sulphonamides are very useful in equine influenza and tonsilitis of the dog. They must be administered every three or four hours to obtain maximum benefit and are therefore somewhat expensive.

Use as an enema has been mentioned (*q.v.*), but glycerin suppositories are easier and cleaner to administer and equally effective.

Intra-uterine injections of glycerin are very popular for the treatment of leucorrhœa and similar conditions in cattle. A useful formula consists of 2 fl. oz. (60·0 ml.) glycerin, 1 fl. oz. (30·0 ml.) 1 : 1000 acriflavine, with water up to 6 or 8 fl. oz. (180·0–240·0 ml.). More glycerin may be used if a very strong action is required. The cleansing and antiseptic action is due to the lymphagogue effect and pain may cause the treated animals to arch their backs and strain for an hour or two.

The most important use of glycerin discovered in recent years is its *glycogenic* action when given orally to cattle and sheep. (Griffiths, 1952; Johnson, 1953; and Blood, 1956). It is administered as a warm 5 per cent. aqueous solution as a treatment for pregnancy toxæmia of the ewe and acetonæmia of cattle. Doses are up to 4 fl. oz. (120·0 ml.) in sheep; given as single daily oral doses at the rate of 3 ml. per kg. bodyweight, glycerin reduced pregnancy toxæmia (artifically induced) mortality from 83 per cent. in controls to 25 per cent. (McLymont *et al.*, 1955). In cattle, doses of 500 ml. (about 1 pint) in food or as a drench should be given twice daily for two to three days.

Propylene Glycol, B.P.C.

This dihydric alcohol, which can be prepared from glycerin by distillation with caustic potash, is a clear viscous odourless liquid with a slightly bitter taste. It is miscible with water, alcohol, ether, and chloroform, but will not mix with fixed oils. It is hygroscopic to a lesser degree than glycerin, restricts mould growth and fermentation better (equivalent in this respect to ethyl alcohol), and in most cases is a better solvent.

Actions and Uses. Externally, Propylene glycol has emollient and humectant properties, but these properties are not so marked as with glycerin. It is, however, used in ointments and lotions mainly because of its

greater solvent properties: most small animal ear dressings have propylene glycol as a base. It is also used as an area disinfectant when dispersed as an ærosol: 1 part in 26 kills staphylococci but not spores.

Internally, Johnson (1953a, 1954) and Maplesden (1954) amongst others reported the glycogenic effect of propylene glycol on acetonæmia. They recommended doses of from 200–400 ml. (6–12 fl. oz.) given twice daily for four days. *Toxicity* is not great, though no post-mortem details on treated animals are available. One cow was given 1800 G. (approx. 3 pints) and later 400 G. (approx. 12 fl. oz.) twice daily, six days a week, for four weeks without any untoward clinical effects.

Fats

This group of emollients differs from fixed oils only in that its members are solid at normal temperatures and consist of glycerides of palmitic and stearic acids (oils are mainly glycerides of oleic and palmitic acids). Beef tallow or suet, pig fat or lard, are fats which are used in ointments to aid penetration and to act as emollients but their use is not so frequent as formally owing to their tendency to go rancid on keeping. 2 per cent. benzoin was often incorporated to prevent or defer rancidity. The Veterinary Codex contains a monograph on lard.

Wool Fat, B.Vet.C.

Described as the purified, anhydrous, fat-like substance obtained from sheep wool, wool fat is a pale yellow thick tenacious fat-like substance with a characteristic odour. It is insoluble in water but will absorb about 50 per cent. of its weight of water. Sparingly soluble in alcohol, it dissolves freely in ether, chloroform, other organic solvents and fixed oils. *Hydrous Wool Fat*, B.Vet.C. (lanolin) is produced by causing the anhydrous fat to take up 30 per cent. of water. This compound is more easily incorporated into ointment bases than is the anhydrous compound and will mix more readily with aqueous solutions and adsorb them in quantities up to two or three times its own volume, forming emulsions.

Chemically, wool fat differs from other animal fats in that the fatty acids are combined not with glycerin but with higher alcohols such as cholesterol, oxycholesterol and others. *Wool Alcohols*, B.Vet.C. contains a number of alcohols, including not less than 28 per cent. cholesterol, obtained by saponification of the crude grease from sheep wool. It is, at normal temperatures, a hard, brittle, dark amber coloured solid which fractures to give a smooth shiny surface. It is plastic when warm. Its solubility is similar to the other wool fat compounds but it is more soluble in alcohol. These compounds do not go rancid very quickly.

Actions and Uses. The ability of these compounds to act as emulsifying agents, and their relationship to normal skin secretions, has made them popular for incorporation into emollient ointment bases, usually in concentrations of 5 or 6 per cent. Examples are *Simple Ointment*, B.Vet.C.

(unguentum simplex), and *Ointment of Wool Alcohols*, B.Vet.C., which contain 5 per cent. of wool fat and 6 per cent. of wool alcohols respectively. Recently, some of the alcohols have been shown by patch tests to promote allergic reactions and wool fat was omitted from the ointments of the U.S.P. XIVth revision, but was reinstated in the XVth revision. Though the newer emulsifying waxes now enable aqueous solutions to be incorporated easily into ointments, lanolin is still very popular and in many cases is a better emollient. Its property of aiding penetration varies according to the nature of the incorporated drugs and the state of the skin, but in general it is the best animal fat available for this purpose.

Waxes

Natural waxes resemble the fats physically, but chemically are more nearly related to wool fat, being composed of esters of the higher fatty acids with high molecular weight alcohols. Beeswax, the main example, contains a high percentage of myricyl palmitate ($C_{30}H_{61}\cdot O\cdot CO\cdot C_5H_{31}$) with some cholesteryl esters, hydrocarbons, and other complex organic compounds. Beeswax is available in the natural yellow form, *Yellow Beeswax*, B.Vet.C., and also a bleached white form *White Beeswax*, B.Vet.C. The solubilities are approximately those of wool fat. These compounds are used as hardeners for emollient ointment and suppository bases, and they are the main ingredients of plasters (or charges) mentioned under counter-irritants (*q.v.*). They are still used as suspending agents in some intramammary injections though superseded by various stearates; and they are also components of Oily Injection of Penicillin, B.P.

Synthetic Waxes. The manufacture of synthetic waxes has become a vast industry and the number of such waxes is countless. Two types have become official and represent the two main groups.

1. Those which combine sulphated and non-sulphated fatty alcohols, the former often as sodium salts. *Emulsifying Wax*, B.Vet.C. is the example.

2. Those which are combinations of fatty alcohols and condensates of fatty alcohols with ethylene oxide. *Non-ionic Emulsifying Wax*, B.Vet.C. is the example.

The first group are anionic emulsifying waxes and the second group are non-ionic. Because of the incompatibility of anionic preparations with cationic substances (detergents and antiseptics, particularly quarternary ammonium compounds and basic dyes), the non-ionic compounds of the second group are becoming more popular.

Emulsifying Wax, B.Vet.C.

The compound is a white or pale yellow solid wax which has a faint but characteristic odour and is insoluble in water, slightly soluble in alcohol, and miscible with oils and organic solvents. It forms emulsions with water.

Chemically, the compound is a mixture of 90 per cent. cetostearyl alcohol and 10 per cent. of sodium lauryl sulphate, an anionic detergent.

Actions and Uses. 30 per cent. emulsifying wax is incorporated in *Emulsifying Ointment*, B.Vet.C., along with white soft paraffin and liquid paraffin. This ointment is miscible in all proportions with water. 30 per cent. of emulsifying ointment is in turn incorporated in *Simple Cream*, B.Vet.C., a water miscible cream base.

As some difficulty was experienced due to incompatibility with cationic agents, non-ionic condensates were developed.

Non-ionic Emulsifying Wax, B.Vet.C.

This is also known as Cetomacrogol Wax, and belongs to the group of non-ionic waxes prepared by combining a fatty alcohol with a polyethylene derivative of a fatty alcohol. This particular wax consists of 20 per cent. Cetomacrogol 1000, B.Vet.C. and 80 per cent. Cetostearyl Alcohol, B.Vet.C. This wax can be used to replace emulsifying wax in any preparation, but especially in those containing cationic drugs. It is therefore used in creams containing quaternary ammonium antiseptics, and is part of the official bases for the two gamma benzene hexachloride creams in the Veterinary Codex.

Polyethylene Glycols, also known as the polyoxyethylene glycols, and in the case of some solid condensates as Carbowaxes, are now widely used either as bases or part bases for many ointments, creams, and suspensions. They consist of long chain, high molecular compounds, made by subjecting ethylene oxide and water to high pressures in the presence of a suitable catalyst. The ethylene oxide and water first produce ethylene glycol ($CH_2{\cdot}O{\cdot}CH_2 + H_2O = HO{\cdot}CH_2{\cdot}CH_2OH$) and as the condensation is continued polymers are made which conform to the formula $H(OCH_2{\cdot}CH_2)_nOH$: 'n' may be as high as 185. The highest of these compounds used normally—polyethylene glycol 4000—contains polymers with 'n' varying from 70–85. The lowest is polyethylene glycol 300 with 'n' = 5–5·75. Between these two there are a number of condensates which have as a suffix the average molecular weight of the polymers. Those with average molecular weights below 700 are liquids, while those above 1,000 are wax-like solids. The viscosity varies directly according to the molecular weight. The liquids are clear, colourless, and viscid, miscible with water, alcohol, acetone and other glycols, but insoluble in ether. They are also miscible with aromatic hydrocarbons (benzene derivatives), but insoluble in aliphatic hydrocarbons (paraffin hydrocarbon derivatives.) They do not, therefore, mix with oils and fats. They are hygroscopic according to molecular weight, varying inversely; polyethylene glycol 4000 is almost non-hygroscopic. The wax-like solids are, at lower molecular weights, similar in consistency to soft paraffin, whereas the high molecular weight compounds are like paraffin wax.

Actions and Uses. The liquid polyethylene glycols act as emollients and humectants in much the same way as glycerin and propylene glycol, and

are used in similar formulæ. The solid preparations are likewise used as part of the water miscible section of cream bases. In many cases, mixtures of the polymers are made so that a cream base is entirely made up of polyethylene glycols. A number of antibiotic formulations are now being made with these compounds as bases, including intramammary creams.

Polyethylene glycols are also used in preparing a series of suspending and emulsifying agents known by various names, of which Polysorbate of the United States Pharmacopœia is one. If ethers or anhydrides derived from sorbitol (a sugar alcohol, isomeric with mannitol), and called *sorbitans*, are combined with fatty acids by partial esterification, oil soluble but water miscible dispersing and emulsifying agents are produced. If these are then combined with polyoxyethylene glycols etc. to give polyoxyethylene sorbitan esters, there is formed a series of powerful water soluble emulsifying agents of which polyoxyethylene sorbitan mono-oleate is one. Depending on the fatty acid and the length of the polyoxyethylene side chains used, a series of emulsifying agents can be formed which vary from predominantly lipophilic at one extreme to predominantly hydrophilic at the other. There are in this series, emulsifiers suitable for all types of emulsions and dispersals.

The mono-oleate mentioned is used in many procaine penicillin and streptomycin buffered aqueous suspensions, of which Distaquaine and Streptaquaine are commercial examples.

Hydrocarbons

The hydrocarbon 'oils and fats' used in veterinary pharmacy are *Light Liquid Paraffin*, B.P., *Liquid Paraffin, White and Yellow Soft Paraffins*, and *Hard Paraffin*, all of the British Veterinary Codex. There are also 'mineral oils' of viscosity lower than the official liquid paraffin which have a wide variety of veterinary uses—from pig rubbing oils to the manufacture of water miscible creams and liniments.

The Soft Paraffins. Unpurified soft paraffins obtained during petroleum distillation are a deep amber colour, but as purification proceeds stage by stage the colour is lightened until the *Yellow Soft Paraffin*, B.Vet.C. is achieved. This product is a soft oily mass with the consistency of butter and a slightly fluorescent pale amber-yellow colour. It is miscible with fixed oils and organic solvents, but not alcohol. It is insoluble in water. *White Soft Paraffin*, B.Vet.C. has the same general characters as the yellow compound but the hydrocarbon has been further purified and bleached until white.

Actions and Uses. The soft paraffins form the major part of all veterinary ointments and are emollient, inert, non-irritant compounds. They act as bulking, suspending vehicles and do not assist penetration in any way. Should absorption of drugs be required, animal fats or emulsifying waxes must be incorporated with the hydrocarbons. It is usual to have 85–90 per cent. soft paraffin, 5 per cent. wool fat and 5 per cent. hard paraffin as a

routine ointment base—Simple Ointment, B.Vet.C. contains 5 per cent. cetostearyl alcohol also. The paraffins exclude air and water from the skin and restrict fluid evaporation. This is advantageous in some circumstances and 'tulle' dressings for burns consist of soft paraffin impregnated gauze; penicillin and sulphonamides are commonly incorporated as bacteriostatics. It is usual to include white paraffin in ointments with white ingredients and yellow paraffin with coloured ingredients but this rule is rarely adhered to in veterinary practice, the yellow substance being used almost universally.

Hard Paraffin, B.Vet.C. is only of significance as a stiffening agent for ointments, particularly if intended for tropical use. The common concentration in Great Britain and similar climates is 5 per cent. In character and consistency it is similar to candle wax but contains hydrocarbons of a lower melting point. Outside pharmacy the compound has numerous uses—as a depilator, and, with various melting points, as an embedding agent for preparing histological and pathological sections.

Liquid Paraffin, B.Vet.C. has already been mentioned as an inert lubricant laxative which has the disadvantage of restricting vitamin absorption and causing anal seepage. As an emollient, liquid paraffins of both high and low viscosities are used as the main ingredients of the oil phase of water-miscible cream bases for both pharmaceutical and cosmetic use. The light mineral oils are useful as bases for liniments, emulsions, and, in conjunction with small proportions of essential oils such as citronella, are used both as pig rubbing oils to prevent thickening and scaling of the skin, so maintaining suppleness, and also as engineering penetrating and lubricating oils. Perhaps one of the most important uses is as the base of many intramammary injections. Parenteral injections should not contain liquid paraffin as the substance is not easily absorbed, and in mammals causes foreign body reactions with severe local œdema and swelling if given subcutaneously: intramuscular injections appear to cause less trouble. Poultry seem to tolerate paraffin based injections better and subcutaneous antibiotic suspensions are available for the treatment of poultry diseases.

Skin Sedative and Protective Powders

The use of emollients is not always indicated in the relief of pruritis, nor are ointments and creams the best treatment for all cutaneous lesions and wounds. In cases of pedal eczema in the dog and clean wounds which are not suitable for stitching, dusting powder applications are most suitable. The ingredients of such dusting powders may be inert protective powders such as chalk and talc, astringent and protective such as oxide or carbonate of zinc, adsorbent such as kaolin, antiseptic such as proflavine, antifungal such as dichlorophen, or local anæsthetics such as chlorbutol, amethocaine and benzocaine. Many of these agents such as dichlorophen and chlorbutol have multiple actions: many are antiseptic, but all are antipruritic.

Zinc Compounds

The insoluble compounds of zinc are almost inert non-toxic compounds and are normally used for external applications only. They are zinc oxide, zinc carbonate and a coloured preparation of either, calamine. The soluble compounds are zinc chloride and zinc sulphate. Both are toxic internally, and the chloride is so caustic as to be unsafe externally except as a disinfectant for drains, though it is relatively inefficient when so used.

Zinc Oxide, B.Vet.C.

The compound is a white or yellow-shadowed, smooth, non-gritty amorphous powder, odourless, tasteless, and insoluble except in acid or alkaline solutions. On exposure it absorbs carbon dioxide and moisture, becoming gritty: if this happens the compound should be discarded as the gritty particles are irritant.

Zinc carbonate is very similar in character to zinc oxide, for which it can be used as a substitute externally: it does not become gritty on keeping.

Calamine, B.Vet.C.

This was originally prepared by calcining native, pink zinc carbonate, but the official compounds are synthetic, consisting in the United States of zinc oxide coloured with red, ferric iron oxide, and in Great Britain of zinc carbonate so coloured. The actual depth of colour varies according to each manufacturer's standards.

Actions and Uses. Externally, these three compounds react similarly. They are all mildly antiseptic, astringent, and protective. They are applied in dusting powders, lotions and liniments, ointments and creams. As *dusting powders* they are usually combined with other protectives, antiseptics etc., such as starch, boric acid, talc, or iodoform; various combinations of zinc oxide, starch, boric acid, and talc are official in the Veterinary Codex, the powders being combined in equal parts. If more active drugs such as iodoform are used they are diluted to concentrations of 1 : 8 by the less active compounds. For pedal eczema in the dog, a powder containing 25 per cent. sulphanilamide and 25 per cent. each of calamine, boric acid, and starch are very useful if a bandage 'boot' is made, about a teaspoonful of the powder put in and the boot pulled over the foot after rubbing some of the powder well into the divisions between the pads. The 'boot' can be kept in place either by pulling up with a draw string or by stitching the bandage to fit the paw. This can be replaced daily in severe cases, or every other day in less severe conditions. For ordinary 'wet eczema', if antihistaminics are not available, a mixture of 4 parts calamine or zinc carbonate, with 1 part each of sulphanilamide, zinc sulphate, copper sulphate, and starch, will cake on the patches, relieve irritation and encourage healing under the scab. There are many such formulæ.

Incorporated in ointments, zinc oxide, carbonate, and calamine are widely used as bland protective dressings. Zinc and castor oil ointment is widely known and is recognized in the Veterinary Codex; an ointment of 15 per cent. zinc oxide in simple ointment base is also official. Similarly a compound ointment and a simple ointment of calamine are official, the latter consisting of approximately 83 per cent. white soft paraffin and 17 per cent. calamine. An eye lotion or ointment made with 10 per cent. zinc oxide in cod-liver oil is very useful in severe conjunctivitis and corneal ulceration, relieving pain and allowing the animal and the eye to rest.

Creams and lotions are also available, though perhaps less popular than in human medicine. Lotion of Calamine, B.Vet.C. contains 15 per cent. calamine, 5 per cent. zinc oxide, 3 per cent. bentonite and 5 per cent. glycerin preserved with 0·5 per cent. phenol, and made up to volume with distilled water.

All these preparations are useful on abraded and irritated skin areas and should be used in preference to sulphonamide and antibiotic dressings unless gross infection has occurred. The zinc oxide ointment is very useful in protecting joint folds and in limiting the spread of counter-irritants and caustics, as in blistering and disbudding or in the caustic removal of warts.

Zinc stearate, though official in the Veterinary Codex, is not frequently used by the practitioner except as part of commercially manufactured ointments.

Internally, the only compound of zinc used is the carbonate, which has recently become popular as a treatment for parakeratosis of pigs—caused by an insufficiency of zinc. The oral dosage suggested by Neumann (1957) and Neumann *et al.* (1957) is 0·2 G. (3 gr.) daily for 4–5 weeks in mild cases; severe cases should be given 0·5 G. (7½ gr.) daily for 3–4 weeks, and very severe cases 0·75 G. (12 gr.) daily for 3 weeks. Toxic symptoms appeared in 4 weeks when giving 1·0 G. (15 gr.) daily to pigs subsequent to recovery from parakeratosis. This dosage has since been used successfully in Great Britain. Lewis *et al.* (1955) and Hoekstra (1955) reported that the addition of 100–500 parts of zinc per million in the food cured the skin lesions and increased body weight gains. A daily injection of 1–2 mg. zinc per lb. body weight for ten days was also effective.

It has been shown that high calcium diets predispose and hasten the onset of parakeratosis whether the calcium is present as chalk or lime, or as bone flour. Diets should therefore be corrected at the same time as zinc treatment is commenced.

Zinc Sulphate, B.Vet.C.

The compound occurs as colourless crystals or a white crystalline powder which is odourless and has an astringent metallic taste. It is soluble in water but insoluble in alcohol.

Actions and Uses. Zinc sulphate is strongly astringent, precipitating superficial protein but not penetrating the barrier so formed. It is only used externally. *Compound Eye Lotion of Zinc*, B.Vet.C. is very useful in mild chronic conjunctivitis. It contains 0·34 per cent. zinc sulphate and 2·29 per cent. boric acid in sterile distilled water. A similar but more active preparation which is very useful as eyedrops contains 2 gr. zinc sulphate and 4 gr. silver nitrate in 1 fl. oz. sterile distilled water (0·4 G. zinc sulphate and 1·0 G. silver nitrate in 100 ml.) This is very effective for corneal ulcers.

Lead, or White Lotion (Lotion of Zinc Sulphate and Lead Acetate, B.Vet.C.) contains 4 per cent. of the zinc compound and 5 per cent. of lead acetate dissolved in water. It is very widely and effectively used as an astringent and sedative lotion for the treatment of superficial strains, bruises, inflammations, and pruritis in the horse and cow. It should not be used on abraded skin because of the danger of lead absorption.

Starch, B.Vet.C.

Many different starches are available, named after their plant origin. There are wheat, maize, rice, and potato starches, all of which differ in the kinds of carbohydrate or their proportions present in the starch. Starch occurs as a white, odourless, tasteless, fine white powder, or easily powdered angular masses. It is insoluble in cold water and in the organic solvents, but forms a clear translucent gel with boiling water. If reacted on by dilute hydrochloric acid its gelling properties are destroyed and a substance is formed which is easily soluble in hot water giving a mobile clear liquid. This is so-called 'soluble starch'.

Actions and Uses. Externally, in powder form, it is absorbent and protective and, as a glycerin gel, emollient. It is used frequently in dusting powders as a sedative and absorbent in all proportions: the official preparations vary in the starch content from 25–75 per cent. The *Glycerin of Starch*, B.Vet.C. contains about 8·5 per cent. starch, and 74·5 per cent. glycerin in distilled water brought up to a gelling temperature. It is one of the finest dressings for chapped and fissured skin when applied once or twice daily. Starch, specially treated to remove its gelling properties, is used as a lubricant for surgical gloves instead of talc, since the latter has resulted in internal foreign body reactions and adhesions when introduced on gloves into wounds and body cavities. Starch is completely absorbed.

Internally, *Mucilage of Starch*, B.Vet.C., containing 2·5 per cent. starch, is a demulcent and an easily digested carbohydrate food—flour gruel is sometimes used instead for this purpose. Starch is also an antidote for iodine overdosage.

Talc, B.Vet.C. and Purified Talc, B.Vet.C.

These are products of a native hydrated magnesium silicate. Also known as 'French chalk', they are fine, white, odourless, tasteless, insoluble powders, sometimes containing aluminium silicate (kaolin).

Actions and Uses. Talc is perhaps more widely used in human medicine and cosmetics than in veterinary medicine where kaolin is more often available. However, these native silicates are extremely good skin sedatives and protectives when incorporated in dusting powders, acting as lubricants on the skin. They should be sterilized if used in wounds or on abraded skin, for they may contain spores, particularly tetanus spores.

Local and General Anæsthetics

Local anæsthetics, particularly amethocaine, benzocaine and chlorbutol, act as skin sedatives, but have been mentioned in the chapter dealing with local anæsthetics (Chapter 15). *General anæsthetics*, by lowering the sensitivity of brain centres and spinal reflexes to peripheral stimulation, also act as skin sedatives but are rarely used therapeutically for this purpose alone.

Astringents and Hæmostatics

The action of skin astringents is the same as that of intestinal astringents, many of the compounds being used in both contexts. The astringent, when applied to the skin, coagulates protein, forming a protective pellicle or scab under which healing can take place. At the same time, should there be any slight hæmorrhage not of arterial origin, the astringent will, by coagulating blood proteins, precipitate them and hasten blood clotting. This process is referred to as a *hæmostatic* or *styptic action*.

The *metallic sulphates*, particularly of iron, copper, aluminium, and zinc, act as external astringents and are used in dusting powders in strengths of up to 5 per cent. On occasions, crystals of these salts can be used but their action then tends to be irritant and caustic, destroying the superficial cells rather than coagulating their protein as a reversible reaction.

Perhaps the best external astringent is *Ferric Chloride*, B.Vet.C. which, as *Strong Solution of Ferric Chloride*, B.Vet.C., a dark brown clear fluid, is a safe, effective, astringent and hæmostatic for application to small superficial wounds and abraded skin. It is also used as a hæmostatic in amputating tails, digits, and small warts of puppies and dogs. For this purpose, the bleeding should be temporarily stopped by pressure, the wound swabbed clean and the chloride immediately applied with a swab made by twisting cotton wool round the tips of a pair of forceps or round a swab 'stick'. The swab should be wetted but not saturated with the chloride, especially if the wound is on an eyelid because of the pain caused if the astringent runs into the eye. If blood is welling from a wound, application of the astringent merely precipitates blood protein in the extravasated blood and not, as required, in the broken end of the vessel; bleeding therefore continues under the mass of precipitated blood, and harm rather than good results. A wound properly treated should be almost dry, clean, but brown from the precipitated chloride.

Lead Acetate in various combinations is also a good astringent and sedative compound.

Lead Acetate, B.Vet.C.

Lead acetate, the only salt of lead used therapeutically, is a white crystalline substance with a sweet astringent taste and an acetic odour. It is very soluble in water—giving a clear solution—and is consequently dangerous—soluble in alcohol up to approximately 2 per cent., and freely soluble in glycerin.

Lead acetate, besides being used in the preparation of lead lotion as described under zinc sulphate, is also used to make *Strong Solution of Lead Subacetate*, B.Vet.C., which consists of a mixture of the acetate with litharge (lead monoxide) and water.

Actions and Uses. Lead lotions are astringent and sedative. Astringency is typical in that lead albuminates are precipitated to form an impenetrable pellicle. The sedative actions of lead lotions is due in part to the astringent non-irritant action but also to the local anæsthesia of nerve endings. Because of the danger of chronic lead poisoning from cutaneous absorption and acute lead poisoning from licking, lead preparations should *not be used internally*, should *not be applied to abraded skin and wounds*, should *not be applied for long periods* and should *not be used on small animals*. Mucous membranes should not be dressed with lead lotions and in particular the eye should not be washed because of the danger of localized permanent white opacities following the healing of corneal ulcers.

Toxicity. Lead poisoning is one of the main hazards of calf rearing. Toxicity very rarely results from maladministration or overdosage of lead salts but is frequently due to the licking of paint from walls, woodwork, or from discarded tins, from grazing herbage contaminated by discharges into the atmosphere from smelting works and similar industrial concerns, and also from lead arsenate crop sprays. *Symptoms* of acute cases are indicative of acute indigestion and nervous system derangement—grunting, grinding the teeth, sweating, convulsions, leaping high into the air, excessively high temperatures and blindness. Chronic cases also show signs of indigestion, blindness, walking in circles or pressing the head against walls or posts.

Treatment consists of intravenous injections of calcium disodium ethylene diamine tetracetate (E.D.T.A.) available commercially as Calcium Versenate. Doses are not finally established but initial doses of 3–6·0 G. intravenously in 500 ml. sterile distilled water, followed by an equal second dose two or three days later if recovery is slow, appear to be most effective (Holm *et al.*, 1954; Lewis *et al.*, 1956; O'Moore, 1956; and Todd, 1957). This treatment should be combined with oral doses of magnesium sulphate to precipitate and evacuate any lead remaining in the intestines.

Antiseptics and Disinfectants

The difference between these two actions is not clearly defined. Literally one means the antagonism or fight against sepsis and agents which

produce sepsis, whilst the other means the removal of infective agents. In practice *antiseptics* are agents used on man and animals to kill or prevent multiplication of infective agents—bacteria, viruses, protozoa etc. They are therefore bactericidal or bacteriostatic. *Disinfectants* are looked upon as agents in the main too toxic to apply to the body but useful in destroying infections contaminating inanimate objects—buildings, feeding and cooking utensils, harness, transport vehicles, surgical instruments, the atmosphere etc. Many undiluted antiseptics will act as disinfectants, while many disinfectants when diluted can be used as antiseptics.

Antiseptics and disinfectants may be classified as follows:

(1) Oxidizing agents:
  (a) Halogens.
  (b) Peroxides.
  (c) Potassium permanganate.
(2) Reducing agents:
  (a) Sulphur dioxide.
  (b) Formaldehyde.
(3) Metallic compounds:
(4) Phenols and cresols.
(5) Dyes.
(6) Nitrofurans.
(7) Detergents.
(8) Antibiotics and sulphonamides.

The assessment of bactericidal or bacteriostatic action is not very satisfactory. The activity of an antiseptic is at present determined in relation to the effect of an equal volume of a standard phenol solution, and is expressed as a 'phenol coefficient'. This coefficient may be expressed as a Rideal–Walker coefficient or a Chick–Martin coefficient, depending on the test used to assess antibacterial effect. Both are *in vitro* tests, the former determined by a straight mixture of bacterial suspension and antiseptic dilution, whilst the latter test involves the mixing of the test antiseptic with a suspension of yeast cells or similar organic material before the bacterial suspension is mixed with the antiseptic. This supposedly simulates the organic matter which will contact the antiseptic *in vivo*, during its use as an antiseptic; but for a true evaluation, additional information is necessary, including data relating to skin reactions, systemic toxicity, reactions to different infective organisms, and suitability for specific requirements. It follows that some antiseptics may fulfil requirements in respect of some of these conditions and yet be useless otherwise and *vice versa*. For example, if anionic detergents—ordinary soap is one—are used on the skin and followed by a cationic antiseptic such as *Benzalkonium Chloride*, U.S.P., the cationic antiseptic in aqueous solution has a greatly reduced activity. If, however, the skin is swabbed with alcohol subsequent to washing with soap, or if the cationic antiseptic is dissolved in a mixture of 50 per cent. ethyl alcohol, 10 per cent.

acetone and water (so called 'tincture' of benzalkonium chloride), the activity of the antiseptic is improved considerably.

Oxidizing Agents

The oxidizing agents can be further subdivided into those which release gaseous oxygen, *the peroxides*, and those which cause oxidation without the release of oxygen gas: the halogens, and potassium permanganate.

Solution of Hydrogen Peroxide, B.Vet.C.

An aqueous solution of hydrogen peroxide is colourless, and odourless, but has a characteristic taste; it bubbles in contact with the oral mucous membrane. Hydrogen peroxide is relatively stable when slightly acidified but decomposes in alkaline media and in contact with organic matter and metals. The official solution is a 20 volume one: solutions of 10 volumes and 100 volumes are also available; the former is official in the United States Pharmacopœia but is less stable than the 20 volume solution, whilst the latter is dangerous if heated or if organic matter is introduced into the container—it will explode. The concentration expressed in 'volumes' relates to the volume of oxygen released by a single volume of the solution.

Sodium Perborate, which is a white crystalline powder, will decompose in solution to give sodium metaborate and hydrogen peroxide, which in turn will gradually evolve oxygen unless heated when oxygen comes off more rapidly. Magnesium, sodium and strontium peroxides will evolve oxygen but are rarely used in veterinary medicine.

Actions and Uses. Hydrogen peroxide has a twofold action. The *first* is an antiseptic and deodorant action by virtue of the strong oxidizing effect of the nascent oxygen produced in contact with organic tissue. The oxygen is produced, in part at least, by the action of the enzyme, catalase.

The *second* action is a mechanical cleansing action resulting from the rapid release of oxygen. A slight increase in the rate of fibrin formation may be responsible for the hæmostatic action of hydrogen peroxide, though the effect is so slight that it hardly merits a mention.

These actions persist only as long as oxygen is being produced: thus, as the end of bubbling is the end of the action, it is possible to keep a close check on its activity.

A 50 volume solution required about 5 minutes to kill anthrax spores and 1 minute to kill pyogenic cocci. Diluted four times, this solution would not destroy even cocci with a 30 minute exposure. Activity in the presence of organic matter is transient and considerably reduced, mainly because of the speed of oxygen release. The peroxides are thus only of value for their mechanical effect and some mild antiseptic action. They are used in purulent pocketing wounds and in ears.

Potassium Permangate, B.Vet.C.

Potassium permanganate consists of dark, odourless, purple crystals with a metallic lustre which are soluble in water giving pink to deep purple solutions depending on concentration. Solutions, particularly in contact with organic matter, have a typical and distinct odour.

Actions and Uses. Solutions of potassium permanganate have strong oxidizing properties without the release of gaseous oxygen and are antiseptic; they are also astringent. Solutions of 1 in 1000 ($\frac{1}{2}$ gr. per fl. oz., approximately) are used as wound and mouth lotions for antiseptic and deodorant purposes, whereas 5 per cent. solutions are astringent and have been used to reduce excessive granulation: footbaths of this strength have been used to harden racing greyhounds' feet. The antiseptic action is rapidly lost in contact with tissue and solutions turn brown; brown solutions are inactive. The staining of tissues is one of its main disadvantages though the stains can be removed by oxalic acid and sodium metabisulphite solutions.

Two actions which are made use of, though the advisability of such usages is debated, are that of antidotal effects against most alkaloidal poisons which have been swallowed—morphine, strychnine and aconitine are examples—and also that of antidotal effect against snake bite. For the former use aqueous solutions of 1 in 5000 (0·2 G. per litre or 1 gr. in half a pint) are recommended, whilst snake bite must be treated by a cruciate incision over the bite into which the permanganate crystals are rubbed. In areas where snake bites are frequent, small packets of permanganate crystals are commonly carried. As the action in both cases is one of destruction of the toxic substance by oxidation, the permanganate must be administered immediately, certainly within five minutes of poisoning, if the treatment is to be of any value.

Where crystals are mixed with Solution of Formaldehyde, B.Vet.C., in the approximate proportions of 1 : 2, formaldehyde gas is rapidly evolved. This process is made use of in fumigation.

The Halogens. The antiseptic halogens are chlorine and iodine, both of which are still used to some degree though giving place to chloroxylenol and quaternary ammonium compounds.

Chlorine

This halogen is a strong oxidizing agent besides being extremely toxic. It possesses antiseptic and deodorizing properties, even in the very dilute concentrations required to avoid toxicity. It is not used in the form of a gas but mainly as unstable hypochlorites which release the chlorine slowly when exposed to the atmosphere or organic material. With organic material it forms chloramines by combining with amino groups of proteins. These chloro-amines are themselves slowly and mildly antiseptic due to their slow release of chlorine.

Chlorinated Lime, B.Vet.C., also known as bleaching powder, is a dull

white powder with a characteristic odour; it is only partially soluble in water and alcohol. It contains not less than 30 per cent. w/w of available chlorine, but decomposes slowly taking up carbon dioxide and releasing chlorine, Calcium oxide (quicklime) acts as a stabilizer. The compound is a powerful disinfectant and deodorizes so long as free chlorine is available. It is used on drains, buildings etc. but should not be used in dairies because of the taint quickly acquired by milk. Six ounces per gallon of water is the usual farm strength, but frequently a handful of the powder is scattered around drains and on the gratings. Care should be taken to avoid contamination of clothing, for the compound bleaches most dyes and rots cloth. Metals are also corroded.

Solution of Chlorinated Lime and Boric Acid, B.Vet.C. (Edinburgh Universities solution—Eusol.) is prepared from *Eupad*, a stable powder consisting of equal parts of chlorinated lime and boric acid. 3 per cent. aqueous suspensions shaken and filtered after standing give a solution which is effective for up to two weeks.

Surgical Solution of Chlorinated Soda, B.Vet.C., better known as sodium hypochlorite or Dakin's solution, contains approximately 0·5 per cent. w/v of available chlorine. It is not very stable and is commercially available in a concentrated form which keeps much better.

Both eusol and the sodium hypochlorite solution are used as lotions for wounds and burn dressings. The latter was used with some success for continuous irrigation of wounds during the Spanish Civil War.

If used for hand baths during operations, these solutions tend to make the skin surface slippery so that handling of instruments is difficult. They are, nevertheless, effective and useful antiseptics for this purpose.

Iodine, B.Vet.C.

Solutions of iodine have been used for many years as antiseptic wound dressings. Iodine itself is an oxidizing agent though less active than chlorine. It is antiseptic in dilute solution but irritant and has a tendency to retard healing. As already indicated (p. 367) repeated applications are counter-irritant and vesicant as well as fungicidal. Internally, iodine is essential for correct thyroid metabolism (*q.v.*) and, as iodides, is useful in breaking down actinobacillosis lesions and in destroying the organism; the iodides are not so successful in actinomycosis—lumpy jaw, though some bacteriostasis is achieved. During excretion, a slight diuretic effect is apparent, and the iodides assist bronchitis by liquefying mucous and fibrinous exudates. Iodized oils are also used as radio-opaque injections in radiography.

For antiseptic and mild irritant action, the *Weak Solution of Iodine*, B.Vet.C.—the common tincture of iodine which contains 2·5 per cent. iodine in an alcoholic solution of an equal amount of potassium iodide—and the *Aqueous Solution of Iodine*, B.Vet.C. (Lugol's) iodine are used, the latter mainly for intra-uterine and vaginal irrigation after dilution to strengths of up to 0·2 per cent.

The bluish-black 'metalescent' crystals of iodine colour all solutions brown and also stain the skin: solutions of ammonia or sodium thiosulphate will remove these stains. When combined with organic compounds such as oleic acid, colourless preparations result (e.g. *Non-staining Ointment of Iodine* B.Vet.C.) which have little antiseptic action though counter-irritant effects are retained.

Toxicity may result from overdosing with the sodium or potassium salts and extensive external application of iodine compounds may cause iodism typified by starecoats, scaly dry skins and discharges from mucous surfaces. The condition resolves when dosing is stopped.

Iodoform, B.Vet.C.

Analogous to chloroform with a formula of CHI_3, iodoform is an intense lemon-yellow crystalline powder with a penetrating and persistent odour. It is almost insoluble in water, slightly soluble in alcohol, but reasonably soluble in ether and chloroform, and soluble in oils.

Actions and Uses. Iodoform is a persistent antiseptic and deodorant. The antiseptic action according to Sollmann, who quotes a number of authors, 'is probably by liberating iodine'. This does not occur *in vitro* but only on contact with organic tissue or secretions. The iodine is evolved so slowly that only mild antiseptic effects result, but there is stimulation of tissue cells with drying of wound exudates and a mild local analgesia. In addition a mild phagocytosis results.

It is used in dilutions of 1 to 4 or 8 with zinc oxide, talc, kaolin, etc., as a dusting powder in seborrhœic conditions of horses, also in otitis in dogs and cats, though its latter use is restricted by the objectionable odour. As pessaries containing about 60 gr. (4·0 G.), whether in a glyco-gelatin or oil of theobromine base, iodoform is widely used in retained placentæ of cattle, partly to limit sepsis but also to act as a deodorant. It is largely being replaced for this purpose by broad spectrum antibiotic or sulphonamide intra-uterine tablets.

As *Paste of Bismuth Subnitrate and Iodoform*, B.Vet.C., commonly referred to as B.I.P.P., iodoform is used to pack very dirty sinuses and fistulæ in horses. Quittor sinuses often respond to spraying with a 1 in 8 ether solution or packing with B.I.P.P. subsequent to the radicle operation. This paste contains 25 per cent each of bismuth subnitrate and liquid paraffin, with 50 per cent. iodoform.

Iodoform Setons—medicated tape—are available commercially for packing sinuses, fistulæ, and wounds.

There are no indications for the use of iodoform internally.

Toxic effects from iodoform are rare. Symptoms are, in part, those of iodism, but cardiac depression, lowered temperature, muscular spasms, and emesis, followed by a coma, are symptoms which occur due to the iodoform itself and not specifically to the iodine released. Treatment consists of sodium bicarbonate orally *ad lib.*, and stimulants where required.

Reducing Agents

Two agents, sulphur dioxide and formaldehyde are conveniently discussed under this subdivision of antiseptics. They are both primarily fumigant antiseptics, though they both have other applications. *Sulphur dioxide* is liberated as a gas when sulphur is ignited. It has been, and is still occasionally, used as a fumigant disinfectant for animal houses, to destroy bacteria and viruses, parasites and vermin. For every 1000 cu. ft. of air 3 lb. of sulphur should be burned. For full effect, the atmosphere should be moist and all ventilation should be sealed. It is common to spray the walls ceilings and floors with water before lighting the sulphur. The dioxide dissolves in the water to form sulphurous acid and it is the reducing action of this acid which is bactericidal. Specially made sulphur candles can be obtained or sulphur may be mixed with 1/40th of its weight of charcoal, which helps it to burn. Buildings should be sealed for at least 12 hours, but preferably 24 hours, subsequent to fumigation.

As sodium metabisulphite, sulphur dioxide is used as a preservative for foods, as a preservative antioxidant for adrenaline or procaine and adrenaline injections of the B.P. and B.Vet.C. amongst others, in strengths of 0·1 per cent. to 0·2 per cent., and also as a 'restrainer' in photographic developers.

Sulphur dioxide has a number of disadvantages which detract from its usefulness as a fumigant. It attacks and corrodes metal, rots fabrics, and bleaches dyes.

Solution of Formaldehyde, B.Vet.C.

Everyone is familiar with the colourless liquid with an irritant vapour and a pungent odour which is universally used as a preservative for dissection specimens. On standing, polymerization occurs and a white deposit of paraformaldehyde forms in spite of the alcohol which is left in the solution to delay the process. The solution contains approximately 40 per cent. formaldehyde gas.

Actions and Uses. Externally, formalin is strongly astringent and antiseptic. If applied undiluted to the skin, protein precipitation occurs and the skin becomes hardened: it has been used in a similar manner to potassium permanganate for hardening greyhounds feet but should be applied diluted 1 in 10 to give a 4 per cent. formaldehyde solution, which is the normal preservative strength. The main external action is as a fumigant disinfectant or as an aqueous disinfectant spray.

For fumigation of buildings it is usual to mix potassium permanganate and solution of formaldehyde in a ratio of 3 to 5, using 1½ oz. to 3 oz. (45·0–90·0 G.) of potassium permanganate for each 100 cubic feet. Rooms to be fumigated should be closed for at least 10 hours and the best procedure in small animal surgeries and waiting rooms is to fumigate each day after evening surgery so that the rooms may be closed overnight. Care should be taken that splashing does not occur, for gas evolves very

rapidly and hot solution may be splashed over a fairly wide area—12 to 14 inch mortars make ideal receptacles. The permanganate, preferably in 'fumigating block' form, should be placed in the generating vessel and the formalin poured on just before vacating and closing the rooms. Spraying a water mist in the rooms prior to fumigation assists the action of formalin. Neutralization of the gas is quickly achieved by ammonia. Aerosols have been used but are not recommended (Krieglsteiner, 1955).

Vermin are not killed by formaldehyde fumigation, but fabrics and dyes are unaffected so that for disinfectant purposes it is preferred before sulphur dioxide. It is an accepted method for disinfecting imported straw clothing, cattle cake, grain etc. under the Foot and Mouth Disease Order. Hay and straw stacks, clamps of roots etc., which cannot be fumigated, may be sprayed with a 2 per cent. formaldehyde solution (the official solution diluted 1 part in 20 parts). Stacks should be 'pulled' after spraying and the 'pullings' burnt.

Formaldehyde is also used in the preparation of formalinized vaccines from bacteria and viruses.

Internally, the main use as an antizymotic has already been mentioned (p. 73). There is now no justification for its intravenous injection, particularly in view of its extremely irritant nature, for sloughing may result if any solution is injected perivenously.

Disinfection by fumigation is giving place to ærosol space disinfection by the continuous or semicontinuous use of electrically heated and driven ærosol generators. Various agents are used including propylene and triethylene glycols.

Metallic Compounds

Compounds of mercury, silver, and copper are the main metallic antiseptics and disinfectants.

Mercury Compounds. Though mercuric chloride, iodide and cyanide are all antiseptics and disinfectants, the considerable danger attaching particularly to their antiseptic use has made them unpopular. They are far too irritant for normal usage and organic mercurials were devised to overcome this attribute. The most useful of these are phenylmercuric compounds of which the nitrate and the acetate are the most active. The halogen derivatives and soap compounds are practically insoluble (phenylmercuric chloride soluble only 1 : 20,000) and are therefore only of historical interest.

Phenylmercuric Nitrate, B.Vet.C. and Phenylmercuric Acetate, B.Vet.C.

Both these compounds are white or almost white crystalline powders which are not very soluble in water (nitrate 1 : 150, acetate 1 : 600). The nitrate is soluble only to the extent of 1 : 1000 in alcohol, but the acetate is readily soluble in alcohol, acetone, and benzene.

Actions and Uses. The action of these two compounds is mainly bacteriostatic. They are less active in the presence of serum and other

proteins and do not kill spores. Their antibacterial action is attributed to interference with essential enzyme activity by combining with sulphydryl groups, and it is the phenylmercuric ion which is mainly responsible. The compounds are used in concentrations of 0·03–0·06 per cent. for swabbing the skin, preferably in a solution buffered with either an organic or inorganic acid. Buffering is required as the phenylmercuric compounds are more stable in acid solutions and any breakdown of the organic ion to produce mercuric and mercurous ions increases irritation. Alcoholic solutions are frequently used because the salts are more soluble, but the added antibacterial effect of the alcohol is also useful.

Buffered solutions are relatively non-irritant, non-toxic, do not stain, and are non-corrosive to all common metals except aluminium, apart from any effect the acid buffer may have. They are widely used in the veterinary field.

The use of 0·05–0·1 per cent. ointments for their antimycotic effect is mentioned in the chapter on fungicides (Chapter 20). A further use for these mercury preparations is as a bacteriostatic compound in injections, ointments, and other pharmaceutical preparations, at a strength of 0·001 per cent.

Thiomersal, B.Vet.C., also known as Merthiolate, a cream crystalline powder very soluble in water and reasonably soluble in alcohol, is another organic mercurial antiseptic. Its actions and uses are similar to those of the phenylmercuric compounds in a strength of 0·1 per cent., but the compound is not reduced in activity by serum proteins. The *Mercocresols*, N.N.R. are a group of antiseptics used in the U.S.A. consisting of a combination of phenylmercuric and cresol compounds and having the combined effect of a cresol and a phenylmercuric salt but the low toxicity of the phenylmercuric component. A mixture of 0·19 per cent. of each component is applied undiluted in alcoholic solutions to superficial wounds and preoperative skin sites, but dilutions of 1 : 5 to 1 : 20 are recommended for mucous membranes.

The antiseptic nature of silver proteinates and copper sulphate are mentioned elsewhere.

Phenols and Cresols

The use of the pure phenols and cresols and simple formulations of them are obsolescent as antiseptics but they are retained for disinfection and for the preparation of sheep dips. They are occasionally used internally as antizymotics and for intratracheal injections. Newer derivatives of the phenols and cresols, such as the various chlorinated cresols and the phenylmercuric compounds have become very widely used in the last two decades, mainly for antiseptic purposes.

Phenol, B.Vet.C.

Pure phenol usually exists as white crystals which become pink on keeping and take in water due to their deliquescence. It has a distinct characteristic

odour and is soluble in 12 parts water, soluble in alcohol and also in other organic solvents, including glycerin and vegetable oils. The compound is extremely caustic and dangerous so that any skin contaminations should be immediately dressed with glycerin and then washed off.

Actions and Uses. Externally, phenol is caustic, antiseptic, disinfectant, and parasiticidal. Its caustic powers are rarely used now except to cauterize corneal ulcers, when a probe is wetted with *Liquefied Phenol*, B.Vet.C., an 80 per cent. solution, and the ulcer just touched. The ulcerated area becomes opaque, but in most cases healing is stimulated and recovery is rapid. On the skin, phenol causes precipitation of protein and forms a white 'eschar', but far from being a protective covering, the phenol continues to penetrate through the tissues below the eschar, poisoning and destroying protoplasm, with very little pain after initial irritation, due to the local anaesthetic effect of the phenol: it is consequently more dangerous. For antiseptic purposes phenol is now no longer used, due to the corrugation and numbing of the skin by the 0·2–1 per cent. solutions formerly used.

As a disinfectant, phenol is 'approved' by the Ministry of Agriculture for use in premises subject to a disinfection order under the Diseases of Animals Acts—as a disinfectant wash and incorporated at a strength of 0·5 per cent. in lime wash for walls. Phenol is still used as a bacteriostat in various injections, and in vaccines and sera. The British Pharmacopœia cites 0·5 per cent. phenol as a suitable bacteriostat and preservative for multidose injection packs.

For many years phenol has been used in parasiticidal sheep dips in a strength of 0·5 per cent.

Internally, *Liquefied Phenol*, B.Vet.C. has been used as an antizymotic for cattle and sheep in doses of 30–90 m. (2·0–6·0 ml.) and 5–15 m. (0·3–1·0 ml.) respectively. It should be well diluted and given orally in the treatment of ruminal tympany and bloat.

Cresol, B.Vet.C.

This compound is an impure liquid mixture of cresols and phenols obtained from coal tar distillation. The straw coloured liquid which darkens with age and exposure is less soluble in water than phenol but soluble in the organic solvents.

Actions and Uses. The actions of cresol are similar to those of phenol, but toxicity is lower. Cresol is very effective against acid-fast bacteria, only slightly so against viruses, and has no effect on spores. It is, however, very useful in that organic matter has relatively little effect on its bactericidal powers. In practice, *Solution of Cresol with Soap*, B.Vet.C., better known as 'lysol', is preferred because of its greater solubility in water. A concentration of 0·5 or 1 per cent. has been used to wash out the uterus of cows following retained placentæ: a similar concentration has been used for 'wet' surgery.

Many of the 'Black Fluid' and 'White Fluid' disinfectants used on farms and on veterinary premises are cresol compounds; they are quite effective, many of them having phenol coefficients of R.W. 18 or more, and dilution factors of 30 to 50. They should not be used in dairies, for the persistent phenolic odour quickly taints milk and milk products.

Cresol sheep dips containing up to 0·36 per cent. of cresol have been used against sheep scab by double-dipping with an interval of 8–14 days between each dipping. The dips are also effective against other parasites but lower concentrations are required. The chlorinated benzene compounds have almost entirely superseded the phenol and cresol dips.

Toxicity. Phenols and cresols are especially toxic to cats and dogs: washing of cat cages with phenols or cresols, and even carbolic soap used for bathing dogs have resulted in death. Symptoms are those of lethargy, coma or convulsions followed by coma, with death supervening as a result of respiratory or cardiac failure. Treatment consists of bathing with liberal amounts of warm water where skin absorption is suspected. Where the compound has been licked off paws or skin, gastric lavage with water or limewater is recommended though not very easy to carry out. Intravenous and subcutaneous saline injection and respiratory stimulants are useful. External contamination with concentrated phenols or cresols should be swabbed with glycerin.

Perhaps the compounds which have done more to out-date phenol and cresol as antiseptics have been the *chloroxylenols*. Two are in common use throughout the world—parachlorometaxylenol (P.C.M.X.) and dichlorometaxylenol (D.C.M.X.) These antiseptics as a group are greatly reduced in efficiency by contact with organic matter and have low Chick-Martin values.

Chloroxylenol, B.Vet.C.

This is xylenol with a chlorine atom in the para-position. The ortho- and meta-compounds are less active. Chloroxylenol is a white or creamy white crystalline substance with a slight phenolic odour. It is insoluble in water (1 in 3000) but soluble in organic solvents and soap solutions—*Solution of Chloroxylenol*, B.Vet.C. is a 5 per cent. chloroxylenol solution with 10 per cent. terpineol and a castor oil soap in alcohol and water.

Actions and Uses. This chlorinated dimethylphenol is a highly effective bactericide against some Gram positive bacteria. Streptococci are most susceptible, staphylococci less so, but many Gram negative organisms such as Pseudomonas and Proteus species are hardly affected. The Rideal Walker phenol coefficient when properly formulated is 62 against *B. typhosum* (*Salm. typhi*), but solutions of 5 per cent., such as the official one, have phenol coefficients of about 3, that is they are three times more effective than a standard solution of phenol. The main advantages of

these solutions are their low irritant properties and very low toxicity. In the majority of people an undiluted 5 per cent. solution causes no irritation apart from that following strong detergent activity due to the alcoholic soap-solution base. A few individuals are hypersensitive to the chloroxylenols and cannot use them.

Solution of chloroxylenol can be used both as an antiseptic and disinfectant but its expense and the fact that the action is greatly reduced by organic matter makes it less useful for the latter purpose. Solution of cresol with soap is preferable for disinfectant purposes.

As an antiseptic, chloroxylenol solutions are very widely used in Great Britain. For pre-operative skin sterilization a dilution of 1 in 4 is recommended, but for wound cleansing and irrigation of the uterus and vagina 1–2 per cent. solutions are better (approximately two teaspoonfuls to 1 tablespoonful in 1 pint of water—10–20 ml. per litre.)

Dichlorometaxylenol, B.P.C. is a more recent discovery, with approximately four times the activity of the single chlorine compound (R.W. phenol coefficient *Salm. typhi* 250, *Staph. aureus* 180 and *Strep. pyogenes* 160), but in addition there is similar activity against many other organisms including *Bact. coli* and *Ps. pyocyanea*. Fungicidal activity is also appreciable. Toxicity is very low (50·7 G. per kg. bodyweight have been given to mice before producing ill effects), and the lower concentrations required because of greater activity reduce it even further.

Dichlorometaxylenol is formulated in a similar way to the monochlor. compound, but using approximately 25 per cent. of the concentrations. It is used in 2 per cent. concentrations in surgical soaps and compares favourably with hexachlorophene. Toilet soaps contain 1 per cent. for deodorant and antiseptic properties.

Hexachlorophene, U.S.P. is similar in bactericidal, physical, and chemical, properties to the chloroxylenols but is a diphenolic compound and has only a slight odour. The R.W. coefficient is approximately 125. The major use of hexachlorophene is in surgical soaps, when it is used in strengths of 0·5 to 2 per cent., at which concentrations it is almost non-irritant.

Dye Compounds

Dyes used for medicinal purposes have been classified under six headings:

(1) The *azo-dyes*, related to the sulphonamides and typified by *scarlet red* which is used for stimulating epithelial growth in clean, dry, but static, wounds and ulcerations.

(2) The *rosaniline dyes*, which are coal tar derivatives, and are typified by *crystal violet*.

(3) The *acridine dyes*, also coal tar derivatives, are exemplified by *acriflavine*.

(4) The *fluoroscein dyes* which have a restricted application.

(5) The *phenolphthalein dyes* which include the *phenolsulphonphthalein* used in kidney filtration tests.

(6) A few dyes which do not easily fall into any of these categories but are of some interest. Methylene blue is one of these.

Of these six groups of dyes, only two are of any value as antiseptics: the rosaniline dyes, brilliant green and crystal violet, and the acridine dyes, acriflavine, euflavine and proflavine.

The Rosaniline Dyes. These dyes are also referred to as triphenylmethane dyes. *Crystal Violet*, B.Vet.C. has been mentioned in the chapter on fungicidal agents, where its activity against Gram positive organisms is described. The dye is rarely used solely for its antibacterial effect but it is frequently incorporated in skin applications as a colouring substance with bacteriostatic effect and occasionally to mark the area and ensure compliance with instructions. When used on intact skin as a lotion or paint it is best applied as a spirit dressing especially on small animals; this ensures rapid drying with localization of the dye and less risk of staining the owners clothing and furnishing fabrics. Aqueous solutions should be applied to wounds, abraded skin and burns, for spirit dressings are painful. Concentrations of 1–2·5 per cent. are used in alcoholic solutions and 0·5 per cent. in aqueous solutions, frequently with equal quantities of brilliant green (*Paint of Brilliant Green and Crystal Violet*, B.Vet.C.)

Brilliant Green, B.Vet.C. is a water and spirit soluble golden crystalline substance. Water and alkaline solutions are green but turn reddish yellow when acidified with hydrochloric acid.

Actions and Uses. Brilliant green, though active against Gram positive organisms in common with the other basic dyes of the rosaniline series, is mainly of value for its selective bacteriostatic action on *Bact. coli*. *Externally*, it is of value in 0·05–1·0 per cent. aqueous solutions for infected wounds and burns, and 0·5 per cent. alcoholic solutions, with or without equal quantities of crystal violet, can be used for pre-operative skin sterilization.

Internally, brilliant green was used extensively for gastro-enteritis in calves and dogs, but since the advent of broad spectrum antibiotics its popularity has decreased. For *white scours* of calves the dye is most frequently used with bismuth salicylate as the unofficial compound, mixture of bismuth salicylate with brilliant green; less frequently it is given as *Mixture of Brilliant Green and Kaolin*, B.Vet.C. The former contains bismuth salicylate, kaolin, and 1 : 5000 brilliant green, and the latter 0·2 per cent. of brilliant green with approximately 14 per cent. of kaolin in water. Tablets formulated on similar lines are also available commercially.

The dye stains the fæces and is not popular with dog owners because of the damage done to floor coverings. In calf scours, acute severe cases do not respond rapidly enough and antibiotic and sulphonamide therapy is preferred, especially if combined with kaolin and administered concurrently with treatment to combat dehydration.

Acridine Dyes. These dyes were of considerable importance as bacteriostatic antiseptics but, as with the other non-specific bacteriostats, their importance has waned with the introduction of sulphonamides and antibiotics. They are, however, still used, frequently in conjunction with antibiotics and sulphonamides, because of their lack of toxicity and non-irritant character, and also because of continued activity in the presence of serum, though blood and pus do cause some decrease in activity. Phagocytosis is very little affected. It follows, that in wounds characterized by copious serous exudates but little bleeding or pus formation, these dyes will be very useful. The drugs are mainly active against pyogenic organisms, particularly streptococci and staphylococci, whilst they possess little activity against Gram negative organisms, and *Ps. pyocyanea* and Proteus species are highly resistant. Antibacterial action is thought to be due to interference with adenine metabolism, including the activity of coenzymes 1 and 11, which is essential to bacterial growth.

The important members of the group are Euflavine, B.Vet.C. (neutral acriflavine), Acriflavine, B.Vet.C., Aminacrine Hydrochloride, B.Vet.C., and Proflavine Hemisulphate, B.Vet.C.

Acriflavine, B.Vet.C.

This is an orange-red crystalline powder, odourless, but with an acid taste. It is soluble in water, alcohol, and glycerin, only slightly soluble in saline, but insoluble in organic solvents other than those mentioned. Dilute aqueous solutions of acriflavine are yellow with a green fluorescence. The neutral compound is a mixture of chlorides precipitated by the addition of sodium chloride to a neutral solution of acriflavine. Acriflavine itself is a mixture of the hydrochlorides of two acridine derivatives and is acid in solution.

Actions and Uses. The neutral compound is often preferred for wound dressing because it is less irritant than the hydrochlorides but otherwise its actions are the same.

Externally, acriflavine is a slow acting bacteriostat against pyogenic Gram positive organisms; it is applied to the skin as Acriflavine Emulsion, B.P.C. containing the dye at a 1 in 1000 (0·1 per cent.) dilution, as a 0·1 per cent. aqueous or 0·1 per cent. saline solution, or as a jelly containing the same amount of dye. The last of these has been used extensively as a burn treatment. Impregnated bandages and gauze are also used, but it has been pointed out that the dye has an affinity for staining cotton and its activity is thereby reduced (Garrod, 1931).

Internally, dilutions of 0·01 per cent. acriflavine were used extensively as udder infusions for the treatment of mastitis before the advent of penicillin and sulphanilamide, and were considered to be the best treatment then available. The method adopted was to inject about 5 fl. oz. of a warm 1 : 10,000 solution into each quarter (150 ml. of a 0·01 per cent.

solution) after stripping out. The solution was left in for from 4–6 hours accompanied by massage of the udder towards the milk sinus. Ammonium carbonate and potassium nitrate powders were given orally at the same time. Reasonable results were achieved with streptococcal mastitis.

Intra-uterine injections containing acriflavine in water and glycerin at dilutions of 1 : 5000 to 1 : 10,000 were frequently used for 'the whites' or leucorrhœa, and pessaries containing 0·1 per cent. are also widely used.

Euflavine has been used as 5 per cent. aqueous solutions given intravenously in the treatment of Babesia infections in horses, dogs, cattle, and sheep. For horses and cattle, 20·0 ml. are required, 5·0 ml. for sheep, and up to 4·0 ml. for dogs. Second doses are not usually needed but should be given if the temperature does not drop within 48 hours of the first injection. The diseases caused are known as *redwater* in cattle and *biliary fever* in horses and dogs. Photosensitization may occur and treated animals should be kept out of direct sunlight for several days after dosing.

Proflavine Hemisulphate, B.Vet.C.

The characters of proflavine are similar to acriflavine, though the crystals are somewhat darker in colour and are less soluble.

Proflavine is less potent than acriflavine but is quicker in action and is less toxic. It is rarely used in veterinary medicine for anything other than skin and wound antisepsis in the form of dusting powders and solutions in concentrations of up to 0·2 per cent. Combination with various sulphonamides are popular.

Aminacrine Hydrochloride, B.Vet.C. is a yellow powder which is slightly more soluble than proflavine. Its effect, toxicity, and irritant properties, lie between those of acriflavine and proflavine.

Incompatibility. All the acridine dyes are antagonized by hypochlorites and these two types of antiseptics should not be used together.

The Fluorescein Dyes. Of this group, only *Fluorescein Sodium*, B.Vet.C. is used to any extent. When one drop of a 2 per cent. solution, which is reddish brown, is placed in the eye at the outer canthus dilution with tears occurs and the eye becomes green and fluorescent. Any corneal ulcerations show up as light green fluorescent patches which are easily seen without a lens; foreign bodies show up as dark areas within the fluorescent zone. The dye is normally drained off through the lacrimo-nasal duct and fluorescent staining will appear at the nostril within a minute of application to the eye unless the duct is blocked. This diagnostic aid is most frequently used in small animals but is equally efficient in other species. More recently, up to 30 ml. of a 10 per cent. autoclaved solution have been injected intravenously in horses suspected of suffering from *periodic opthalmia* or iridocyclitis; if the disease is present, fluorescence is noticeable in the aqueous humour within ten minutes. The same phenomenon is shown in dogs with intra-ocular inflammation if up to 60 gr.

(4·0 G.) are given orally in aqueous solution (it dissolves in an equal volume of water, but more dilute solutions are preferable); up to twenty minutes may elapse before fluorescence is observed in the anterior chamber. Normal eyes do not show fluorescence. As with the acridine dyes, photosensitization occurs and animals should be protected from direct sunlight for up to two days after dosing.

The Azo-Dyes. Scarlet red or Sudan IV is the only azo-dye used in veterinary medicine, if the coloured sulphonamides are excluded. It has been used in clean, granulating wounds to stimulate epithelial growth, and it is recommended that a 4 per cent. ointment is used, alternating every forty-eight hours with a bland emollient ointment. Stronger concentrations may cause necrosis and, if applied over too long a period, irritation may occur. It is of little value in indolent ulcers.

The Phenolphthalein Dyes. Phenolphthalein itself is an irritant laxative and purgative besides being a laboratory indicator which is red in alkaline and colourless in acid media. A related dye phenol red or *phenolsulphonphthalein*—is used as a means of determining renal filtration rate. The test consists of an intravenous injection of 1·0 ml. of isotonic alkaline saline containing 6·0 mg. phenolsulphonphthalein. Excreted urine is collected and either titrated with sodium hydroxide or compared with a standard after alkalization. About 25–30 per cent. should be excreted in the first 15 minutes, about 50 per cent. in the first hour, and up to 85 per cent. in the first two hours. The dye should first appear within ten minutes. Phenol red is also used as a laboratory indicator for pH estimations.

Miscellaneous Dyes. Many dyes are used as bacteriological and histological stains, as antiparasitic agents against blood parasites, as supravital stains, and for use in colouring tumour tissue or for differentiating normal tissue from any dead or abnormal tissues. Methylene blue, trypan blue and mepacrine may be cited as examples.

The Nitrofurans

These are a group of compounds developed in recent years which possess antibacterial properties thought to be due to inhibition of oxidative enzyme systems. They are mainly of value as external antibacterial agents, but have also been developed for oral use against coccidiosis and salmonellosis in birds, and also salmonella infections in pigs.

Nitrofurazone, B.Vet.C.

This is an odourless, lemon yellow, crystalline powder which turns brownish on exposure or heating: it is almost tasteless initially but develops a bitter after taste. Its greatest solubility is 1 : 350 parts of polyethylene glycol.

Actions and Uses. Nitrofurazone is both bacteriostatic and bactericidal, according to concentration, against both Gram positive and Gram

negative organisms, including Salmonella species and the common streptococci and staphylococci which occur in skin infections. There is practically no effect on Pseudomonas species (N.N.R., 1955).

Externally, nitrofurazone is applied as a 0·2 per cent. cream, the base consisting of water miscible polyethylene glycol mixtures, or as a lotion using a fluid vehicle containing polyethylene glycol and a complex phenylether. The cream is useful for contaminated wounds, burns, scalds etc., whilst the solution is of value in otitis in small animals except where Pseudomonas is a complicating factor. Opthalmic solutions are also available.

Individual susceptibility to nitrofurazone occurs and in these cases human experience indicates that skin rashes may develop with 5–10 days continuous usage.

Internally, nitrofurazone has been shown to be of value as a coccidiostat in chickens without interfering with weights and gains when fed prophylactically at concentrations of 0·005–0·01 per cent. or curatively at 0·02 per cent. of the diet. In the drinking water, levels of 0·01 per cent. give results similar to the higher concentration in the food. Curative doses must be given very soon after infection and continued for seven days if the best results are to be achieved. There is evidence to indicate that higher levels tend to prevent birds acquiring immunity so that carriers may precipitate dangerous outbreaks subsequent to withdrawal of the drug.

The drug has been used experimentally by mouth in pigs against *swine paratyphoid* and in poultry against *pullorum disease* but clinical support is not yet available.

In the United States, nitrofurazone has been used either with or without penicillin as aqueous udder infusions, but the necessity for three or four single daily injections of the 0·2 per cent. infusion and the recommendation of leaving the infusion in the udder for the whole 24 hours between dosage makes antibiotic injections preferable.

Furazolidone is another nitrofuran which has proved of value in poultry diseases and there are numerous reports on its use in B.W.D. (*bacillary-white-diarrhœa*—due to *Salmonella pullorum* infections) in chickens, *blackhead* and *hexamitiasis* in turkeys. Blount (1955), however, points out that the gonads of the male chickens are affected by furazolidone and that further work is required. Doses in use are 0·011–0·015 prophylactically, and up to 0·04 per cent. curatively, in food.

Other compounds such as Nitrofurantoin, N.N.R. are extremely useful for resistant urinary infections but expense and scarcity prevent its veterinary use in Great Britain.

Toxicity. At the recommended concentrations, toxicity is negligible but an accidental concentration of 0·1 per cent. nitrofurazone in the food was reported (Blount, 1955) to have given 60 per cent. mortality before the cause was diagnosed. Topical dressings should not be applied in deep

pocketing wounds because of the danger both of local toxicity and of systematic toxicity following absorption.

Detergents

This group of compounds is part of a large group collectively referred to as *surface-active agents*, which all have the property, in some degree, of reducing surface and interfacial tensions—the properties of emulsifying agents. Other properties of surface-active agents are those of 'wetting', spreading, penetrating, foaming and, in some cases, anti-foaming, and detergent activity. One agent may possess one or more of these attributes and perform these several functions at the same time. Thus *detergents* are classified as emulsifying and cleansing agents which frequently possess antibacterial properties, though the term is becoming a common household name for a chemical cleansing agent. Some detergents have stronger antibacterial properties than others, but antibacterial effect is not related directly to surface-activity.

Surface-active agents are of two main types, those which ionize—ionic—, and those which do not—non-ionic. The detergents belong to the ionic group and are of two types: (1) those which are active in mildly acid solution by virtue of active anions—*anionic detergents*, and (2) those which are active in alkaline solution and in which the detergent property is vested in the cation—*cationic detergents*.

The antibacterial activity of detergents is greatly reduced by the presence of organic matter such as blood, serum, and pus, and ionic detergents have little or no effect on viruses, spores, or fungi.

Anionic Detergents. Included in this group are the alkaline earth salts of organic acids with high molecular weights, sulphated alcohols, and sulphonated oils. Examples of these used in the veterinary field are the soaps (sodium or potassium oleates, etc.), calcium and ammonium mandelates, bile salts, and sodium lauryl sulphate.

Only the soaps and sodium lauryl sulphate are of any significance as antibacterial and cleansing agents, and their antibacterial activity, which is not great, extends only to Gram positive bacteria, so that for most purposes stronger and more comprehensive antibacterial agents must be incorporated with them.

Soaps have been used as detergents for many years. Their cleansing properties are widely known and are due mainly to the emulsification of grease and the loosening of keratin, dirt, and similar debris. Their antibacterial properties are low and any benefit arising from pre-operative skin cleansing arises from removal of dirt and debris to which bacteria are adherent. Soaps are therefore combined with stronger antibacterial agents such as alcohol, hexachlorophene, phenylmercuric nitrate. There are two official soaps.

Hard Soap, B.Vet.C., sometimes referred to as castile soap, is an off-white, almost odourless, solid substance obtained by the reaction of a

vegetable oil with sodium hydroxide. It consists mainly of sodium oleate, is moderately soluble in cold but freely soluble in hot water, and is almost completely soluble in alcohol. When dry, it is easily powdered and can then be incorporated in bath powders. Curd soap, which is similar, consists of sodium soap made from animal fats.

Actions and Uses. Hard soap is a surface tension reducing agent and can be used as an emulsifying and dispersing agent. 15 gr. (1·0 G.) will emulsify 1 fl. oz. (30 ml.) of a volatile oil such as turpentine, or 2 fl. oz. (60·0 ml.) of a fixed oil, and the soap is used for this in the preparation of soap liniments. Its cleansing properties are well known and evidence is available to demonstrate some degree of antibacterial effect. It is used, amongst other things, as a lubricant enema or rectal suppository in the treatment of fæcal impaction. Pharmaceutical hard soap is used as an excipient for pills and horse balls, and as a detergent basis for parasiticidal shampoo powders.

Soft Soap, B.Vet.C. is a brown to yellowish-white petroleum-jelly-like substance, the lighter colour being a purer product. It is frequently coloured green with such dyes as chlorophyll. The compound is a potassium soap of a vegetable oil and is soluble in water and alcohol. It may contain free caustic and is usually considered unsuitable for skin cleansing because of this.

Actions and Uses. Soft soap can be used as an emulgent in much the same way as the hard soap, and 240 gr. (16·0 G.) will emulsify 1 fl. oz. (30·0 ml.) of a volatile oil and 2 fl. oz. (60·0 ml.) of a fixed oil. Many liniments are made using these proportions. Alcohol and ether soaps contain soft soap—*Soap Spirit*, B.Vet.C. contains 65 per cent. of soft soap and is used in the preparation of liquid shampoos. As with hard soap, the potassium compounds have some antiseptic action which is enhanced by the inclusion of spirit and other antibacterial compounds.

Sodium Lauryl Sulphate, B.Vet.C. is a white or yellowish fine powder or crystals with a faint odour. It is irritant to mucous membranes. The compound is soluble in water giving turbid solutions but is only partially soluble in alcohol.

Actions and Uses. Sodium lauryl sulphate is a surface-active compound with useful wetting and detergent properties. It is used as a wetting and dispersing agent in cattle drenches containing phenothiazine, hexachlorethane, or light vegetable powders, and in parasiticidal dips and sprays containing gamma benzene hexachloride and dicophane. It is also used extensively in shampoos and dips, sometimes combined with soaps. The compound is active in reasonably acid or alkaline media and also in hard water, as the calcium and magnesium salts of the alkyl sulphate are also soluble. The inclusion of soap powders retards the formation of insoluble calcium and magnesium soaps and therefore maintains activity.

As an emulsifying agent, sodium lauryl sulphate is used in many ointment bases including *Emulsifying Ointment*, B.Vet.C. and *Emulsifying Wax*, B.Vet.C.

The antibacterial properties of the compound are typical of anionic detergents. No effect is exerted on Gram negative organisms.

All anionic detergents are antagonized by cationic compounds and vice versa.

Cationic Detergents. These compounds are sometimes referred to as 'reversed soaps'. They consist therefore of neutral salts of bases with high molecular weights, and include the quaternary ammonium compounds and the rosaniline and acridine dyes. In contrast to the anionic compounds, these cationic detergents are more active in alkaline media.

As a group, these agents are active against both Gram positive and Gram negative bacteria, but higher concentrations are required against the latter group.

The dyes, which have been referred to previously, possess useful antibacterial effects, but the most important cationic detergents and antiseptics are the quaternary ammonium compounds.

The Quaternary Ammonium Compounds. These compounds can be regarded as ammonium (NH_4) compounds in which the four hydrogen atoms have been replaced by organic groups. If one of these organic groups is a long chain fatty or paraffin-like chain a typical cationic detergent is produced which has strong antiseptic properties, but if two groups are long chains a cationic detergent is produced with very strong antiseptic powers and greater stability over the pH range. The two types are more effective in alkaline solution and activity is reduced in the presence of pus, blood and serum, due to their adsorption and chemical reaction with a large variety of substances, including proteins. They are, for example, completely adsorbed by charcoal. The double chain compounds are claimed to be less reactive with organic matter.

Quaternary ammonium compounds have no effect on viruses and though some effect against spores is claimed for them this should be discounted in practice. When used as disinfectants for instruments and utensils these should first be heat sterilized to destroy spores, after which, provided all organic matter has been scrubbed off, the quaternary ammonium antiseptics will maintain sterility. It is advisable with many of these antiseptics to include antirust compounds such as sodium nitrite in the solutions. Some antifungal action is exerted, but no clinical use of this has been made so far.

The quaternary ammonium detergents form a film on the skin which is strongly antiseptic externally but unreactive internally so that pathogenic bacteria may exist under the film. This indicates that sterilization of operation sites by this group of compounds alone is almost impossible

(NNR. 1955). Anionic detergents, if used first and thoroughly rinsed off, will assist, but possibly the best method to overcome this phenomenon is to include alcohol in the quaternary ammonium solutions.

Cetrimide, B.Vet.C. is a compound of the quaternary ammonium group of detergents which is very widely used. It is a fluffy white or creamy-white powder which is soluble in water and alcohol. It is a strong foaming agent.

Actions and Uses. These are typical of the group. Solutions of 1 per cent. are used for skin cleansing and wound or burn dressings; 0·1 per cent. concentrations are used for solutions in which udder cloths, milkers' hands and utensils are rinsed and 0·5 per cent. creams are applied to the teats and hands as prophylactic procedures in mastitis eradication. Instruments are kept in 1 per cent. aqueous solutions containing 0·2 per cent. sodium nitrite to prevent rusting.

As with many of these cationic compounds toxicity and irritant properties are relatively insignificant in the concentrations and quantities normally used.

Benzalkonium Chloride, U.S.P. is another typical cationic detergent with strong antibacterial properties. For skin sterilization, a 0·1 per cent. alcoholic solution should be used, but for mucous membranes and deep wounds, 0·01–0·05 per cent. concentrations are better. Instruments require 0·02 per cent. for storage, with sodium nitrite as an antirust agent.

Note: It is important to remember that soaps are antagonistic to all cationic detergents. Where soap is used to clean the skin prior to operations it should be well rinsed off and the area preferably swabbed with alcohol before applying any cationic antiseptic.

The Antibiotics and Sulphonamides

Certain antibiotics may only be used topically because of their toxicity when administered systemically. Tyrothrycin is an example. Besides the antibiotics restricted to topical application some of those used systemically are also used topically with safety. Amongst these are penicillin, oxytetracycline (Terramycin), chlortetracycline (Aureomycin), and chloramphenicol (Chloromycetin). Some sulphonamides are also used topically as antiseptics both as powders and solutions.

Both these groups of antibacterial chemotherapeutics are detailed elsewhere (See section III.)

Antihistaminics

Many of the secondary skin conditions of animals are traceable to self-inflicted trauma which has resulted in local histamine release. The release of histamine causes capillary dilation, extravasation of fluid, and hæmoconcentration. These conditions cause skin wheals with stretching and irritation of nerve endings which in turn induces further self-inflicted

damage. Large oozing eczematous areas are so produced 'wet eczema' in the dog, 'flea' or 'fish' eczema of cats and 'sweat itch' of horses, are common examples.

In recent years, a series of compounds which are specific histamine antagonists have been developed and these may be used systemically or locally. They are particularly effective by reason of local anæsthetic properties as well as their anthistaminic activity. For local effect they are usually applied in the form of creams or lotions.

Examples of histamine antagonists in common use are *Antazoline Hydrochloride*, B.P.C., *Diphenhydramine*, U.S.P., *Mepyramine Maleate*, B.Vet.C. and *Promethazine Hydrochloride*, B.Vet.C. These drugs are detailed in the section dealing with drugs which affect the peripheral circulatory system (Chapter 10).

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CHAPTER 21

AGENTS AFFECTING THE SKIN

(iii) PARASITICIDES

A PARASITICIDE, when the term is used in its widest sense, is any compound which will destroy any parasite. In veterinary medicine, however, the name is applied only to those substances which are active against parasites living on or in the skin of animals. These parasitic organisms may be metazoan animal parasites, known as ectoparasites, or they may be fungus parasites. Those substances which destroy the fungus parasites are usually called fungicides or antimycotic agents.

The ectoparasites of domestic animals include

(1) The *Arachnida*, or relatives of the spider, which are:

(a) The *ticks*, affecting mainly cattle and sheep, but some species also parasitize dogs and poultry.

(b) The *mites*.

(i) *Family Sarcoptidæ* includes the mange mites which cause sarcoptic, psoroptic, chorioptic, notœdric, and otodectic mange, in the different species, and also the depluming itch and scaly leg of poultry.

(ii) *Family Demodicidæ* includes the parasite causing demodectic mange.

(iii) *Family Gamasidæ* includes the various 'mites' of poultry, e.g. red mite.

(iv) *Family Trombidiidæ* includes the harvest mite, the larva of which causes so much trouble in dogs and cats throughout the summer.

(2) The *Insecta* or flies and their relatives, comprising three orders, Diptera, the flies; Anopluma, the lice; and Siphonaptera, the fleas.

A. Order Diptera.

(a) Suborder Athericera. This group contains several families of free living flies, some of which feed on the blood of the host, whereas others are only parasitic during the larval stages of their life history. Amongst the former are *Glossina* species, or tsetse flies, whilst among the latter are species of *Lucilia*, the sheep maggot fly, species of *Hypoderma*, the warble fly, *Gasterophilus*, the horse botfly, and *Œstrus ovis*, the sheep nostril fly.

(b) Suborder Pupipera. In this group belong the *keds* or *Family Hippoboscidæ*. The sheep ked, *Melophagus ovinus*, is wingless, but the horse ked, *Hippobosca equina*, and the deer ked, *Lipoptena cervi*, are both winged.

B. Order Anopleura. These are the *lice*, wingless creatures classified according to whether they merely bite the host:
Suborder Mallophaga, which includes lice of the dog, sheep, horse, cow, goat, cat and also poultry:
or whether they suck the blood of the host:
Suborder Siphunculata. These lice affect the pig, horse, cow, sheep, goat, dog and man.

C. Order Siphonaptera. These are the *fleas*, which suck the blood of the host, injecting irritant substances at the same time to slow up blood clotting. They are wingless insects and attack the dog, cat, poultry, rats and man. The 'chigger flea' affects pigs as well as man and the dog.

These parasites can be broadly divided into three main groups: 1. Those which migrate through the tissues of the host, 2. Those which burrow into and live in the superficial skin layers, and 3. Those which live on the skin, though biting through into the deeper tissues.

The parasites of the first group are mainly the horse bots, warbles and sheep nostril fly larvæ. None of these have so far been effectively destroyed during their migratory phases and therefore considerable damage can occur before the parasites can be attacked. At the moment bots are treated with carbon disulphide on reaching the stomach and warbles by external dressings of derris, gamma-benzene hexachloride, or dicophane, once the skin has been punctured by the larvæ for respiratory purposes. Recent work on the effect of oral dosing with phenothiazine together with hexachlorethane has so far produced disappointing results: (Kenney *et al.*, 1955 and Cobbett *et al.*, 1957). However, subcutaneous injections of dieldrin in oil have shown that this method of treatment may become very useful (Roth *et al.*, 1955). *Œstrus ovis* larvæ are treated by local nasal injection, the best being an emulsion of benzene hexachloride (Du Toit, 1956).

The second group consists of parasites which burrow into the skin or penetrate deeply into the hair follicles. They are the mange mites. Surface applications are at present the best treatment. They should be used in vehicles which contain detergents and keratin softening agents such as the alkali hydroxides and sodium carbonate, or oleaginous lubricating agents, all of which aid penetration of the active agent. As with other ectoparasites, feeding and injecting the host with therapeutic agents have been used with moderate success, but toxic effects have restricted the wide use of these routes.

The third group contains parasites living on the skin surface which can be effectively treated with sprays, washes, and dusting powders, and more

recently, low pressure ærosols. Thus lice, poultry mites, fleas, keds, ticks, and the larval stages of the harvest mite, are all fairly easily dealt with. The maggots or larvæ of Lucilia species which cause strike in sheep are also dealt with by surface applications, whilst the adult flies of Hypoderma, Œstrus and Lucilia genera can also be destroyed or repelled by surface applications. More recently, investigations have been going on to develop the oral or subcutaneous route of administration of compounds with parasiticidal activity against these types, though not without accident (Bolle, 1956; Roulston, 1956; and Norris *et al.*, 1956).

An ideal parasiticide should:

(1) Destroy all parasites at every stage of their life history.
(2) Be rapid in action.
(3) Be non-toxic to the host.
(4) Be compatible with the various bases and vehicles required for application.
(5) Be economically practicable.

A further point can be added from recent experience and that is—the parasiticide should not create species resistance in the parasites. This development of drug resistant species has become a grave problem to the research workers, for some important parasites such as the ticks of genus Boophilus have developed resistance to each successive parasiticide as it has been used. The need to retain the initiative in the battle is fully appreciated by all who are working in this field.

Needless to say, no parasiticide has yet been discovered which fulfils all these requirements.

In a review of insecticides, Harbour (1955) states a preference for the use of certain parasiticides against particular types of parasites.

For sheep blow flies, which cause strike—Lucilia spp. in Great Britain—dieldrin is extremely efficacious and persistent, giving 3–4 months protection.

For sarcoptic and psoroptic manges Gamma Benzene Hexachloride, B.Vet.C. has proved of immense value. Along with Dicophane, B.Vet.C. (DDT), it has provided complete protection against lice and keds—and against the common sheep tick of the British Isles, *Ixodes ricinus*.

Cattle ticks provide a number of problems because of the variety of ticks responsible for infestation. For three host ticks of Amblyomma and Rhipicephalus genera, benzene hexachloride, dicophane, and toxaphene, have been widely and successfully used and are tending to replace arsenical dips. Two host ticks respond similarly but, as already mentioned, one host ticks, particularly of genus Boophilus, are becoming resistant to most known insecticides, though different areas of the world seem to have different resistance problems. Organic phosphorus parasiticides are being investigated as a further line of defence should DDT resistant strains become widespread.

Old Type Parasiticides

Most of these are still in effective daily use but have been grouped together, mainly because of their non-specific character and, in general, their lower activity.

Nicotine, arsenic, phenol and cresol, have been widely used as sheep dips, often combined, in the case of the first two, with sulphur-arsenic and sulphur dips are still in world-wide use for sheep and cattle dipping, though they are gradually being supplanted by the newer parasiticides owing to the development of parasite resistance.

Arsenic has been used at a strength of 0·1 per cent. sodium arsenite for repeated rapid dipping, and 0·3 per cent. for less frequent dipping. In Great Britain the yellow dips of arsenic and sulphur were very popular and are still used. A typical formula for the preparation of one of these is:

℞ Arsenic Trioxide, Potassium Carbonate, Sublimed Sulphur *āā* 20 lb.
Soft Soap ..... 4 lb.

Stirred and boiled in 10 gallons of water and diluted to 1000 gallons, this gave an arsenite concentration of 0·2 per cent. The main disadvantage of these dips was the danger of poisoning from skin absorption, particularly on hot days.

Nicotine is not frequently used now because of its great toxicity, though red mite on poultry are still destroyed by painting the perches with nicotine sulphate solution and restricting the ventilation of the poultry house. The heat of the bird causes evaporation of the nicotine salt and destroys the parasites by fumigation. (This is carried out at night when the mites have migrated from the building onto the birds.)

Sulphur. In its various forms sulphur has been used both internally and externally throughout the centuries. Its irritant laxative action when administered orally is now rarely resorted to, though many will still remember the 'brimstone and treacle' weekly dose. The laxative effect is due to the production of irritant sulphides by reaction of the sublimed sulphur or brimstone with the intestinal acids and alkalis. Externally, sulphur was the best anti-mange dressing available for veterinary use until the advent of the chlorinated benzene derivatives. It is still used extensively for routine baths for dogs. The various compounds may be applied as ointments or oily suspensions at a concentration of 1 : 8: as powders diluted with talc, kaolin etc.: as dispersible bath powders combined with soaps and wetting detergents: as aqueous solutions of 1 : 8 up to 1 : 60, combined with lime, arsenic, phenol etc. for sheep dips. For area disinfestation and disinfection, fumigating candles can be used.

Sublimed Sulphur, B.Vet.C. (Sulphur sublim.).

This lemon yellow slightly gritty powder, which is tasteless and odourless when freshly prepared, is commonly known as 'flowers of sulphur'. When

kept for a short period a slight odour and acid taste develops due to oxidation. It is insoluble in water and alcohol.

Actions and Uses. Sublimed sulphur is the form of sulphur most commonly used. *Ointment of Sulphur*, B.Vet.C. contains 10 per cent. of sublimed sulphur, but other concentrations varying from 1 : 8 to 1 : 20 are frequently used. Triturated into rape oil or white mineral oil at a concentration of 1 : 8, sublimed sulphur forms the once widely used *sulphur liniment*. The substance was also used in powder form diluted to 1 : 8 by calamine, zinc oxide, kaolin, talc, or similar skin sedatives. Lime and sulphur sheep dips were prepared by putting 2 parts by weight of quick lime with five parts by weight of sublimed sulphur in a sack, simmering for 24 hours in 100 parts of water, and then diluting to 1000 parts. For fumigation, the equivalent of between 2 and 4 lbs. is required per 1000 cu. ft.

The parasiticidal effect is due to the same chemical reaction that causes the laxative action internally. Thus, in contact with the skin, the inactive sulphur is slowly converted into irritant and parasiticidal sulphides and polysulphides. Mange was effectively treated with sulphur dressings by repeated dipping of horses, cattle and sheep, and by repeated oleaginous applications in pigs and dogs. A course of treatment usually took three months or more and local treatment with ointment on resistant patches was required at the end of that time. Pigs are still frequently treated for lice infestation by rubbing sulphur in lard on their backs. It is a cheap and ultimately effective home remedy.

Frequent use of sublimed sulphur on delicate skinned animals occasionally causes an irritation dermatitis which aggravates the original condition.

Precipitated Sulphur, B.Vet.C. (Sulphur Præcip. or Milk of Sulphur) is a pale yellow smooth powder without odour or taste and is used as a substitute for sublimed sulphur on all occasions, but particularly where there is a danger of sulphur dermatitis.

Sulphurated Potash, B.Vet.C. (Potass. Sulphur. or Liver of Sulphur) is a complex polysulphide, sulphite, thiosulphate compound, consisting of greenish yellow lumps which fracture giving a smooth liver brown surface which soon goes yellow. The compound has a strong odour of hydrogen sulphide. It was used to prepare dips as it is very soluble in water, one ounce (30·0 G.) being dissolved with soap in one gallon (5·0 litres).

The main disadvantages of these sulphur compounds are their tendency to give the dressed animal a highly unpleasant smell, and their lack of persistence making repeated dressing necessary. Organic sulphur compounds were therefore developed which did not possess this odour and which, moreover, were more powerful, and active over a wider field.

Monosulfiram, B.Vet.C., known commercially as Tetmosol, is probably the most outstanding of these organic sulphur compounds. It is a yellow,

or yellowish brown, crystalline powder which is insoluble in water but soluble in alcohol. It has a faint odour and a bitter taste.

Actions and Uses. Monosulfiram is active against fleas, lice, ticks, and mites, and is also a potent fungicide. In all cases, it is advisable to scrub the skin clean of all scales and scabs first, applying the dressing while the skin is still moist but not wet.

For use against ectoparasites a dilution of 1 in 10 of the 25 per cent. alcoholic solution is brushed well into the skin. In farm animals if the condition under treatment is mange, the dressing should be repeated every two or three days until the condition is cured, but in cats and dogs three dressings should be sufficient.

Surface living ectoparasites can easily be controlled by washing with a 5 per cent. soap at suitable intervals—two to three weeks.

Mesulphen, B.Vet.C., commercially known as Sudermox, is a yellow oily preparation which in emulsion form is very useful as an antipruritic, a skin softener, and a parasiticide. The compound should be massaged into the affected area or applied with a brush, making sure that the dressing contacts the skin and is not merely applied to the coat. Dressings should be repeated every two or three days until the condition is cured. Animals should not be dressed completely on any one occasion and extra care should be taken when applying the compound to cats. The preparation is neither so cheap, so easy to apply, nor so persistent as the newer chlorinated benzenes.

Iodine has already been referred to in the section on counter-irritants and must be mentioned later as a fungicide, but it also has uses as a parasiticide, especially as an alternative treatment in demodectic mange, particularly of dogs. It should be applied in the form of 'colloidal iodine', a mineral oil solubilization. Large areas should not be dressed, for sufficient iodine may be absorbed to cause an acute iodism instead of the mild chronic iodism which is required to exert a parasiticidal effect.

Sodium Fluoride has been used as a dusting powder for the treatment of lice in poultry and occasionally in pigs, and solutions of 0·5 per cent. sodium fluoride have been used for fortnightly or monthly leg dressings in poultry affected with 'scaly leg'.

It has also been used as a very effective ant killer, when ants are encouraged to eat medicated cake or bread by smearing it with jam. The 'doctored' food should be sealed in a tin which has had several holes knocked in it, and placed near the nest. The fluoride is carried into the nest and fed to the larvæ and queens so that within a week the whole nest is dead, for the workers also feed on the material. The food is sealed in the tin to prevent accidents due to children eating it.

Derris, B.Vet.C. and Lonchocarpus, B.Vet.C.

Derris is the rhizome and root of leguminous plants originally obtained from the East Indies, Malaya, Burma, and Siam area, but other sources

were exploited during the recent war. From these rhizomes are made *Prepared Derris*, B.Vet.C., which is a powder containing about 5 per cent. of rotenone, the main active ingredient and parasiticide.

Actions and Uses. Rotenone is an effective parasiticide which acts more rapidly than benzene hexachloride, but less rapidly than pyrethrum. It is not persistent and must therefore be used frequently: an interval of seven to ten days is optimal. The substance acts on the parasite both by surface absorption and following ingestion, and is therefore termed a 'contact and stomach poison'.

Prepared derris may be applied as a wash or dip with 5–20 per cent. soap or detergent to assist in wetting the powder. It was used extensively for 'double-dipping' sheep in the treatment of 'sheep-scab', but the chlorinated benzene derivatives have superseded it. In this form it is effective against all the 'superficial' parasites, ticks, keds, fleas, and lice, and has been used against these parasites in all species, but is now mainly used against sheep keds and lice, and fleas and lice in dogs. In this form also it is still the agent of choice against warbles in cattle and is specified under the Warble Fly (Dressing of Cattle) Order 1948, when it should contain 1½ oz. of derris resins or equivalent, and four ounces of soap, per gallon of dressing. Applications should be made four times between March 15th to June 30th directly into the warbles in the skin. The wash may be scrubbed on, sprayed on, or the animals may be dipped.

Derris is also used in dusting powder form for small animals, when it is diluted to 1 per cent. rotenone, with talc and similar diluents. It is applied in this manner infrequently in large animals because of the danger from 'burning' where the dressing concentrates in drainage channels through the coat when the animals are exposed to rain.

Rotenone itself is a white crystalline powder now used mainly as a 2 per cent. solution in cod-liver oil, or similar bland oil, as an alternative dressing in demodectic mange of dogs.

Lonchocarpus, B.Vet.C. was used as an alternative to derris in the recent war and owes its activity to a 3 per cent. rotenone content. It is therefore used in exactly the same way as derris. None of these preparations are effective in mange.

Toxicity. Derris and lonchocarpus were originally used by natives as a fish poison and their effect is one of nervous system paralysis preceded by convulsions. Death results from respiratory paralysis. River pollution by waste dips should be avoided, for fish are extremely susceptible to rotenone poisoning. It is unlikely that toxicity will be seen in mammals under normal conditions.

Pyrethrum Flower, B.Vet.C.

When powdered, these dried flower heads of a chrysanthemum produce a compound known for many years as *Dalmatian insect powder*. The active

principle, mainly in the form of *pyrethrins* should be present in a concentration of at least 1 per cent. An extract, *Pyrethrum Extract*, B.Vet.C., contains approximately 20 per cent. pyrethrins in kerosene (fuel paraffin). Two pyrethrins are known, of which pyrethrin 1 is the more active in aqueous suspension, but in other forms the two are equal in effect.

Actions and Uses. Pyrethrins are contact poisons which have a rapid paralytic action preceded by muscular excitation and convulsions, giving a 'knock-down' effect, from which some insects may recover. However, for this 'knock-down' effect they are frequently combined with the slower acting but more lethal chlorinated benzene derivatives. Pyrethrum powder was once extensively used on its own as a treatment for fleas and lice. One such commercial powder was very widely known as 'Keating's Powder'. More recently, synergistic agents, of which piperonyl butoxide is one, have been discovered. These intensify and prolong the effect of the pyrethrins and form a useful insecticidal combination. Even so, they do not persist and therefore have an application limited to fly spraying and to occasional baths for small animals.

Benzyl Benzoate, B.Vet.C.

This compound exists as an oily liquid or a crystalline colourless solid, with a typical aromatic odour and burning taste; it is insoluble in water but soluble in alcohol and other organic solvents.

Actions and Uses. Benzyl benzoate is effective against most external parasites in domestic animals, and has been used against sarcoptic, otodectic, and demodectic mange, in the form of a 25 per cent. emulsion, and, as an alcoholic solution, against fleas, lice, and harvest mites on dogs. It is also active against ringworm fungi.

When the whole of an animal is affected, small areas only should be dressed at a time, or a diluted bath should be used. For bathing, the alcoholic solution should be diluted by 50 per cent. water and rubbed into the animals coat after a thorough wetting. After a ten to fifteen minute interval the greater part of the dressing should be washed off and the animal rubbed dry.

When applied as a 25 per cent emulsion in the treatment of sarcoptic mange the animal must be clipped and the dressing massaged well into the skin. This is time consuming and unnecessary with the newer dressings; moreover, it has no residual effect so that weekly dressings are required.

Toxicity. Benzyl benzoate is a nervous system depressant, and toxic effects include vertigo, inco-ordination, coma; and death from respiratory and cardiac depression. Where vertigo is noticed, immediate washing followed by dosing with caffeine and other stimulants are measures which are normally effective. Though widely used as an ear dressing in cats against *Otodectes cynotis*, its use in this respect is not very safe and it is not recommended for cats.

Modern Parasiticides

The first of the modern parasiticides were *Dicophane*, B.Vet.C., commonly referred to as DDT, and *Gamma Benzene Hexachloride*, B.Vet.C., both of which were developed during the recent war, and are chlorinated hydrocarbon compounds. Since then, many new chlorinated hydrocarbons have been produced, some related directly or indirectly with these first two. Amongst these, methoxychlor, chlordane, toxaphene, aldrin and dieldrin are outstanding, but toxaphene and dieldrin show most promise.

Parallel in development there has appeared a series of organic phosphorus compounds which are being urgently examined as possible parasiticidal successors, should parasite resistance to all known chlorinated hydrocarbons develop.

Both groups of insecticides are toxic but the phosphorus compounds which act by inhibiting cholinesterase enzyme breakdown of acetylcholine are by far the more dangerous. Toxic symptoms are group specific, but post-mortem pictures vary widely within each group. Excitement, convulsions and high body temperatures typify the symptoms of poisoning with the chlorinated hydrocarbons, whereas dyspnœa profuse salivation and stiffness are the outstanding symptoms shown in poisoning due to the phosphorus compounds (Radeleff, 1958).

Along with the newer parasiticides, new methods of application have been developed, such as the high pressure spray cattle races, and the small portable low pressure sheep spray races for use with dieldrin. These have provided large economies in time, labour, and material costs, without loss of efficiency.

Dicophane, B.Vet.C.

Dichloro-diphenyl-trichloroethane or DDT is a white or off-white crystalline powder which is usually odourless. It is impure and specified to contain not less than 75 per cent. of the active agent. Insoluble in water for normal purposes, it is soluble to the extent of 2 per cent. in alcohol and 10 per cent. in fixed oils. Other organic solvents readily dissolve the compound.

Actions and Uses. Dicophane is a neurotoxic contact poison. It may also act as a stomach poison following ingestion. The precise method of action is not known but it affects both the motor and sensory nervous system in a manner common to the chlorinated hydrocarbons as a group. The first signs of toxicity, which appear immediately on contact with an ærosol spray, is a frantic attempt to rub off the substance followed by general excitability, inco-ordination, paralysis and death. The 'knock-down' action on flies of pure ærosol sprays takes several minutes to take effect which compares unfavourably with the immediate action of those containing pyrethrins.

The toxic effect on parasites is shown by a considerable increase in irritability of the host as the parasites increase their pre-paralytic activity. This period may last up to 30 minutes or more depending on the type of

preparation and concentration used. Thus, if powders are used the period will be longer than if oily dressings, which increase absorption, are used. The toxic effect of dicophane on *small animals* has made the compound unpopular for dogs and cats, but it is occasionally used against fleas and lice as a bath powder containing 0·2 per cent., or a dusting powder containing 5 per cent., though only for healthy adult dogs. Cats, puppies and birds, are susceptible to poisoning and, if bathed with dicophane, animals should be thoroughly rinsed after a few minutes. Dusting powders should be brushed out of the coat after a period of 15–30 minutes.

In *large animals*, DDT has been of immense value in irradicating mange, lice, keds, and ticks, in sheep, cattle, and horses, and has also assisted in clearing areas of disease bearing insects such as mosquitoes, house flies, etc. It is used in dusting powders containing 5 per cent. but more especially in sprays and dips in concentrations varying from 0·2 to 1 per cent. depending on the parasite and species to be treated.

In *sheep*, dicophane, though being replaced by dieldrin, was for several years preferred for protection against strike. The action was mainly directed against the adult fly but thorough dipping ensured some protection against the larvæ. Larval control was improved by dressing locally with emulsions or aqueous dispersals, though in this respect benzene hexachloride was superior. Sheep scab has been eradicated from Great Britain with the aid of dicophane, but its activity against mange mites is inferior to that of benzene hexachloride. Lice and keds are disappearing, though where dipping has been discontinued or intermittent, increases have been noticed. Dicophane is less effective than benzene hexachloride against sheep ticks in Britain.

In *cattle*, dicophane has been perhaps the best single parasiticide in the battle against cattle ticks. In spite of signs of a few pockets of resistance developing, its use has not been followed by the development of resistant strains to the same degree as most other parasiticides. It is consequently regarded as a reserve to be used in emergency where parasites, particularly one-host ticks, develop resistance to other agents.

Residual effects are shown by dicophane. Applied as a concentrate spray or a paint at the rate of 100 mg. per square foot, dicophane will give insecticidal activity for as long as six weeks. Reliable protection is dependent on the thoroughness of application and is approximately 3–4 weeks.

Toxicity. Absorption of dicophane through intact skin is not of great significance unless oil solutions are used. In small animals particularly, the licking of dicophane from dressed areas may cause trouble, but the greater danger results from dressing young animals with dusting powders in confined spaces. Kennelled puppies, for example, will inhale enough powder to kill them, even if the bitch alone is dressed. In large animals, toxicity dangers are slight, particularly as they are the least susceptible

species, but sufficient may be excreted in milk to cause toxicity to children, and great care should be taken when dressing milking cows. Symptoms are those expected of neurotoxic agents, hyper-excitability, convulsions, paralysis, and death. Post-mortem signs are similar to those of chloroform poisoning with fatty changes of the liver. Pentobarbitone is recommended to control the nervous symptoms and subanæsthetic doses should be combined with cessation of the dicophane treatment and removal of dressings by washing or brushing. Calcium borogluconate intravenously in doses of 30–45 gr. (2·0–3·0 G.) is an effective antidote in dogs (Vaz *et al.*, 1945).

Benzene Hexachloride, B.Vet.C.

The compound is a synthetic preparation containing approximately 12 per cent. of the parasiticidal gamma isomer. It is a light buff powder with a disagreeable and persistent odour; it is not soluble in water but partially soluble in the organic solvents. This impure compound is used commercially for the preparation of dusting powders and dips.

Gamma Benzene Hexachloride, B.Vet.C.

This is the pure parasiticidal gamma isomer and is a white crystalline solid with a slight but characteristic odour. It is insoluble in water but soluble in most of the organic solvents.

Actions and Uses. The action of gamma benzene hexachloride against insects is reported by Kirkwood *et al.* (1946) to be through interference with inositol metabolism. The substance is essentially a contact poison and the effect on the parasite is similar to dicophane but paralysis occurs at a slightly faster rate. A 'knock-down' agent, usually pyrethrin, is used in most B.H.C. fly sprays. As with dicophane, animals will show increased irritation following dressing, but some of this is due to irritant isomers if the impure benzene hexachloride is used.

In *small animals*, benzene hexachloride preparations have been used extensively, but, although the pure gamma isomer is four times less toxic than dicophane, there is still some danger of toxicity. Dogs may be bathed in concentrations of up to 0·2 per cent. using dispersible commercial bath powders, but cats and puppies are best dressed with dusting powders containing from 0·2–0·5 per cent. gamma isomer which, if the whole body is dressed, should be brushed out of the coat after about thirty minutes. This will prevent the licking and swallowing, or the inhalation, of toxic quantities. Dusting powder of Gamma Benzene Hexachloride and Pyrethrum, B.Vet.C. contains 0·5 per cent. of the isomer and 0·4 per cent. pyrethrins. B.H.C. is also used in ear dressings in concentrations of 0·1 per cent. Higher concentrations may cause toxic reactions in cats. For localized areas, creams containing up to 0·2 per cent. gamma isomer are frequently used.

The compound is effective against all parasites of small animals,

especially sarcoptic mange. It is being frequently used against demodectic mange with reasonable success. An effective though expensive dressing can be made to the following formula:

℞	Gamma benzene hexachloride (1 per cent. alcoholic solution)	1 fl. oz.
	Industrial methylated spirits	1 fl. oz.
	Glycerin	up to 10 fl. oz.

This can be applied daily in squamous demodectic mange. Fleas and lice are easily eradicated with B.H.C., particularly if bedding and kennels are sprayed or washed with suspensions or solutions of up to 0·25 per cent. strength.

In *large animals*, benzene hexachloride has been of great value. Its lower chronic toxicity and its earlier discovery have made it more popular than dicophane. It is the parasiticide of choice for the treatment of mange in all species.

In *sheep*, dips and sprays at a concentration of 0·06 per cent. have proved extremely effective against scab, and have enabled single dipping to be adopted in Great Britain. Against *Ixodes ricinus*, the common British sheep tick, benzene hexachloride has also proved to be the best agent available, although not 100 per cent. effective. Keds and lice have been almost eradicated in some areas and Harbour (1955), referring to 'strike', has stated that B.H.C. is 'the best insecticide for killing the larvæ quickly and bringing them out of the wound', although dressings containing either dicophane or dieldrin in addition to the gamma isomer gave better protection against further 'strike'. Du Toit *et al.* (1956) have reported the effective use of a 4 per cent. B.H.C. preparation against *Œstrus ovis* larvæ in the nasal sinuses of sheep. Three treatments were required at 3–4 week intervals, but neither lambs nor suckling ewes should be treated owing to the interference with their sense of smell.

In *cattle*, B.H.C. is as useful as it is in sheep but some resistance has developed in a few strains of Boophilus ticks. A report by Roulston (1956) indicates that against *B. microplus* cattle ticks, B.H.C. subcutaneous injections at the rate of 25 mg./kilo prevented reinfestation with larvæ for up to 22 days and adults did not appear for 43 days. Though aldrin and dieldrin were better, DDT, toxaphene, and the phosphorus compounds diazinon and malathion, were useless at the same dosage.

Dips containing B.H.C. have remained stable as long as six years, but they should incorporate copper sulphate at the rate of 0·03 per cent. as a bacteriostat. Erysipelothrix growth in dips has been responsible for post-dipping lameness, particularly in lambs.

Residual effects are not maintained quite so long as with dicophane owing to the more volatile nature of B.H.C. For normal purposes 3–6 weeks is the average period of protection but occasionally protection may persist longer. Weather conditions, method of application, and type of parasite, all modify the residual period.

Toxicity. The chronic toxicity of Benzene Hexachloride, B.Vet.C. is greater than that of the pure gamma isomer, but acute toxicity is not so severe. This position stems from the relatively rapid excretion rate of the gamma isomer and the tissue retention of the beta isomer. In general, the toxicity is slightly greater than that of dicophane, but the symptoms and treatment of both are the same.

Dieldrin ($C_{12}H_8Cl_6O$)

This complex chlorinated hydrocarbon is a white crystalline odourless compound, insoluble in water but soluble in most organic solvents. It is stable in alkaline solution unlike most other similar compounds with the exception of its near relative *Aldrin* ($C_{12}H_8Cl_6$).

Actions and Uses. Dieldrin is a stomach and contact poison. Its action is slow, taking as long as 24 hours to kill adult sheep blow flies, and from 24–36 hours to kill newly hatched larvæ (Stones *et al.*, 1954). Residual efficiency, however, was very great, for all larvæ were killed that hatched over a period of 24 weeks. This is an improvement on DDT, until now the best anti-blowfly dip in Great Britain, which, though preventing oviposition, persists for only 8–19 weeks. These workers also report protection of twenty weeks for dieldrin, as against five weeks by the same concentration of B.H.C. In practice, dips containing 0·05 per cent. dieldrin will protect against bodystrike for 3–4 months and against crutch strike for 8–10 weeks. Another property not possessed by other members of the chlorinated hydrocarbon group is its ability to diffuse down the wool fibres as they grow. This property means that the compound can be applied as a surface low pressure spray and yet maintain efficient larvicidal action. This has made it possible to dispense with dipping against blowfly and to use portable low pressure spray units. A considerable saving in energy, man-power, and time, has been possible, particularly in Great Britain where one spraying can give cover for a complete season.

Dieldrin is also being used experimentally in the systemic application of parasiticides. Along with B.H.C. it has proved quite promising when given subcutaneously in doses of 25 mg./kg. body weight dissolved in arachis oil. Protection against tick infestation has persisted for 25 days compared with 22 days for B.H.C., whilst DDT, toxaphene, and some phosphorus parasiticides, were ineffective. When given at the same dose rate as an ointment applied on the neck, dieldrin and B.H.C. killed all ticks on the whole body and prevented reinfestation for 21 and 11 days respectively.

Dieldrin thus promises to be a most valuable parasiticide when its full potential is established.

Toxicity. Relative to dicophane, this parasiticide is about three times as toxic, with an oral L.D. of 85 compared with dicophane's 250. However, when these figures are related to a minimum dipping concentration of 0·2

per cent. for dicophane and 0·05 per cent. for dieldrin the true toxicity relationship becomes apparent. Symptoms and treatment, are similar to those of other chlorinated hydrocarbons.

Toxaphene

Toxaphene, also known as chlorinated camphene, with a probable formula of $C_{10}H_{10}Cl_8$, is an amber, wax-like solid, with an odour of pine. It is insoluble in water but soluble in organic solvents. Strong alkalis cause it to decompose.

Actions and Uses. Toxaphene is both a stomach and contact poison, but requires a knock down agent if used as a fly spray. Its principal use is for cattle tick sprays or dips, used in concentrations of 0·25 per cent. to 0·55 per cent. Its value is mainly because of its 2–4 weeks residual effect, which is superior to that of any other similar dressing for cattle. It has become an important factor in stock control in some areas of Africa where the tick-borne East Coast Fever has hitherto been a great problem. Toxaphene provides sufficient residual protection to allow cattle to be moved through the infective zones in safety, as all the ticks are destroyed before the Theileria they carry can be injected into the blood stream of the cattle during feeding.

Toxicity. Toxaphene has been variously reported with regard to toxicity. In general, its acute toxicity is up to four times greater than dicophane but its chronic toxicity is less. Symptoms are indicative of medullary stimulation and consist of dyspnœa, cyanosis, muscular tremors, and convulsions. Chronic toxicity is the same as for all other chlorinated hydrocarbons. Treatment follows the same principles as for other members of the group.

Chlordane, with a basic formula of $C_{10}H_6Cl_8$, is a contact, stomach and fumigant, parasiticide falling between dicophane and B.H.C. in most of its attributes. It is widely used as an alternative dip against sheep and cattle ticks but is not commonly used for other purposes.

Organic Phosphorus Parasiticides

Parasiticides containing phosphorus have been developed mainly as non-persistent, highly toxic, crop sprays. In general, their toxicity is very great; *parathion* for example, is about eighty times more toxic than dicophane, and *three times more toxic than nicotine. Malathion* on the other hand is about eight times less toxic than dicophane and encourages the hope that effective non-toxic organic phosphorus parasiticides will be developed, even though they have been described as the most potent poisons so far used in agriculture (McGirr *et al.*, 1953).

Parathion has the empirical formula $C_{10}H_{14}NO_5PS$. It is a yellow to deep brown liquid with either a slight or a strong odour resembling garlic.

It is slightly soluble in water and miscible with organic solvents except petroleum products such as kerosene and the light mineral oils used for insecticide sprays.

Actions and Uses. Parathion is a contact poison working by inhibiting the action of cholinesterase. It has been used with reasonable success, but quite a few accidents, in dips and sprays at 0·01 per cent. and 0·005 per cent. concentrations against ticks which have become resistant to the chlorinated hydrocarbons.

Toxicity. Parathion is extremely toxic and its use presents a hazard both to the men handling the material and to the animals dressed. At least six men have been killed by parathion. Symptoms are related to parasympathetic reactions and include vomiting, diarrhœa, acute colic, excessive salivation and sweating in those species where the sweat glands are cholinergic. Nicotine-like reactions produce irregular muscular contraction and weakness. Dyspnœa, cyanosis, and raised blood pressure, are also present. Symptoms progress into a coma. Antidotal use of atropine at hourly intervals is recommended.

Diazinon, an organic phosphorus compound, with a toxicity between that of parathion and malathion, has been used in strengths varying from 0·008 per cent. and 0·04 per cent. as dips for blowfly strike. The stronger concentration has protected sheep for as long as 33 weeks (Riches *et al.*, 1957).

Diazinon has also been used by McGregor *et al.* (1954) as a 5 per cent. solution in arachis oil for subcutaneous injection in the treatment of warble infestation. They used doses varying from 5 to 50 mg./kg., which killed all larvæ present and all those which appeared in the two weeks following the injections.

Malathion has been widely used in the treatment of poultry ticks and lice. 1 per cent. sprays and 2 per cent. or 4 per cent. dusts have been used with very good effect. The compound, like most of the phosphorus parasiticides, is effective against both parasite and eggs.

Fungicides

Fungicides are drugs which destroy parasitic fungi: *fungistatic drugs* are those which prevent growth and multiplication of fungi. Collectively these drugs are often referred to as antimycotic drugs, the majority being fungistatic and not fungicidal.

That fungi cause external diseases is well known; it is less widely recognized that fungi also cause internal diseases—*Aspergillus fumigatus* is one such organism, and is responsible for 'brooder pneumonia' in chickens and 'mycotic abortion' in cattle. Though successful treatment of internal fungoid diseases has been claimed (Mantovani *et al.*, 1952), it is

the cutaneous fungoid diseases which are most successfully treated: ringworm is the most common and widely known of these fungus skin diseases of animals.

The *ringworms* of animals and birds are caused by species of fungus belonging to two genera—*Trichophyton*, large spored fungi, and *Microsporum*, small spored fungi.

Trichophyton verrucosum var. *discoides* causes the majority of outbreaks in cattle, but is transmissible to man and occurs occasionally in horses, dogs and goats, (Ainsworth *et al.*, 1955; Mortimer, 1955). *T. mentagrophytes* parasitizes dogs and cats, and *T. equinum*, horses. *T. gallinæ* is responsible for favus in poultry. *Microsporum canis* causes the majority of cat and dog ringworm, whilst *M. equinum* is responsible for occasional outbreaks in horses.

All these ringworms are transmissible to man, and Microsporum species are especially contagious. Cattle ringworm, though transmitted, does not parasitize people as readily as it does cattle. Lesions in man occur both in hirsute and hair free areas, contrary to the belief held for many years that *Tinea capitis* was not caused by ringworm of animal origin. In recent years numbers of reports have appeared drawing attention to the high incidence of human ringworm caused by fungi from animals (Walker, 1950; Carlier 1954; La Touche, 1955). The Public Health aspect of the disease is of considerable importance, whereas the economic importance to the farmer is yet not clearly defined in Great Britain though some economic loss might be inferred from Canadian work.

Treatment. The whole field of veterinary mycology is under intense investigation and the increased knowledge of the conditions of infection, establishment and development of lesions and their response to changes in environment, should lead to more rational methods of treatment.

It is probable that skin humidity and temperature have a great bearing on the establishment and proliferation of dermatophytes. Any agent, therefore, which can affect these two factors can be expected to modify the growth of ringworm. This hypothesis is supported by the improvement in cattle ringworm when a mild iodism is created by the injection of sodium iodide intravenously. Other factors, however, are involved and the creation of iodism is not the complete answer. In many cases a temporary improvement is shown no matter what type of dressing is used, but sooner or later a state of equilibrium is reached and only a change to a new type of dressing will induce further progress. Several changes may be required before a cure is effected. This reaction is shown particularly when the older mercurial or iodine dressings are used, but some of the more recent compounds such as *Dichlorophen*, *B.Vet.C.* are less likely to produce such reactions. It is also noticeable that a dressing which gives admirable results in one individual will not be so successful in a second animal affected with the same type of fungus. This may be due to a variety of causes; differences in skin metabolism, skin secretions, humidity, temperature and tissue

antibodies may each play a part. The occurrence of spontaneous recovery also increases the difficulties of making a true assessment of the value of antimycotic drugs in the field.

Treatment of ringworm should therefore not be commenced with preconceived ideas. If the response to a dressing is unsatisfactory, a different type of fungicide should be resorted to whilst remembering that the ineffective dressing might be extremely effective in other cases and therefore should not be discarded permanently.

Many cases of ringworm due to species of trichophyton frequently exhibit lesions covered by a thick hard crust, and most types of ringworm cause an increase in skin scales and serous exudates. These barriers must be overcome if the antimycotic drugs are to be used efficiently. There are several ways of achieving this:

(1) Fungicides capable of penetrating the barriers can be used: some mercurials are reasonably efficient in this way and fatty acid derivatives are also useful.

(2) Adjuvant drugs which soften and aid exfoliation of keratin (keratolytics), such as *Salicylic Acid*, B.Vet.C., can be used in conjunction with a fungicide.

(3) Vehicles which aid penetration are helpful: animal fats and alcohol are good examples.

(4) Oral and parenteral administration may replace topical application.

(5) In all cases where topical application is used, the removal of the barrier of scabs and the scrubbing and cleaning of the area with detergents (unless these are antagonistic to the fungicide) are essential if the best results are to be achieved. The dangers of contagion frighten attendants and these procedures are often neglected.

Antimycotic Drugs

A great number of drugs have been used for the treatment of ringworm, probably because most are only fungistatic and not very active so that drug resistance on the part of the parasite is easily achieved. Modern derivatives of some of these, as for example, Monosulfiram, B.Vet.C., and other new type compounds however, are strongly fungistatic or even fungicidal, and most are sufficiently powerful to kill the organism before resistance can develop.

1. Old type antimycotic drugs comprise:
   Mercury preparations, organic and inorganic.
   Iodine preparations.
   Copper sulphate.
   Sulphur preparations, organic and inorganic.
   Benzoic and salicylic acids.
   Resorcinol.
   Rosaniline dyes.

2. New type ringworm therapeutics include:
   Dichlorophen.
   Fatty acid derivatives.
   Salicylanilide and its derivatives.
   Antibiotics.

Old Type. *Mercury preparations* of an inorganic nature have been used for many years as antimycotic dressings.

All inorganic mercury preparations are fungistatic but, though active against both large and small spore ringworms, their toxicity restricts their use mainly to cattle ringworm.

Yellow Mercuric Oxide, B.Vet.C. has been used for ringworm occurring around the eyes where more active but highly irritant dressings are not advisable. It is usually applied as a 1 per cent. ointment: 'Golden Eye Ointment' (Eye Ointment of Mercuric Oxide, B.Vet.C.) is the preparation, used as a daily application. Though once widely used for the treatment of corneal and eyelid ulcers, this eye ointment, apart from it's antimycotic use, is retained only for the dressing of the eyelids in cases of purulent conjunctivitis where there is a tendency for the upper and lower lids to stick together. Such a condition may occur in canine distemper, but even in this disease sulphonamide and antibiotic ointments will prevent the inflammation developing to a purulent stage. Elsewhere on the body *Mercuric Iodide*, B.Vet.C. as a 5 per cent. ointment and *Ammoniated Mercury*, B.Vet.C. as a 2·5 per cent. ointment (White Precipitate Ointment) are useful anti-fungal preparations. *Ointment of Mercury*, B.Vet.C. (Trooper's or Blue Ointment) containing 30 per cent. of metallic mercury has been used with good effects but the danger of absorption and the advent of more efficient drugs has made it obsolete.

Of the organic mercury preparations, Phenylmercuric Acetate, B.Vet.C., the chloride, the Nitrate, B.Vet.C., and the more complex phenylmercuric derivatives have distinct antimycotic action when applied in ointments and alcoholic solutions of strengths from 0·05–0·1 per cent. The compounds are applied daily or with intervals of up to one week between dressings. The preparations are non-toxic but are somewhat selective as evinced by Ford's (1956) report that phenylmercuric acetate appeared to have little influence on the rate of recovery of *T. verrucosum* lesions in cattle.

Iodine preparations, though used for many years, still retain a place in ringworm therapy, particularly as an alternative to dressings which have ceased to be effective. Iodine is also useful in that it can be applied in alcoholic solutions with a brush and penetrates sufficiently to make prior preparation of mild lesions unnecessary so that contact with the lesions is avoided. *Strong Solution of Iodine*, B.Vet.C. brushed on lesions at intervals of 5–7 days, and *Weak Solution of Iodine*, B.Vet.C. used at shorter intervals, are reasonably effective in both Trichophyton and Microsporum

infections but, as with mercury preparations, continued use may result in severe irritation and dermatitis. *Strong Ointment of Iodine*, B.Vet.C. is also used.

Perhaps the most useful form of iodine treatment of ringworm is that of sodium iodide injected intravenously in aqueous solution into cattle. For calves of six months 420 gr. ($\overline{3}\overline{\overline{\text{vij}}}$ or 28·09 G.), and for adults of two years and upwards 960 gr. ($\overline{3}\overline{\text{ij}}$ or 64·09 G.), with doses proportionate to age between these quantities, should be injected once only (Crawshaw, 1957). This treatment is particularly effective in generalized ringworm. Doses less than these may prove less efficient (Ford, 1956). Calves under 6 months old should not be treated with sodium iodide.

Copper Sulphate, B.Vet.C. is widely used by farmers as a home remedy for ringworm, when it is used as an ointment or paste in strengths of up to 5 per cent., or as aqueous solutions of 1–2 per cent. applied daily.

The compound is quite strongly fungicidal, partly by virtue of its astringent and caustic nature, and partly by the specific effect of the copper ion. This effect is utilized in some commercial fungicides which combine copper and fatty acids—copper undecylenate is particularly effective.

Sulphur preparations, in the form of ointments with or without other compounds such as resorcinol, have been used against ringworm in all species, but with poor results, and it was not until complex organic sulphur compounds were devised that any real effect was achieved. *Monosulfiram*, B.Vet.C. is one of the most active fungicidal organic sulphur compounds. For cattle ringworm it is applied with a brush as a 25 per cent. alcoholic solution following the removal of scabs and thorough cleansing of the lesions. Dressings should be repeated every two or three days. The recovery rate is slow. For small animal ringworm, solutions of 2·5 per cent. are safer though slower in effect.

Benzoic Acid, B.Vet.C., apart from forming balsams when combined with resins (cf. Balsam of Tolu) and acting as an expectorant in cough mixtures, also has bacteriostatic and fungistatic properties. These last actions are exerted in acid solutions when the pH is lower than pH 5. It is therefore used in industry as a preservative of fruit and similar foods. It has been used for very many years as a ringworm dressing with salicylic acid in the form of Whitfield's ointment or *Compound Ointment of Benzoic Acid*, B.Vet.C. This ointment contains 6 per cent. benzoic acid and 3 per cent. salicylic acid. It is most effective against Trichophyton cattle ringworm in man, but Goodman (1944) pointed out that the benzoic acid played a very small part in the action.

Salicylic Acid, B.Vet.C. is a white crystalline powder, almost odourless, with a bitter-sweet taste. It is almost insoluble in water but soluble in alcohol and alkali citrate solutions.

Actions and Uses. Salicylic acid is an antipyretic but is rarely used as such because of its irritant nature; sodium salicylate and acetylsalicylic acid (aspirin) are preferred. Salicylic acid is also antiseptic, with an activity approximating to phenol, but has relatively no toxicity owing to its lack of penetration. The major use of salicylic acid is as a *keratolytic* when it softens the keratin layer of the skin and aids exfoliation without causing other than slight and beneficial irritation to underlying tissues. During the casting of the keratin layers ringworm mycelia are also cast and the activity of the acid as a fungistatic is mainly due to this effect.

Salicylic acid is more efficient when applied in water-miscible creams and it is now incorporated with more active antimycotic agents for its keratolytic powers.

Derivatives of salicylic acid are amongst the most active of fungistatics and fungicides. *Salicylanilide* and various *chlorosalicylanilides* are amongst the newest antimycotic discoveries and have been widely used in human mycosis. Salicylanilide is a white or pinkish-white crystalline substance which is odourless, slightly soluble in water but freely soluble in most organic solvents.

Actions and Uses. Salicylanilide is effective against Microsporum species and some Trichophyton species. Its fungistatic action *in vitro* is approximately eight times that of undecylenic acid and is also very high *in vivo* (ringworm agents frequently exhibit little fungistatic activity *in vitro* and yet are effective *in vivo*). The compound is applied as an ointment in strengths of up to 5 per cent.; higher concentrations may be irritant. Daily applications are usual. To overcome the irritant effect of the salicylanilide it is frequently combined with mono- and di-chlorosalicylanilides and undecylenic acid. The chlorosalicylanilides are from 5–150 times more active *in vitro* than salicylanilide, depending on the compound: this gives them a minimum of 40 times greater activity than undecylenic acid.

Resorcinol, B.Vet.C. is a white crystalline substance which turns pink, and eventually dark purple, on exposure to air and light. It is soluble in both water and fixed oils and in most organic solvents.

Actions and Uses. Resorcinol has been used for many years for its antiseptic, antipruritic, and fungistatic properties. It has keratolytic properties but is less powerful than salicylic acid and more irritant. It is used as a human ringworm dressing in the form of 'Castellani's paint' and various modifications of it, which contain phenol, fuchsin, (forming carbol-fuchsin) and 10 per cent. resorcin in an alcohol-water solution. Lassar's pastes, containing 20 per cent. and 10 per cent. resorcinol in the strong and mild forms respectively, have also been widely used. More active and less irritant agents are now available.

The rosaniline dyes are widely used as bacteriological stains but many of

them are also highly efficient and commonly used therapeutic agents. Methyl violet, crystal violet, and gentian violet, are all methylrosaniline chlorides; brilliant green and fuchsin are also members of this group of drugs. Crystal violet is an effective fungistat against Microsporon and Trichophyton species.

Crystal Violet, B.Vet.C. is well known as dark greenish purple metallic looking, coarse crystals which are soluble to 1 : 200 in water, fully soluble in alcohol and chloroform, but not in ether. It is hexamethylpararosaniline hydrochloride, whereas methyl violet is mostly the pentamethyl derivative with some hexa- and tetra-methyl derivatives. Gentian violet is a mixture of methyl and crystal violets.

Actions and Uses. The methylrosaniline compounds are actively bacteriostatic and bacteriocidal to Gram positive organisms; they are also anthelmintics and are used in the human field against oxyurids and Strongyloides species. They are efficient fungistatic agents, mainly used for ringworm in small animals.

As an antibacterial agent, crystal violet is used on wounds and burns in conjunction with brilliant green and either acriflavine or proflavine, as a jelly or aqueous solution.

Compound Paint of Crystal Violet, B.Vet.C. is an aqueous solution: 3 per cent. tragacanth is used to form a gel base in which crystal violet is incorporated at a strength of 1 per cent.

The compound is also used in 0·5 per cent. aqueous solutions as an ear dressing for otitis externa in the dog, mainly because of its action against *Pseudomonas pyocyanea*.

Crystal violet is used in preparing attenuated bacterial and virus vaccines of which swine fever–crystal violet vaccine is an example.

For fungistatic purposes it is painted onto ringworm lesions as a 1 per cent. alcoholic solution. Daily dressings control the lesions within a few days and recovery usually follows in two or three weeks.

The dye is very persistent, and in common with all dyes used externally, has the disadvantage of staining the dresser's hands and any object contacted. The use of 95 per cent. alcohol as a vehicle makes application easier by evaporating quickly and leaving the dye adherent to the skin.

Basic fuchsin is another rosaniline dye used as a bacteriological stain but which is also an effective fungistat. It is incorporated in Castellani's paint for this purpose (see Resorcinol p. 432).

Other dyes such as acriflavine and malachite green are occasionally used as 1–2 per cent. solutions for their antimycotic effect.

New Types. New fungicides and fungistats are appearing in numbers, and only a few of those in common use are mentioned below.

Salicylanilide and its derivatives have already been mentioned in relation to the parent compound salicylic acid.

Dichlorophen, B.Vet.C.

This compound is an effective tænicide and has already been referred to in the chapter on anthelmintics which affect cestodes. Besides this important action, dichlorophen is also one of the most useful fungicides available. At a concentration of 2 per cent. it is used in ointment form and in alcoholic solutions. One of its main advantages is the low number of dressings required. Though daily dressings or applications every third day give the best and most rapid results, bovine ringworm has been cleared up following two dressings only.

Dichlorophen is also bactericidal (for *Staphylococcus aureus*) with a phenol coefficient of 100 at 37°C. This is useful when lesions are infected. The compound is non-irritant and in many cases even relieves irritation within a few hours of the first application. *Toxicity* is very low and the compound is effective against both Trichophyton and Microsporon species. With these attributes dichlorophen is therefore suitable for the treatment of all types of ringworm in all domestic animals.

Fatty Acids and Their Salts. Two saturated acids, propionic and caprylic, and one unsaturated fatty acid, undecylenic acid, are used in antimycotic dressings. Their activity *in vitro* is slight, whereas *in vivo* activity is in some cases quite strong. Both the acids and their salts are used, either together or alone. The compounds are frequently used in conjunction with other drugs, partly because of their antimycotic action, and partly because they aid penetration. Undecylenic acid, for example, is a component of human sweat, and it would be expected to disperse and penetrate readily when applied to human skin. The related fatty acids act similarly. They are usually applied in ointment or powder form.

Undecenoic Acid is also known as undecylenic acid. It is an oily yellow liquid with a characteristic fatty odour. The acid is almost insoluble in water but soluble or miscible with organic solvents and oils.

Actions and Uses. Undecylenic acid is fungistatic mainly to Microsporum species and can be used in concentrations up to 10 per cent.: more tends to be irritant, and it is therefore commonly combined with its zinc or copper salts in ratios of 2–5 per cent. with 15–20 per cent. of the salt. It may be used as a cream in a water miscible base or as a powder with talc.

Zinc Undecenoate, B.P.C. is a white greasy powder with a characteristic odour and is insoluble in water or alcohol but miscible with oil. It is used in antimycotic ointments and powders in strengths varying from 10–25 per cent., for its antipruritic and fungistatic effect. It is active mainly against microsporum species.

Sodium Propionate, B.P.C. is a white crystalline solid with a pungent acetic acid odour. It is deliquescent and soluble in water, but slightly soluble in alcohol.

Actions and Uses. This fatty acid salt is used in the baking industry to control mould growth, but it is an efficient fungistatic and fungicidal agent against both Trichophyton and Microsporum species as well as possessing bactericidal properties. It is used in ointment form at strengths of up to 15 per cent., and as aqueous solutions of up to 10 per cent. strength (Tucker, 1952). The compound is most efficient when in an acid pH and it is therefore combined with propionic and other fatty acids and their salts.

Sodium propionate is also used extensively in up to 8 oz. (240 G.) oral daily doses for acetonæmia. Field reports show the compound to be a useful addition to the number of drugs already used for this condition, particularly if used in conjunction with other glucogenic drugs.

Caprylic acid is used mainly in the form of its sodium and zinc salts—sodium and zinc caprylates or caproates. The salts are also known as octoates. The sodium salt is a water soluble yellow granule but the zinc compound is a white insoluble powder. Both are used as fungicides and are reported to be the most active of the fatty acid antimycotic agents so far produced. They are effective against all species of ringworm and are applied as ointments containing up to 15 per cent. either of one or a mixture of the two.

These compounds are used mainly in small animal treatment.

Antibiotics. So far few antibiotics have been discovered which have effects on fungi comparable to their effects on bacteria. Though *subtilin* and *neomycin*, amongst others, have some slight antifungoid action, only two antibiotics have so far proved of any clinical value—Nystatin, originally known as Fungicidin (United States Dispensatory 25th edit. 1955 p. 1567) and griseofulvin. The compounds have mainly been used in human mycosis, but experimental evidence indicates that systematic and cutaneous fungoid diseases of animals may soon be treated with these or similar antibiotics (see p. 551).

The need for effective and safe fungicides for systemic and local use is becoming more urgent, for the destruction of bacterial flora by antibiotics is leaving a biological vacuum and there are increasing signs that this vacuum is being filled by yeast and mould organisms which, uncontrolled, may become dangerously pathogenic.

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PART THREE

CHEMOTHERAPY

CHAPTER 22

INTRODUCTION

CHEMOTHERAPY is the treatment of a disease by the use of pure chemicals which have specific antagonistic effects on the organism causing the disease. The action is achieved by interference with the metabolic processes of the organism either directly or indirectly, by neutralizing enzymes or by preventing coenzyme formation, thus starving the organism of a substance essential for normal life. Examples of chemotherapeutics in three different fields are: sulphanilamide and other sulphonamides used in the treatment of mastitis due to *Streptococcus agalactiæ*; piperazine salts used for the treatment of ascarid worm infestations; and quinuronium sulphate used against the protozoan blood in parasites, the babesias or piroplasms which cause hæmolytic anæmias in domestic animals.

Although chemotherapy has been practised for centuries, as for example by the use of quinine against malaria since 1630, the principle of chemotherapy was first postulated about 1900 by Paul Ehrlich, who gave this name to the compounds produced by a systematic search for chemicals which would attack infecting organisms without harming their host. He stated that chemotherapeutic agents should be 'maximally parasitotropic and minimally organotropic', and thereby established the modern assessment of therapeutic value—the *Therapeutic Index* represented by the ratio of $\frac{\text{minimum curative dose.}}{\text{minimum toxic dose.}}$ The wider the Index, characterized by a small figure above and a large figure below the line, the more valuable is the drug.

Since Ehrlich and his collaborators discovered arsphenamine, which is of value in the treatment of trypanosomiasis and syphilis, by the systematic substitution and interchanging of organic chemical nuclei and side chains, a fabulous army of scientists has been engaged in investigating the biological activity of vast numbers of organic chemicals and whole series of related compounds. This work has continued concurrently with, and sometimes co-ordinated with, research into the metabolic minutiæ of parasite and host metabolism.

It has been found, for example, that methylthionine hydrochloride (methylene blue—one of the early interests of Paul Ehrlich) and other oxidizing antiseptics act by diffusing into the organism and there blocking essential reduction processes. Other substances combine with an essential metabolite, or growth factor, forming a compound which the organism

cannot utilize: still other chemotherapeutics react with enzymes, forming a combination which is similar to that normally produced, owing to the chemical similarity of essential growth factor and chemotherapeutic, and yet is dissimilar in a way that makes it useless for normal metabolism; the chain of metabolic reactions is thus broken. This last process is thought to be the method by which the sulphonamides impose bacteriostasis, for the basis of all these compounds is para-aminobenzoic acid, which is part of the vitamin B. complex and an essential growth factor for many bacteria as well as for animal life.

The aim of modern chemotherapeutic research is to discover a peculiarity of an organism's metabolism which is not common to that of the host, and having found it, to devise a chemical which will attack the organism through that peculiarity, whilst not interfering in any way with the metabolism of the host. So far this is only a dream and the end point only achieved, and that rarely, by painstaking trial and error; but, by collating all known evidence, biochemists are now beginning to be able to forecast, with reasonable accuracy, that particular organic groupings when attached to a nucleus in a certain position will increase the compound's activity against a particular organism, whereas other groupings will decrease its activity or usefulness. As an illustration of this Findlay (1951) quotes Fourneau and his colleagues—'As a result of these observations it was believed that the methoxy group in position 6 in the quinoline nucleus is not essential for antimalarial action, while the substitution of (—OCH_3—) for (—OC_2H_5—) appears always to exert an unfavourable action, as does the group(—$C.CH_2$—O—R) placed in the diamino chain. In at least one compound replacement of (diethylamino—) by (diethylamine) reduced toxicity ten times.' This was in reference to investigations into the antiplasmodial effect of the homologues of pamaquin. (Plasmodia are the protozoan blood parasites causing malaria).

By researches of this nature, tempered with patience and industry, and assisted by chance, two important groups of antibacterial chemotherapeutics, the sulphonamides and the antibiotics, have been discovered and new powerful anthelmintics and insecticides developed.

CHAPTER 23

ANTIBIOTICS

(i) INTRODUCTION

THE antibiotics are a group of complex organic chemicals which are produced, initially, by micro-organisms during their growth and which in minute quantities have a detrimental effect on other organisms. They are therefore metabolites produced by bacteria and moulds. These antibiotics are effective against living bacteria, some rickettsiæ, some viruses, some fungi, and a few helminths. An average single dose of penicillin for injection into a cow's udder in the treatment of streptococcal mastitis is 100,000 international units. This quantity of penicillin represents approximately 62·5 mg. weight, which is just under one grain. A further indication of activity is the blood level of penicillin which is effective in most systemic infections—about 0·1 i.u. per ml., which is equivalent to 0·06 mg. per ml. or approximately 1 gr. in 200 gallons of blood.

Manufacture. The composition of many of the commonly used antibiotics is known, but so far only one antibiotic, chloramphenicol, is manufactured synthetically, the others being prepared from fluids on, or in which the moulds and bacteria have been grown. The usual process is known as the 'deep vat culture' or 'submerged culture fermentation' method, which is a mass production process developed during the second world war by British and American collaboration, following the failure of the original surface culture methods to produce sufficient quantities to meet world requirements.

The method consists of inoculating cultures into a suitable fluid medium contained in vats holding as much as 20,000 gallons of medium. During the fermentation period air is blown through the culture and temperatures are maintained at the optimum for growth of the particular organism. The whole process is carried out under strictly aseptic conditions, for it can be imagined what damage could be done if the mould culture, air, or vat were contaminated with an organism capable of growing more rapidly than the mould, especially if that organism produced a substance which destroyed the antibiotic.

Following fermentation, the fluid is filtered off and subjected to various extraction and filtration processes and finally the resulting crystalline antibiotic is sterilized and packed into sterile containers.

To obtain the maximum yield of the correct type of antibiotic (there

are four main forms of penicillin but only one has outstanding properties), particular strains of mould and particular combinations of fermentation conditions have been developed. It is now common practice also to include certain 'medium supplements' which assist in increasing the antibiotic production by the organism or encourage the production of particular forms of the antibiotic. Many of these substances are preformed parts of the antibiotic molecule.

Assay. Once prepared, the antibiotics produced biologically must be standardized biologically, but the synthetic chloramphenicol can also be standardized by light absorption methods.

Biological standardization is achieved by comparing the bacteriostatic effect of a standard sample of the antibiotic with that of the unknown, using a standard strain of a susceptible organism. The bacteriostatic potency is expressed in International Units, the unit of penicillin, for example, being defined as 'the specific penicillin activity contained in 0·6 mg. of the International Penicillin Standard'. The International Standard preparations for each antibiotic are kept at the Department of Biological Standards, National Institute for Medical Research, Mill Hill, London, but National Standards are maintained in each country and each working laboratory carries its own Working Standard which has been accurately assayed against the National Standard. The test organisms are available from the various National Collections of type cultures; the British one now being kept at the Central Public Health Laboratories, Colindale, London.

Chemical or gravimetric standards are also available.

Assay Methods. These may be classified into three groups:

(1) The serial dilution method.
(2) The plate diffusion method.
(3) Chemical methods.

There are numerous modifications used which are adaptations, for specific purposes, of these three.

1. *The serial dilution method* consists essentially of inoculating a standard suspension of a susceptible bacterium type culture into a series of test tubes containing graded broth dilutions of an antibiotic of unknown potency. These tubes are incubated for a given period alongside a similar series containing known dilutions of the antibiotic standard preparation. At the end of the period the tests are read either by determining the dilution at which minimum growth occurs or by recording culture turbidities by subjecting the tubes to an absorptiometric test, if the so-called turbidimetric method is being used. Graphs are plotted, the standard and unknown preparations are compared, and the potency of the unknown calculated. Accuracy to within errors of 4 per cent. and 10 per cent. have been given by the turbidimetric and broth dilution methods.

Serial dilution methods are only suitable where the activity of the preparation is known within close limits, for high dilutions must be used because of the great activity of the compounds and only a narrow range of dilutions can be tested at one time. Also, where impure preparations of an unknown antibiotic are to be standardized, potentiators or inhibitors may form part of the impurities and affect bacterial growth in a way which cannot be reproduced in the standard tubes.

Some of these disadvantages are avoided by diffusion methods of assay.

2. *Diffusion methods.* There are two main methods but both are essentially the same. The *cylinder-plate* method consists of comparing the antibacterial effect of known phosphate buffer dilutions of standard and unknown, quantities of which are pipetted into porcelain diffusion cylinders just embedded in the surface of petri dish or sheet plates of agar. The agar sheets are previously seeded with a test suspension of a standard susceptible bacterial culture. After the filling of the cylinders the plates may either be incubated immediately or allowed to stand at room temperature for 1–1½ hours before incubation; this latter delay favours diffusion, enlarges the zone of inhibition and gives clearer and better results. With given dilutions, a more sensitive test with less error is achieved, for the larger zone decreases the proportion of the error but also a clearer zone with sharply defined edges is given as the antibiotic is able to repress growth from the commencement of incubation. The plates are incubated overnight at 37°C. and the following day the diameters of the clear zones created by the absence of bacterial growth within the diffusion zone of the antibiotic are measured with calipers or an illuminated scale. Graphs are plotted using the diameter and the logarithm of the concentration, which should give a straight line, and comparisons are drawn between unknown and standard. The greater the number of cylinder tests for each dilution the more accurate will be the results obtained.

The *cup plate* method is very similar, differing only in that discs of agar are cut out of the seeded plate with a cork borer and removed carefully so that the edges of the circle are not lifted. Into these 'cups' are pipetted the antibiotic dilutions and it will be realized that were the edges of the circle lifted from the glass these solutions would underrun the agar and give useless diffusion zones. Greater accuracy is required in measuring the quantities of fluid placed in the cups than is needed in the cylinder method.

Accuracy of both these methods is approximately 4 per cent.

Other modifications are used, one of which consists of using filter paper discs which have been soaked in antibiotic solutions and dried, instead of the cups or cylinders. This method is simple, quick, and can be adapted for testing antibiotic content of body fluids. Rapid methods have been devised involving up to 3 or 4 hours incubation instead of 12 hours or more.

Differential methods are used in which different test organisms are used

to identify different types of a given antibiotic as, for example, penicillin F.G.X. and K.

A further development from the standard methods is the use of paper chromatography.

3. *Chemical Methods.* These consist in converting the antibiotic salt into a form which can give a colour reaction when treated. The conversion of penicillin to penicilloic acids by penicillinase is a widely used example. Gravimetric methods by which a compound containing the antibiotic is precipitated, filtered off, dried, weighed, and the amount of antibiotic calculated according to its proportion in the molecule, are also used.

Bacterial Sensitivity Tests. These tests are modifications of the methods used for biological standardization. Some are laboratory diagnostic procedures aimed at determining the most suitable antibiotic for treatment of a case or a series of related cases.

Conversely, there are tests which are used to determine the susceptibility of numbers of strains or types of organisms to one antibiotic.

The first type of test consists of a modification of the cylinder-plate assay method. A petri dish plate is poured, using agar seeded with the organism previously isolated in pure culture from the patient. The plate is placed over a paper disc which is divided into segments; these segments are drawn on the bottom of the plate using a grease pencil. Each segment is then numbered or code-lettered. A compressed diffusion disc containing a known amount of each available antibiotic is then embedded in the surface of the agar plate within each segment according to the code letter or number. The whole plate is then incubated for a given period depending on the organism and clinical requirements. Measurement of each zone diameter will indicate the most active antibiotic *in vitro*. A disadvantage is that *in vivo* responses do not always follow those *in vitro*. Nevertheless, the tests provide a rapid and reasonably useful guide. Impregnated paper discs are replacing compressed tablets.

The *second* type of test is of less clinical significance, though it can be adapted to serve clinical as well as laboratory needs. Known as the 'ditch-plate' sensitivity test, it consists of a nutrient agar or, if required, a special solid medium plate from which a 'V' ditch has been cut across the diameter. Into this is run sufficient agar to fill it containing a known quantity of the antibiotic under test. When set, the plate is streaked at right angles to the ditch with various organisms. The sensitivity of each organism is shown following incubation by the linear zone of growth suppression on either side of the ditch.

Both these tests are easily carried out in any small laboratory equipped for simple bacteriological procedures using media tablets for the preparation of plates.

Safety Tests. In addition to assays to determine potency, antibiotics must be sterile and free from extraneous toxic material such as pyrogens,

which are toxic products of bacterial lysis. Cultural tests for sterility and pyrogen tests on rabbits (a temperature reaction is given if pyrogens are present in toxic quantities) are therefore routine procedures carried out before batches of antibiotic are released for sale.

Stability. The antibiotics as a group cannot compare in stability with other chemotherapeutics. The major factors influencing the stability of antibiotics are listed below:

1. *Moisture.* Some antibiotics, and particularly penicillin, are hygroscopic, and though they may keep for several years as dry powders in sealed containers, the intake of moisture after exposure is followed by a rapid reduction of potency. This refers also to the stability of unbuffered water or saline solutions: oxytetracycline hydrochloride solutions retain potency for about four days at room temperature but penicillin solutions are stable for only a few hours under the same conditions. At refrigeration temperatures, the potency of solutions is retained much longer. In practice it is usual to make up solutions only when required: solutions for ocular use *must* be kept in a refrigerator between use and renewed every 3–4 days; solutions for injection should be used immediately but if storage is unavoidable they must be kept below 4°C. If this is not possible 5 per cent. dextrose solutions are usually more stable than plain aqueous or saline solutions and frequently dilute solutions are more stable than concentrated ones.

2. *pH.* This is probably the most important factor affecting antibiotic stability. Solutions should be buffered to the optimum pH for the individual antibiotic-pH 6·8 for penicillin. Alkalinity causes rapid loss of potency. Amino-acids and their salts, such as sodium glycinate, are widely used as buffering agents, but phosphates and citrates are also used.

3. *Temperature.* Stability of antibiotics is markedly affected by temperature, particularly when in solution, although some are more stable than others,—oxytetracyline hydrochloride 1 per cent. aqueous solution at pH 2·5 shows no loss after 30 days at 25°C.

4. *Oxidising agents.* These, as well as reducing agents, may cause rapid loss of potency. Chlorates, permanganates, peroxides, hydrogen sulphide, and sulphur dioxide, are all antagonistic to antibiotics.

5. *Enzymes.* Some antibiotics may be destroyed by selective enzymes. Penicillin, for example, is rapidly inactivated by penicillinase, an enzyme which is elaborated by a number of bacteria of which *B. subtilis* is one.

6. *Miscellaneous agents.* A widely varied list of substances and conditions in addition to those already mentioned will affect antibiotics. *Heavy metals* such as copper, iron, zinc, and mercury, will all inactivate penicillin; *light* affects most antibiotics, particularly when they are in solution; *cysteine* and other sulphydryl substances will rapidly destroy streptomycin and penicillin activity; *alcohols* are antagonistic to penicillin, which means

that where syringes are kept in a spirit bath they should be well rinsed before injections of antibiotics are made with them.

Actions and Uses. The antibiotics are all *bacteriostatic*, that is they prevent the growth and division of bacterial cells. It has been observed that with some bacteria, if concentrations lower than those which inhibit growth completely are used, some organisms increase in size, commence chromosome division but are unable to complete it so that abnormally large forms are produced: other bacteria join in long chains of swollen forms, whilst yet others are morphologically unaffected. (McKee *et al.* 1945; Fischer, (1946). These abnormal bacteria *in vivo* are highly susceptible to destruction by the body's natural defences.

Some antibiotics are also *bactericidal* and destroy bacteria when conditions are suitable: *bacteriolysis*, or solution of bacterial bodies, occurs in some cases.

These actions are achieved in different ways by different antibiotics, but as yet the complete process for even one antibiotic is not known. Penicillin, for example, is believed to prevent the build-up of amino-acid—sugar compounds within bacteria, so disrupting cell wall formation but this is only part of the bacteriostatic process, for bacteria are affected which do not require amino-acids for maintenance.

Because chemotherapeutics act by interfering with cell metabolism and division, their greatest effect is exerted, as would be expected, when organisms are in a state of rapid growth and division. All bacterial cultures after inoculation show three stages of growth, a primary 'lag' phase, a logarithmic phase in which rapid multiplication occurs, and an ultimate resting phase. It is in the logarithmic or prelogarithmic phase that antibiotics—all chemotherapeutics—exert their strongest effect.

Antibiotic Spectrum. This term has been adopted to define the field of antibacterial activity of an antibiotic.

A *narrow spectrum* antibiotic is one in which the antibacterial effect is restricted to a relatively small number of organisms. Penicillin, which is active mainly against Gram positive organisms and polymyxin B, which is active only against Gram negative organisms, are two narrow spectrum antibiotics.

A *broad spectrum* antibiotic is one which is effective against a wide variety of organisms—Gram positive and Gram negative bacteria, possibly rickettsiæ and the larger viruses, and even protozoa and helminths: chloramphenicol, chlortetracycline hydrochloride, and oxytetracycline hydrochloride are examples. Some antibiotics may have broad-spectrum activity *in vitro* and yet be restricted to use as a narrow spectrum antibiotic *in vivo* because of toxicity or other considerations.

Combined Antibiotic Therapy. Where mixed infections occur, or where larger doses of an antibiotic are required but may not be given because of toxicity, it may be useful to use two antibiotics together. In mixed infections, antibiotics which have a selective action on each particular organism

may be used so that the total infection is promptly controlled. In the second case, a massive attack can be made on a particular organism without administering a toxic dose of either antibiotic: the combined use of streptomycin and dihydrostreptomycin is an example. A further advantage occurs where an antibiotic successfully controls the majority of organisms but is unable to affect resistant strains: a second antibiotic may either render the strain sensitive to the first antibiotic once more or may itself control the resistant strains.

If two antibiotics are to be used together they must be carefully chosen, for some antibiotic combinations are actually less effective than either used singly.

A general guide has been given by Jawetz and his colleagues in several papers published between 1950 and 1952. The antibiotics fall into two groups—(1) Narrow and medium-broad spectrum antibiotics, penicillin, streptomycin, bacitracin and neomycin; (2) Broad spectrum antibiotics: chlortetracycline hydrochloride, chloramphenicol and oxytetracycline hydrochloride. With a few reservations these react as follows:

(a) Pairs from group 1 are frequently synergistic, occasionally additive but very rarely antagonistic. This is amply borne out in practice, where combinations of penicillin and streptomycin are used routinely in mastitis due to penicillin resistant organisms: where bacitracin and neomycin are very effective when applied topically in skin infections; and where penicillin and bacitracin have been effectively used in penicillin resistant infections.

(b) Pairs from group 2 may be additive but are rarely synergistic or antagonistic.

(c) Where pairs drawn from group 1 and group 2 are used against organisms sensitive to the group 1 member then the action of the group 1 antibiotic may be antagonized by small quantities of that from group 2. This is easily demonstrated by combinations of penicillin or streptomycin and chloramphenicol, or by combinations of penicillin and chlortetracycline. This antagonism is not always functional in reverse for:

(d) The action of members of group 2 is not usually impeded by the addition of small quantities of a group 1 member and may under certain circumstances even be synergized by it.

In all cases, synergism only occurs if both antibiotics are active against the infective organism even though bacterial inhibition by one of them may occur in concentrations higher than are therapeutically practicable. Thus chloramphenicol and oxytetracycline hydrochloride combinations with penicillin have both been used effectively in the treatment of human bacterial endocarditis where penicillin and streptomycin have failed.

Antibiotics Combined with Other Chemotherapeutics. The treatment of tuberculosis in man provides several examples for useful combinations of antibiotics and other chemotherapeutics. Streptomycin and dihydrostreptomycin, which must be used over long periods, soon lose their

effect due to the development of bacterial resistance. If the antibiotics are combined either with para-aminosalicylic acid (PAS) or with iso-nicotinic hydrazide and related compounds the development of bacterial resistance is considerably delayed.

Sulphonamide and antibiotic combinations are probably the most popular examples of joint therapy but antibiotics are also combined with inorganic salts such as potassium iodide in the treatment of actinomycosis, and with enzymes such as streptokinase which, by activating fibrinolysin, assists in penetrating blood clots and exposing bacteria buried therein to the action of the antibiotic.

Factors Influencing Clinical Use. There are a number of important details of antibiotic activity concerning absorption, circulation, and metabolism within the animal, that must be considered if the full benefit is to be obtained and the antibiotics used correctly.

1. The use of combined antibiotics and joint use of antibiotic and other chemotherapeutics has already been mentioned.

2. Reaction with blood and tissue fluids. Some antibiotics such as penicillin are not decreased in potency by contact with blood, serum, pus, cerebrospinal fluid etc., whereas others such as streptomycin are influenced unfavourably by these fluids (*cf.* sulphonamides.)

3. Physiological barriers. There are a number of physiological barriers which some antibiotics will pass across quite easily whereas others pass only with difficulty. These barriers consist of (a) The blood-brain barrier, which is a physiological division between the blood and cerebrospinal fluid. Some antibiotics such as penicillin and streptomycin do not pass the blood-brain barrier except when the meninges are inflamed, and even then therapeutic levels may not be achieved in the cerebrospinal fluid. Intrathecal injections should therefore be given at least to initiate treatment. Other antibiotics such as oxytetracycline will normally achieve therapeutic concentrations in the cerebrospinal fluid only when the meninges are inflamed. A further group, of which chloramphenicol is outstanding, passes the blood-brain barrier fairly easily and achieves concentrations in the cerebrospinal fluid as high as 50 per cent. of the blood levels.

(b) The placental barrier does not normally resist the passage of antibiotics.

(c) The intestinal barrier. When given orally a few antibiotics, of which streptomycin and neomycin are the most important, are not absorbed into the system in therapeutic concentrations. The reverse also holds good, for little streptomycin is excreted into the intestinal lumen except through the biliary system. This is important, for only parenteral injection is suitable for treating systemic infections and only the oral route can be used for treating intestinal infections so far as these two particular antibiotics are concerned. Species differences may also be involved, for oxytetracycline is not absorbed to any appreciable extent from the intestines of poultry.

(d) Serous membranes. Some antibiotics will not readily pass either way across the pleural or peritoneal membrane, whereas others diffuse quite readily into the pleural and peritoneal cavities. Penicillin is a good example of the former and chlortetracycline hydrochloride of the latter group.

(e) Milk. Most antibiotics diffuse into the milk in small quantities, but concentrations achieved do not warrant the systemic use of antibiotics for the treatment of mastitis, with one or two exceptions.

4. Antibiotic resistant bacteria. A great deal of controversy exists concerning this aspect of antibiotic therapy. The fact remains that if bacteria are submitted to non-lethal antibiotic concentrations those bacteria may develop resistance to that antibiotic and sometimes related antibiotics also. This has occurred with tuberculosis in human medicine and with *Bact. coli* causing 'white scours' in calves. A further possibility—and a strong possibility—is that antibiotics may destroy all susceptible strains of an infecting organism, but leave untouched resistant strains which may then proceed to multiply and produce a disease which cannot be controlled by the normally indicated antibiotic. This would appear to be the case with staphylococcal mastitis in this country, where the number of penicillin resistant strains isolated from cases of clinical mastitis seem to be on the increase (Loosemore, 1957: Tee, 1957).

A more dangerous situation has been reported quite frequently in human medicine where broad-spectrum antibiotics have eliminated bacterial flora leaving the field free for the multiplication of yeasts and fungi which have taken on pathogenic attributes. So far this danger would not appear to have occurred widely in veterinary medicine, but the use of antibiotic feed supplements may eventually precipitate such a situation.

A related situation arises when it is necessary to identify a pathogen and to determine its sensitivity to chemotherapeutics: antibiotic treatment may alter the morphological, cultural, and biochemical reactions of a bacterium, particularly if resistance is developed, and make it impossible to achieve either of these aims. Where mastitis surveys and laboratory diagnoses are being undertaken samples must always be taken *before* treatment is commenced.

5. Antibiotics and immunity. Some diseases do not recur because natural recovery from an attack is achieved by mobilization of the body's defences and the creation of immune bodies in the blood and tissues. If, however, large doses of antibiotics, or indeed if any other anti-infection agents are given and the infection rapidly eliminated, the immunological reactions cannot mobilize and the body is susceptible to further infection as soon as the antibiotic is withdrawn. Such situations have arisen in the control of coccidiosis by chemotherapeutic food medication. In human medicine this situation has been overcome by using intermittent therapy whereby massive doses of an antibiotic have been given at intervals instead of lower doses continuously over a longer period. Attention must

be given to the danger of creating drug allergy or sensitization if this intermittent dosing method is used.

Principles of Antibiotic Therapy. In recent years the spectacular results achieved by antibiotic therapy, the relatively rare incidence of toxic effects, and the commercial pressure of interested manufacturers, have combined in suggesting that antibiotics are the only therapeutics and that broad-spectrum antibiotics are the best. Intelligently and judiciously used, these therapeutics are invaluable, but before antibiotics are resorted to there are a number of questions that should be asked, considered, and answered by the veterinary surgeon.

1. Is an antibiotic required or would another drug cure the animal, perhaps less quickly and spectacularly yet with less interference with the normal bacterial flora of the body and the development of natural immunity?

2. If an antibiotic is indicated because of the specific nature, or acuteness and severity of the disease, is it possible to use one of the narrow spectrum antibiotics which are more selective and therefore less likely to cause disruption of the normal resident bacteria?

3. If an antibiotic is to be used, for how long should it be used and at what dosage rate? It is far better to give high doses for a short period *providing the organism is totally eliminated*, for there is then less likelihood of antibiotic resistant strains of bacteria developing. Should the infection not be eliminated, then a relapse may occur or the infection become chronic and the illness protracted. This is particularly important in the treatment of pyogenic infections when chronic abscesses may be formed.

4. Is it safe and economic to give an antibiotic in these doses over this period or would the longer period and less active drug be safer and, perhaps because of this, more economic in the end?

If an antibiotic is to be used, then it should be as specific as possible and given immediately. It should be applied to achieve the maximum concentration in the tissues in as short a time as possible, and continued until 48 hours after disappearance of symptoms, unless signs of toxicity are shown. The reasons are:

(1) Bacteria are more effectively dealt with in their early logarithmic phase, and therefore the earlier the treatment the more likely are the infecting bacteria to be at this stage of development.

(2) As the interference process is usually one of molecular diffusion and absorption into or adsorption onto the bacterial cell, the activity of a given dose will be inversely proportional to the number of bacteria present (this is another principle which applies to most, but not all, chemotherapeutics). Because of this it is advisable to use large doses as early as possible whilst the bacterial numbers are low. Polymyxin is an exception, for its activity is not affected by the number of bacteria present.

Besides using large doses of a specific antibiotic as early in the disease process as possible, the rapidity of action can also be affected by choice of route and form of administration. It is advisable in systemic infections to use parenteral administration of soluble and easily diffusible forms for initial doses so that blood levels, upon which depend tissue levels and therefore antibacterial activity, are rapidly achieved. These blood levels can then be maintained by continuous slow absorption from 'depots' of less soluble and slowly diffusible antibiotic forms. As an illustration, the treatment with penicillin of equine strangles due to *Streptococcus equi* might be quoted. Presuming that the case is in a young animal and the infection is severe, with signs of septicæmia, the first dose of antibiotic would be about 500,000 units (0·5 mega) of sodium penicillin intramuscularly. (In the case of penicillin intramuscular injections promote therapeutic blood levels at a rate only very slightly below that of intravenous injections). At the same time a 'depot' or 'repository' injection in the form of procaine penicillin aqueous suspension would be given intramuscularly, the dose being about 2,000,000 units (2·0 mega). No further antibiotic need be given for about 24 hours when the repository dose would be repeated. It is probable that in such early cases only one, or at the most two, further doses would be needed. Commercial penicillin injections are available combining water soluble and insoluble salts so that immediate absorption and repository forms can be given at one injection.

Agricultural Food Additives. Most common antibiotics are now available as animal *feed supplements*. Though supposedly only used for fattening and not breeding stock, feed supplements, either as 'premix' concentrates or as a ready mixed food are available to farmers and are widely and often indiscriminately used. Their mode of action is still hotly debated in view of their great dilution but, apart from any vitamin which may be present in some of the 'spent waste' obtained during processing and used in supplements, there is undoubtedly a beneficial effect due to the depressing of pathogenic or symbiotic bacteria in the intestines, and possibly the body. This booster effect given to meat stock during their first few weeks of life improves their food conversion rate and shortens the birth to killing period. A further problem now associated with food additives is the creation of resistant strains of bacteria. This action could cause considerable trouble and losses due to the neutralization of the therapeutic effects of antibiotics, and considerable concern has been voiced in some quarters (Smith, 1957, and 1958.).

Food Preservation. Investigations are proceeding into the preservation of food by the use of antibiotics. Subtilin has been tried in the canning industry to inhibit heat resistant sporulating organisms; chlortetracycline and oxytetracycline have been used in ice and as a dipping solution for fish preservation, and streptomycin has been used to preserve meat; various antibiotics have been used in spirit distillation and the preservation

CHAPTER 24

ANTIBIOTICS
(ii) PENICILLIN

PENICILLIN is a narrow-spectrum antibiotic which, in its many various forms, is officially recognized in all the pharmacopœias of the world.

History

Penicillin was the first antibiotic discovered. It is also noteworthy in that it has yet to be superseded as the most useful and least dangerous of all antibiotics.

The first report indicating a major medical discovery appeared in 1929 when the late Sir Alexander Fleming of St. Mary's Hospital, Paddington, London, described the lysis of staphylococcal colonies near a contaminant mould on a bacteriological plate. He also described the culturing of the mould on the surface of a peptone broth and his attempts to concentrate and isolate the active principle which he had shown to be present in the culture medium. He failed to isolate the substance, but continued to use the crude filtrate to depress unwanted bacterial growth of cultures of resistant organisms including those which cause whooping cough (*Hæmophilus pertussis*), calling the filtrate *penicillin*, a word derived from the generic name of the original contaminant mould, *Penicillium notatum*. Fleming's efforts to isolate the substance were continued by Raistrick, Clutterbuck and Lovell (now Professor of Veterinary Bacteriology, Royal Veterinary College, University of London) at the School of Tropical Medicine, London. They were only able to demonstrate how difficult the problem was and showed that, while it was possible to make ethereal extracts of the substance, these extracts lost their activity on evaporation in air. The advent of the sulphonamides in 1933 focused attention away from penicillin until Florey (since knighted) with his colleagues at Oxford, interested themselves in the problem and published, in 1939, the initial paper on the chemotherapeutic activity of their crude penicillin powder. With this powder, probably containing no more than 1 per cent. of penicillin, they were able to inhibit staphylococcal growth *in vitro* with a dilution of 1 : 500,000, and to protect mice against streptococci, staphylococci and *Clostridium septique*.

Later research has provided methods of manufacture and purification so efficient that Sodium Benzylpenicillin, B.Vet.C., which can now be purchased as cheaply as 2/-. per 1,000,000 units (1·0 mega unit), contains a minimum of 93 per cent. total penicillins.

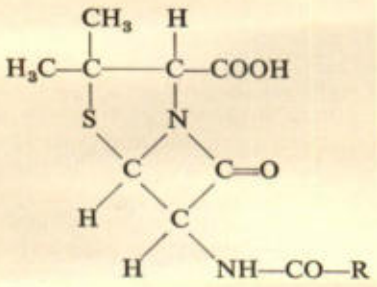
Manufacture

Penicillin, originally made on a small scale from surface broth cultures of the mould, is now manufactured on a vast scale by deep vat culture methods using various 'medium supplements' and various strains and species of penicillin moulds, so that different forms of penicillin can be produced at will in high concentration. Purification processes are such that, instead of the originally manufactured yellow, amorphous, impure penicillin, the product now marketed is a white crystalline substance with a high degree of purity.

Chemistry

Penicillin exists both as an amorphous powder, now rarely used, and a white crystalline substance, Benzylpenicillin, B.Vet.C., which is the sodium or potassium salt of the acid. Benzylpenicillin contains not less than 1480 units per milligram (potassium salt) or 1500 units per milligram (sodium salt). It is soluble in water, but insoluble in fixed oils and the paraffins, and has a faint mould-like odour and salty taste.

The final crystalline substance produced from *Penicillium* moulds is a mixture of the salts of five main penicillins—organic acids with a common root formula represented by:



known as the β lactam formula.

Represented in this manner it has a nucleus formed by a five membered thiazolidine ring and a four membered β lactam ring. The five membered ring is comparatively stable, but the four membered ring is very unstable and is probably responsible for the instability of the compound.

The five acids differ only in the constitution of the side chain attached to the β lactam ring and designated R in the graphic formula. They are named as in the table on page 455.

All are active, though penicillin IV (K) is the least active and penicillin II (G) the most active.

There are many other penicillins, which are spoken of as *biosynthetic penicillins* because their formation by the mould has been encouraged by the addition of preformed organic groups as medium supplements: phenoxymethyl penicillin or penicillin V is probably the best known of

Pharmaceutical Name		Chemical Systematic name	Side chain R
British:	American:		
I	F	Pent-2-enylpenicillin	$CH_3{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_2$—
	Dihydro F (flavicidin)	n-amyl penicillin	N—C_5H_{11}—
II	G	Benzylpenicillin	$C_6H_5{\cdot}CH_2$—
III	X	p. hydroxy-benzylpenicillin	$HO{\cdot}C_6H_4{\cdot}CH_2$—
IV	K	n-heptylpenicillin	N—C_7H_{15}—

these, but allylmercaptomethyl penicillin or penicillin O is medically prominent, because it causes less allergic response than benzyl penicillin.

The penicillins themselves are most unstable and relatively insoluble. They are therefore converted into various salts and esters by the substitution of sodium, calcium, potassium, procaine, alkyl groups, etc. in place of the hydroxyl group or hydrogen of the carboxyl group.

Note:•The isolation of 6-aminopenicillanic acid from fermentations (Batchelor *et al.*, 1959) holds out hope for cheaper production of the penicillin nucleus than the synthetic methods announced previously (Sheehan, 1958). This may lead to the discovery of further penicillins.

Stability

Penicillin is the least stable of the commonly used antibiotics.

1. *Moisture.* Penicillin is hygroscopic, although the potassium salt is less so than the sodium or calcium salt, and deterioration by hydrolysis is rapid. When dry, the salts will keep for two to three years, but when in unbuffered aqueous solutions the salts lose about 16 per cent. activity at 4°C. and 78 per cent. at 24°C., in seven days. (Clapham, 1950). It follows that solutions, once made up, should be used immediately or kept in a refrigerator and used within seven, but preferably four days.

2. *pH.* Acids and alkalis cause rapid deterioration in the potency of penicillin solutions. Following the determination that penicillin is most stable when solutions are kept within a range of pH 6–6·5 (Benedict *et al.*, 1956), phosphate and citrate buffers are frequently used to stabilize solutions. Sodium citrate will maintain 90 per cent. of sodium benzylpenicillin solution potency for 3 days at 24°C. (slightly above room temperature), and for two weeks at 4°C. With procaine penicillin suspensions, citrate buffering enables loss to be reduced to no more than 5 per cent. in two years at room temperature. Strong solutions tend to deteriorate more rapidly than weak solutions.

3. *Temperature.* As already indicated in the preceding two paragraphs, deterioration rate increases with temperature, and even dry powders will not withstand autoclaving or heating at 100°C. for any length of time. All solutions for injection must therefore be prepared by aseptic methods.

4. *Oxidizing*. All oxidizing agents rapidly destroy penicillin. Reducing agents are similarly destructive and should not be used with penicillin.

5. *Enzymes*. The stability of aqueous solutions referred to above applies only to sterile solutions. If solutions of penicillen are contaminated by many of the airborne and waterborne penicillin resistant organisms such as *Bact. coli* and its relatives, the enzyme *penicillinase* produced by these organisms rapidly destroys the penicillin. Though most resistant organisms produce this enzyme some do not produce it in detectable amounts and the quantity of enzyme produced is no criterion of the degree of organism resistance. Enzyme action and pH are mainly responsible for the destruction of orally administered penicillin.

6. *Miscellaneous*. Penicillin is markedly affected by a number of heavy metals, amongst which copper, mercury, iron, and zinc, are the most important, particularly as zinc compounds are used as 'fillers' in the production of rubber bungs and piping. These metals attack the thiazolidine ring. Alcoholic groups, and thiol-containing compounds such as cysteine are also antagonistic. The significance of destruction by alcoholic groups is that the keeping of syringes in alcohol is contra-indicated unless they are thoroughly rinsed before use.

Pharmacology

The chemotherapeutic actions of all the salts and esters of penicillin are fundamentally the same, any difference between the penicillins being concerned with absorption and excretion rather than antibacterial activity.

Absorption and Administration Routes. The *inorganic salts* of penicillin—the sodium salt is the one most frequently used—are absorbed very rapidly from parenteral injection sites when aqueous solutions are used. Adequate blood levels are achieved within thirty minutes from intramuscular sites and in a slightly longer time following subcutaneous injection: there is very little reason for administering penicillin by the intravenous route, especially as thrombophlebitis may result from repeated injections of concentrated solutions. Most penicillin, as with other parenterally administered antibiotics, is administered by the intramuscular route.

Delayed absorption is frequently required to maintain adequate antibiotic concentrations in the blood and tissues, especially as excretion is rapid and the slowing of excretion unpracticable. There are two methods of delaying absorption:

1. If inorganic salts are suspended in oily vehicles, the water soluble salts will diffuse out slowly and continuously over a given period. Official injections of sodium or calcium benzylpenicillin suspended in arachis oil with beeswax were widely used for a short time.

2. If complex, sparingly soluble organic salts such as Procaine Benzylpenicillin, B.Vet.C. or Benzathine Penicillin, B.P., U.S.P., are given as aqueous suspensions with buffering and suspending agents, absorption is

also slow and blood levels may be maintained for 24–48 hours with one injection.

If these two principles are combined so that 'insoluble' penicillins are suspended in oil with aluminium monostearate, blood levels may be maintained for several days with one injection.

With all these 'long-acting' penicillins, the dosage must be large enough to provide a depot throughout the required period.

The *insoluble penicillins* are, because of their low solubility, only very slowly absorbed. Procaine benzylpenicillin is the most popular and in aqueous suspension will establish therapeutic blood levels in 2–3 hours and maintain them for 24 hours, when given in correct doses. Should high levels be required quickly, a 'loading' dose of a water soluble inorganic salt may be given simultaneously. With benzathine penicillin, adequate blood levels may be maintained for 7 days by one single injection because of the very slow rate of absorption: acute and severe cases, if treated with this salt, should be 'primed' with either a dose of a soluble inorganic salt, a dose of the procaine salt or a combination of both, otherwise therapeutic blood levels may not be reached for many hours.

The *oral route* is not very satisfactory for the administration of the inorganic or procaine penicillins as these compounds are largely destroyed by gastric acidity and bacterial action. If large doses of buffered salts are given the absorption rate is sufficient to achieve therapeutic blood levels. The advent of phenoxymethylpenicillin (Penicillin V), which is remarkably stable when given orally, has made the oral route more practicable and it should find a place in small animal practice, most probably as a means of maintaining blood levels after establishing them by parenteral injections.

Blood Levels. The blood level required for all normal uses is 0·03 to 0·05 units per ml. blood (0·02 to 0·03 micrograms per ml.). These levels are bacteriostatic: 0·5 units per ml. is bactericidal. These levels in themselves are not important except that they are an indication of the levels in the tissues where the bacteria are multiplying, unless, of course, septicæmia (multiplication of bacteria in the blood stream) is present. Once the tissue levels are adequate they may be retained long after the blood levels have dropped below 0·03 units per ml. On this supposition Thomsett *et al.*, (1949) recommended intermittent massive doses, between which there would be times when no penicillin would be detectable in the blood. This technique is not generally used.

Barriers. 1. *Blood-brain barrier.* Penicillin does not diffuse through into the cerebrospinal fluid unless the meninges are inflamed, and even then massive intramuscular or even intravenous doses are required to achieve any degree of therapy. It is advisable to give an initial intrathecal loading dose with isotonic solutions of penicillin, but great care must be taken as penicillin can cause severe collapse and death when administered by this

route. Solutions containing 20,000 to 50,000 units per ml. are isotonic. Bedford (1949) recommends a maximum non-convulsive dose of 10,000 units for injection into the cysterna magna of a dog. Convulsions, when they do occur, can be controlled by barbiturate injections.

2. *Placental barrier.* Penicillin does not readily pass from the maternal circulation to that of the fœtus but, as with the blood-brain barrier, if the doses are large enough therapeutic levels can be achieved in the fœtal circulation. It is of little practical significance at the moment.

3. *Intestinal barrier.* Penicillin is slowly and irregularly absorbed from the intestines and doses from 3–10 times larger than parenteral doses are normally required. Phenoxymethyl penicillin is superior to other penicillins when given by this route.

4. *Serous membrane barriers.* Penicillin diffuses poorly across serous membranes unless they are inflamed, and even then diffusion is not good. This means that pleurisy and peritonitis are best treated by injections directly into the serous cavities. The same applies to sinovial membranes and, where action within a joint is required, intra-articular injections are indicated.

5. *The milk barrier.* Diffusion of penicillin into the milk in therapeutic concentrations is achieved only by massive doses given intravenously. It is neither economical nor practical to treat mastitis by this route, though that does not preclude parenteral antibiotic therapy in mastitis where high temperatures and bacterial invasion of the body are present.

Excretion. Following an intramuscular or intravenous dose of a water soluble penicillin, detectable concentrations appear in the urine in a few minutes, and between 50 per cent. and 80 per cent. can be recovered from the urine in an active form within six hours. Part of the remainder is metabolized, while small amounts are lost in the bile and saliva. It has been estimated in renal clearance tests that approximately 20 per cent. of the excreted penicillin is lost by glomerular filtration and 80 per cent. is excreted by the tubules.

Toxicity. There is no toxicity problem with penicillin in veterinary medicine. Occasionally allergic skin reactions may occur in small animals following previous treatment, and there are a few reports of similar reactions in thin skinned horses (Jones, 1954, 1955). Veterinary surgeons who are themselves sensitive to penicillin must use it with care. Where accidents have happened and penicillin sensitive humans are affected, antihistaminic creams applied locally will counteract skin reactions but severe reactions should be referred to a hospital or doctor. Animals showing allergy should be treated with antihistaminics locally and systematically. Intrathecal injections used in attempts to alleviate neural symptoms of distemper in the dog showed that penicillin was dangerous when used in this way. Experimentally it has been shown that 10,000 units should be the maximum intrathecal dose.

Some laboratory animals, but particularly guinea pigs, show a specific sensitivity to penicillin.

Action

Penicillin has powerful bacteriostatic action with minimum blood levels of 0·03 units per ml. and is bactericidal at 0·5 units per ml. when used against susceptible bacteria. Its action is unaffected by blood elements or the products of tissue breakdown, including pus, nor does it affect leucocyte metabolism. It is, however, advisable to remove dead tissue and pus, as these non-vascular substances restrict the diffusion of the penicillin.

Penicillin is active against Gram positive organisms and with a few exceptions inactive against Gram negative organisms. The antibiotic is effective only when bacteria are multiplying and is thought to interfere at two stages of metabolism. The antibiotic interferes with the assimilation and concentration of glutamic acid within the bacterial cell and it has been suggested that penicillin also interferes with the nucleotide balance within the cell (Mitchell, 1949). More recently Park and Strominger (1957) have suggested that this interference in nucleotide metabolism results in an inability of the bacterial cells to produce sufficient cell wall for their needs, so that they outgrow their walls and become lysed, as the protoplasm flows through the gaps under the influence of osmotic pressures.

If bacteriostatic concentrations are present in the blood and tissues the affected bacteria become very susceptible to attack by the body defences—leucocytes, antibodies etc., and remain so for several hours after the disappearance of effective blood levels. This time lag for staphylococci is about four hours *in vitro*, (Eagle *et al.*, 1949), but it varies according to the duration of exposure to the antibiotic, the concentration of the antibiotic, and the type of organism.

With bactericidal concentrations, the natural body defences are called upon to a lesser degree, but are still required to remove dead bacteria and to combat the toxic products of bacteriolysis and the toxins which may be produced by the live bacteria. It is very important to remember that *no antibiotic will neutralize bacterial toxins;* with such diseases as those caused by *Cl. perfringens* (formerly *Cl. welchii*)—pulpy kidney, lamb dysentery etc.—and *Cl. tetani* (causing tetanus) it is essential to give doses of antitoxin sera, even though antibiotics may be given to destroy the bacteria.

Antibacterial Spectrum. Penicillin is a narrow spectrum antibiotic and should normally be considered as effective against streptococci only. It is still the best antibiotic for the streptococci which affect animals. Other Gram positive bacteria are affected but insensitive strains occur and the general response is less satisfactory. A few strains of Gram negative cocci which affect man are susceptible but in general Gram negative bacteria are insensitive to penicillin. Some rickettsial response is shown and the

viruses of psittacosis and ornithosis are partially sensitive: other antibiotics have greater activity and are preferred for treating diseases due to these organisms.

In vitro studies show that the following organisms are sensitive to normal bacteriostatic concentrations of penicillin:

Organism.	Disease caused.
Streptococci	Mastitis.
Staphylococci	Systemic and local infections in all species.
Corynebacterium pyogenes	
Corynebacterium renale	Pyelonephritis in cattle.
Erysipelothrix rhusiopathiæ	Swine erysipelas.
Actinomyces bovis	Lumpy Jaw in cattle.
Clostridia	Tetanus, pulpy kidney, lamb dysentery etc.
Leptospira canicola	Leptospiral nephritis.
Vibrio fœtus	Vibrionic abortion.
Bacillus anthracis.	Anthrax.

In vivo, the picture is very different, for pathogens may either produce lethal substances which are not susceptible to antibiotic activity or they may produce tissue reactions which prevent access of the antibiotic to the organism. For example, *Clostridium welchii* type D, which causes 'pulpy kidney' in sheep, multiplies mainly in the intestines, producing a toxin which, when absorbed, causes the typical lesions and death: this toxin is not affected by an antibiotic so that once the toxin is produced the destruction of the organism is of no significance: orally administered penicillin also is mostly inactivated before it can have much effect. Similarly, in staphylococcal and *C. pyogenes* mastitis large amounts of pus, œdema, or fibrous tissue, are produced, within masses of which the organisms multiply: any intramammary or systemic penicillin injections are unlikely to reach the organisms quickly enough or in sufficient quantity to materially affect the course of the conditions.

Insensitive organisms include:

Pseudomonas species. Non-pathogenic under normal conditions, these organisms occasionally become pathogenic or exist as secondary complicating organism. A recent report (Winter *et al.*, 1957) discusses the case of a cow which died following mastitis and generalized lesions due to this organism.

Pasteurella and Hæmophilus species. These are responsible for pneumonic or septicæmic infections.

Coliform and Salmonella species. Both groups of organisms cause gastroenteritis, septicæmias, and *Bact. coli* causes about 1 per cent. of mastitis cases.

Brucella species. Bovine abortion, kennel cough in dogs, Malta fever, tularæmia and other diseases of man and animals.
Fungi and most viruses are also unaffected.

Penicillin Resistant Strains. Penicillin is remarkable in that bacterial resistance is very slow to develop. There are very few proven instances of organisms developing resistance to penicillin, though the incidence of resistant strains of staphylococci is becoming greater in cases of clinical mastitis.

Diseases and Penicillin Therapy. By far the most important animal disease for which penicillin therapy is the prime indication is streptococcal bovine mastitis. Other specific diseases for which penicillin is indicated are: anthrax in all species, erysipelas infection of sheep, pigs and birds, strangles and joint-ill of horses, some clostridial diseases of cattle and sheep. Penicillin has been used with variable results in actinomycosis and pyelonephritis of cattle. Local treatment of burns, scalds, wounds, eye and ear conditions, is very effective and though penicillin usage is not always advisable, elevated temperatures due to unknown causes, and secondary invaders complicating virus diseases frequently respond favourably.

Bovine Mastitis

A variety of organisms have been isolated from clinical cases of bovine mastitis including streptococci, staphylococci, *Corynebacterium pyogenes*, *Bacterium coli*, *Pseudomonas æruginosa* (*pyocyanea*), acid fast bacilli including *Mycobacterium tuberculosis*, and various yeast-like organisms. Some of these organisms are primary causal factors, others are pathogens of secondary importance to some mechanical or other primary factor. Only streptococci respond well to penicillin: some cases of staphylococcal mastitis respond slowly, but infection with all other types of organism should not be treated with penicillin alone.

1. *Streptococcal mastitis.* These cases may produce three types of bacteria when milk is cultured, *Streptococcus agalactiæ*, *Strep. dysgalactiæ*, and *Strep. uberis*. The first is the primary causal agent of severe acute and occasionally subacute and chronic cases of infectious streptococcal mastitis, but it is believed (Wilson, 1954) that in most cases *Strep. dysgalactiæ and Strep. uberis* are of less significance than poor management and milking methods in the causation of mastitis where these organisms are implicated. Of the three streptococci, *Strep. agalactiæ* responds very well (75–90 per cent.), *Strep. dysgalactiæ* well, but *Strep. uberis* only fair and may require larger doses or occasionally the use of sulphonamides (Hemsley, 1956).

Treatment. Penicillin was originally applied as an aqueous solution of 20,000–50,000 units in 50 ml. sterile water infused as a warm solution into the udder. Reasonable results were obtained but repeated injections

were required at intervals of four to six hours and the method was not economic. With the development of oil suspensions which maintained milk levels for prolonged periods, it became possible to use two or three doses at intervals of 24–72 hours, depending on the type of penicillin and the dosage used:

Penicillin	Base	Dose	No. of doses and interval between doses
Sodium benzylpenicillin	Oil with 2 per cent. Aluminium Stearate	100,000 units	3–24 hours
Procaine benzylpenicillin	Oil with 2 per cent. Aluminium Stearate	100,000 units	3–48 hours
Procaine benzylpenicillin	Oil with 2 per cent. Aluminium Stearate	300,000 units	2–72 hours

These three injections are the treatments most favoured in Great Britain. Reports are available, however, that better results are obtained especially with mastitis due to *Strep. zoöepidemicus*, by large dose (up to 1·0 mega unit) intraparenchymatous injections of aqueous solutions or oily suspensions (Begg *et al.*, 1950; Petrillo, 1956).

All intramammary injections should be made only after stripping the quarter as clear as possible. The teat should be cleaned and dressed with either spirit or a detergent antiseptic. Following the expression of any nozzle plug that may be present in the tube, the elongated nozzle should be introduced through the teat sphincter and the total contents of the tube squeezed into the teat canal. Closing the teat end between finger and thumb, the injection should then be pushed and massaged up into the milk duct system and the udder tissue.

Subsequent milking between doses can be carried out normally without affecting treatment, but it must be remembered that milk will contain sufficient penicillin to restrict 'cheese starter' growth (lactobacillus) for 72 hours after the last injection. This period may be extended with the larger 300,000 unit injections. Any milk containing penicillin should not be included in batches intended for manufacturing or human food.

Strep. agalactiæ will persist in the udder during the dry period (Howell, 1956) and it is becoming the practice to inject one dose of 300,000 units of procaine penicillin into each quarter after the last milking. Such injections may be repeated at intervals of six weeks.

2. *Staphylococcal* (*micrococcal*) *mastitis*. This type is most frequently due to *Staphylococcus aureus* (*Micrococcus pyogenes: aureus*) which is much more resistant to treatment, mainly because of the œdema and

fibrosis which the organism causes. There have, however, in recent years appeared several reports estimating from 12–18 per cent. penicillin resistant strains of staphylococci isolated from cases of mastitis (Aynsley, 1953; Stableforth, 1953; Hughes, 1954) so that combinations of antibiotics and sulphonamides are used as well as broad-spectrum antibiotics—chlortetracycline and oxytetracycline. A recent report (Tee, 1957) adds considerable emphasis to the problem of penicillin resistant staphylococci, for the 11 per cent. reported in 1954 had become 47 per cent. in 1956. Penicillin and streptomycin or dihydrostreptomycin, due to their synergistic bactericidal effect against staphylococci (Manten, 1956), are now widely used in Great Britain for the treatment of penicillin resistant organisms. Procaine penicillin 100,000 units with 0·1 G. or 0·25 G. dihydrostreptomycin base are the usual proportions. Penicillin with soluble sulphadimidine as infusions (Christian, 1948: Gibbons, 1948), or in normal oil/stearate suspensions, are also effective.

The use of anti-inflammatory agents such as ACTH systemically—100 units plus 50 units 48 hours later (Hindson, 1956), and prednisone experimentally combined with penicillin or streptomycin (Foley, 1957 and 1957b), indicate a new trend in staphylococcal mastitis therapy.

Oil infusions of penicillin are non-irritant and reactions rarely occur following their administration. This is not the case with aqueous solutions, for reports are published from time to time concerning allergic type reactions with œdema of the udder and febrile reactions, suspected of being caused by pyrogens in the vehicle (Murnane *et al.*, 1955). Similar reactions have been met with occasionally following intramammary injections of broad-spectrum antibiotics.

It must be impressed on all associated with dairy management that attention to such details as cleanliness and health of attendants, disinfection of udder cloths and teat clusters, the segregation at the end of the milking line of cows suspected of carrying infection, the use of antiseptic teat creams and correct vacuum pressures, immediate removal of clusters once milk flow has ceased, adequate stripping, regular milking times and all other details which comprise correct management and husbandry, are absolutely essential if the full benefits of antibiotic treatment are to be achieved and maintained. With a combination of good management, husbandry, and antibiotics, streptococcal mastitis at least, can be eradicated and herds kept clear: without this ancillary assistance antibiotics can neither achieve nor maintain freedom from mastitis.

Specific Systemic and Organic Diseases. These are the diseases in which penicillin is specific, and in most cases the most active of the antibiotics.

Strangles

This is a condition of horses caused by *Streptococcus equi*. The organism is susceptible to penicillin more than other antibiotics *in vitro* (Rahman,

1957), but clinical response varies according to the stage at which treatment is instituted. The disease is typified by upper respiratory tract inflammations and by abscess formation in the lymph glands of the throat. Difficulty in penetrating abscess capsules due to their slight vascularity is an accepted failing of penicillin and it is therefore not surprising that opinions differ concerning the clinical effect of penicillin in this disease. (Morcos, 1945; Semtner, 1945; Bryan, 1946; Minett *et al.*, 1945; Roberts, 1945.). Variations in dosage may also have some bearing on these differing opinions. *Dosage* should include an initial loading dose of a soluble antibiotic which can be supplemented by less soluble forms. Large doses—up to 50,000 units per lb. bodyweight per day, should be used to offset the extra resistance shown by *Strep. equi* when compared with standard group A streptococci as described by Rahman.

The use of antibiotics does not relieve the owner of the onus of isolation of infected and contacts from healthy young stock nor of observing the usual cleanliness and disinfection that must be rigorously applied.

Anthrax

This septicæmic disease which affects cattle, sheep, goats, pigs, and dogs has been efficiently controlled by the use of penicillin. The general principles of therapy apply in that penicillin must be given early with large initial doses of the soluble salts supplemented by repository doses of procaine penicillin. *Cattle.* As early as 1947 Wessels and his colleagues had reported good results in cattle from 8-hourly doses of 125,000 units of a beeswax and oil suspension of a soluble salt in conjunction with 100,000 units injected at the sites of inoculation (the infection was transmitted during anaplasmosis immunization). Riggs *et al.* (1947) also reported the saving of 42 out of 44 cattle by three doses of 100,000 units soluble penicillin at 12 hourly intervals. Since then further reports have confirmed that penicillin is a useful therapeutic in this disease. *Sheep and pigs.* Little information is available, but the course in sheep would be expected to be similar to that in cattle. Clinical results in pigs indicate the drug to be at least as useful in cattle. *Dogs.* Experimental evidence (Prawiranata, 1954) shows that the course of the disease following penicillin therapy is similar to that in humans; the disease would seem to respond to the normal daily dose used in small animal practice, providing the initial dose is a soluble penicillin and is given soon after infection. Puppies require proportionately higher dosage than adults just as children require more when treating cutaneous anthrax (White, 1956).

A report by Clarenburg *et al.* (1956) emphasizes the difficulties facing laboratories when attempting to diagnose anthrax post mortem after antibiotic therapy. No organisms were found in blood smears of a cow that was slaughtered after a high body temperature of unknown ætiology had been treated for two days with penicillin and streptomycin, yet following culture and mouse inoculation typical organisms were recovered.

prevent both hypostatic congestion and excoriation of all bony prominences ('bed-sores'). Penicillin wound dressings are an effective prophylaxis.

Blackleg. Clostridium chauvœi, and occasionally *Cl. œdematiens* and *Cl. septique*, cause a muscular and connective tissue 'gas-gangrene' in cattle and sheep. These organisms, which multiply in the affected tissues, do not produce such powerful exotoxins as other clostridia and if maximum doses (5000 units per lb. bodyweight) of penicillin are injected early enough a good percentage of recoveries can be achieved. Treatment must be undertaken before muscle damage is great enough to necessitate slaughter for humane reasons. (Aitken, 1949 and 1951).

As a prophylactic against gas gangrene and blackleg, penicillin has been used in dog bites and wounds of sheep (English, 1956), and it has been recommended that sheep not vaccinated against blackleg should receive one or two injections of 0·5 mega units following dystocia (Buddle *et al.*, 1953).

Botulism. Although *Clostridium botulinum* has been shown to be highly sensitive to penicillin *in vitro* (Anderson *et al.*, 1953), this fact is of little clinical significance, for botulism is an exo-intoxication, the toxin being produced by the organism multiplying saprophytically in dead vertebrates and invertebrates. Ingestion of the toxin alone in very small quantities can be lethal to birds, horses, dogs, etc.

Pyelonephritis

This disease of cattle is typified by destruction of kidney tissue, partly by bacterial attack and partly by pressure of the tremendous amounts of pus produced. The organism responsible is *Corynebacterium renale*, which is sensitive *in vitro* to penicillin (Lovell *et al.*, 1947), but the character of the clinical condition is such that results in all except early cases are not encouraging (Beck *et al.*, 1945; Morse, 1948; Arthur, 1949; Lovell, 1951). Where clinical cures have been achieved, bacteriological examination has repeatedly demonstrated the organisms in the urine. Treatment should consist of a minimum daily doses of 1·0 mega unit of procaine penicillin, but preferably more, continued for at least a week. The most that can be achieved in all but the very earliest cases is to maintain a cow until the completion of a pregnancy or lactation or to enable fattening and slaughter.

Actinomycosis

'Lumpy jaw' is caused by an organism, *Actinomyces bovis*, which is susceptible *in vitro* to penicillin. The lesions consist of purulent and granulating masses surrounded by bone produced at the periphery of areas in which bone is being resorbed: the whole jaw bone becomes an enlarged mass of bone honeycombed with 'abscess' cavities filled with pus. Some of these pus filled cavities communicate with the exterior, and sometimes the mouth, through sinuses from which the pus exudes. The pathology of the disease may thus be considered as abscesses in which

the capsule is bone and not fibrous tissue, and unless these abscesses can be drained and irrigated with penicillin little improvement can be expected. This agrees with clinical experience, and any benefit is only derived from penicillin injected into the centres of suppuration though this is difficult to achieve, and temporary regression is the best that can be obtained with penicillin (Bayles, 1947; Lewis, 1947; English, 1956), although Kingman *et al.* (1957) and Piper (1953) have claimed favourable results, the former with streptomycin alone and the latter with 2·0 G. intravenous oxytetracycline, and intramuscular penicillin with streptomycin daily for four days.

Actinobacillosis caused by a Gram negative organism *Actinobacillus lignieresi*, which affects soft tissues only, is not markedly sensitive to penicillin, though 'wooden tongue' may benefit from its use due to elimination of secondary invaders; sodium iodide or sulphonamides intravenously are most effective. A recent report credits iso-nicotinic hydrazide (isoniazid) with some activity against actinobacillosis (Brega, 1956).

Streptococcal infection in puppies, often referred to as 'BHS infection', responds well to injections of the bitch during pregnancy—procaine penicillin on three occasions, at mating, mid-pregnancy and just before parturition. Injection of the puppies at birth with 30,000–50,000 units soluble penicillin or procaine penicillin will also prove successful.

Non-Specific Systemic Diseases. Penicillin has been widely used as a routine treatment for fevers, the cause of which is unknown, especially in dogs and cats. In septicæmias such as navel-ill in calves and foals, which is often caused by streptococci, (streptococcus zoöepidemicus in foals), penicillin is often very effective, but as the condition in foals is more frequently caused by *Bacterium equirulus* (*Shigella equirulus*) and *Bact. coli* (*Escherichia coli*), it is advisable to use a combination of penicillin (4–5,000 units per lb. bodyweight daily or 10,000 units per kg.) and streptomycin (5·0 mg. per lb. daily or 11·0 mg. per kg.). In sheep and goats streptococcal infections have responded to penicillin (Grini *et al.*, 1956), and *Corynebacterium ovis* has been reported as susceptible to penicillin *in vitro* (Bürgener, 1955), though clinical information is not available.

Metritis in cattle and mares has been treated with intra-uterine penicillin but results are variable as would be expected in view of the mixed infections which frequently exist, and combination with streptomycin should prove superior either locally or systemically. Combinations of penicillin with streptomycin or sulphonamides have been recommended for *Vibrio fœtus* infections in both cows and bulls.

Easterbrooks and Plastridge (1950, 1951, 1953) in various papers have used and recommended 0·5–1·0 G. streptomycin, with or without up to 400,000 units penicillin, injected into the uterus in 15·0–20·0 ml. sterile distilled water at any stage of œstrus, whilst McTaggert (1955) used 1·0 mega units of penicillin with 40·0 ml. of 33⅓ per cent. sulphadimidine

sodium solution. Edgson *et al.* (1954) used 1·0 mega unit of soluble and insoluble penicillins with 1·0 G. dihydrostreptomycin in 50 ml. arachis oil, massaged into the bulls penis daily, after drawing with epidural anæsthesia, for five days.

Other uses of penicillin include the control of secondary invaders in the virus diseases of dogs and cats. Broad spectrum antibiotics give better results, but cost very much more than penicillin. Penicillin has also been used in the treatment of the pustular form of demodectic mange in the dog but if combined with streptomycin results should be better.

Local Uses. Penicillin has been combined with sulphanilamide, sulphadimidine, and sulphathiazole for wound, burn, and scald, dressings. The first two are superior to sulphathiazole, for these two sulphonamides diffuse more easily into the tissues around the wound and are therefore more effective. Proportions are usually 5000 units of sodium or potassium penicillin per gramme of sterile powder. Solid penicillin bougies have been used for insertion into puncture wounds of joints etc. Lotions and ointments have been applied to eyes with very good effect, but broad spectrum antibiotics are better for 'New Forest disease'—*Moraxella bovis* caused infectious keratitis of cattle. In the treatment of abscesses, antibiotics should either be given in the very early stages before a fibrous capsule forms or not until the abscess has matured, been opened, and the pus evacuated. Should the penicillin be administered during development of an abscess, it is more probable that the abscess will neither mature nor heal, and a chronic condition may ensue which is very difficult to treat.

In a recent review Johns (1958) has drawn attention to the effect of procaine penicillin in the treatment of bloat in cattle. Doses varying from 50 mg. to 200 mg. daily have been used with good control in a high proportion of cases, though there are individual animals which will not respond. Personal experience indicates that where the farmer will take the trouble of individual dosing the treatment can be used prophylactically as well as therapeutically. Fermentation resistance is aquired but bloat continues to be controlled though not so well (Johns, *loc. cit.*)

Dosage.

Parenteral: 2000–5000 units per lb. bodyweight.

This dosage should be given every 4 hours if a soluble salt is used in aqueous solution, every 12 hours if a soluble salt in oil with stearate or wax, every 24 hours if procaine penicillin is used either as an aqueous or an oil suspension, and once or at most twice at an interval of 24 hours with benzathine penicillin. Adult stock should receive the higher dosage rate only if the condition is severe and acute, but young stock and small animals should be given the higher dosage rate on all occasions, and up to 10,000 units per lb. in severe cases.

Where soluble and insoluble penicillins are used together, the ratio should be about 1 : 3.

Oral: Small animals: 3–5 times the parenteral dose, or 100,000–300,000 units every four hours, if mineral or procaine salts are used. Phenoxymethylpenicillin is given at the rate of 8·0 mg. per kg. bodyweight three times daily. For pigs and poultry 16 mg. per kg. bodyweight twice daily is more convenient Jaksch *et al.*, 1954; Henderson *et al.*, 1956.)

Official Preparations

Penicillin is available in official form as a cream, eye ointment and eye-drops, ointment, tablets, parenteral injections, and intramammary injections.

Cream of Penicillin, B.Vet.C. (Crem. Penicil.)

This is the cream of the B.P. and, unless otherwise requested, contains 1000 units of benzylpenicillin with sodium citrate as a buffering agent and chlorocresol as a preservative. The base consists of 7 per cent. w/w emulsifying wax, 5 per cent. w/w hard paraffin, and 41 per cent. w/w liquid paraffin, with water up to 100 per cent. The proportions of paraffins may be varied according to climate and the need for a hard or soft cream. It should be kept in a refrigerator and used within 7 days.

Eye Ointment of Penicillin, B.Vet.C. (Oculent. Penicil.)

This also is the B.P. preparation and normally contains 2000 units per gramme of a salt of benzylpenicillin. The basis is a sterile mixture of 5 per cent. liquid paraffin and 95 per cent. soft paraffin. The preparation will keep in cool storage conditions, little deterioration occurs when kept for 12–24 months.

Eye-Drops of Penicillin, B.Vet.C. (Gutt. Penicil.)

A soluble penicillin salt is dissolved at the rate of 2500 units per ml. in solution for Eye-Drops, B.Vet.C., with 0·5 per cent. w/v of sodium citrate as a buffer. The solution contains fungistatic proportions of methyl and propyl hydroxybenzoates in freshly boiled and cooled distilled water. The drops should be stored in a cool place and used within seven days. If kept in a refrigerator, the solution *must* be allowed to reach room temperature at least, before use.

Ointment of Penicillin, B.Vet.C. (Ung. Penicil.)

This also is a B.P. specification containing 1000 units per gramme of benzylpenicillin in 5 parts liquid paraffin and 95 parts soft paraffin. It keeps well in cool storage conditions.

Tablets of Penicillin, B.Vet.C. (Tab. Penicil.)

These are the tablets of the B.P. containing 200,000 units of sodium or potassium benzylpenicillin. They contain up to 5 per cent. by weight

sodium citrate, taking the penicillin as reference, and are usually coated to obtain some protection from the gastric juices.

Injection of Penicillin, B.Vet.C. (Inj. Penicil.)

The preparation conforms with the B.P. specification, consisting of soluble salts of amorphous penicillin or crystalline benzylpenicillin, with or without a buffering agent, for fresh solution with Water for Injection. Vials containing the sterile powder are available commercially with 0·1, 0·2, 0·5, 1·0, 5·0, 10·0 and 200 mega units. Solutions are best used immediately they are made, but storage at 4°C. or less maintains potency reasonably well for 4 days with unbuffered and 7 days with buffered solutions.

Injection of Procaine Benzylpenicillin, B.Vet.C. (Inj. Procain. Benzylpenicil.)

This complies with the B.P. specification, consisting of the procaine salt of benzylpenicillin with a dispersing agent and with or without a buffering agent. It is made into a suspension by adding Water for Injection, B.Vet.C. and shaking. Vials containing the sterile powder are available commercially with 0·3, 0·9 and 3·0 mega units. The suspension will keep for 7 days when refrigerated.

Injection of Procaine Benzylpenicillin with Benzylpenicillin, B.Vet.C. (Inj. Procain. Benzylpenicil. c. Benzylpenicil.)

Sometimes referred to as Fortified Injection of Procaine Penicillin G., this conforms to the B.P. specification and contains the previous two injections in proportions of 1 : 3. The addition of Water for Injection gives a solution and suspension. It is available in vials containing 0·4, 1·2 and 4·0 mega units. Once prepared the combination should be used in 4 days even if refrigerated, because of the soluble penicillin content.

Stabilized aqueous suspensions of penicillin containing 0·3 mega units of procaine benzypenicillin per ml. with buffering and dispersing agents are available commercially. They are stable at room temperature with a shelf life of about one year, and are supplied in 10·0 and 30·0 mega unit sizes.

Intramammary Injection of Penicillin, B.Vet.C.

This is a suspension in a bland vegetable or mineral oil, with or without aluminium stearate, of a soluble salt of benzylpenicillin. Normally the penicillin content is 100,000 units. Commercially, concentrations of 20,000 and 50,000 units are also available.

Intramammary Injection of Procaine Benzylpenicillin, B.Vet.C.

This preparation is similar to the preceding one but contains procaine benzylpenicillin instead of the 'soluble' salts. The official preparation contains 100,000 units, but tubes containing 300,000 units per dose are marketed.

Intramammary Injections of Procaine Benzylpenicillin and Dihydrostreptomycin, B.Vet.C.

The injection is similar to the preceding injections but contains 100,000 units procaine benzylpenicillin and 0·1 G. (100,000 units) of dihydrostreptomycin base as the sulphate.

Intramammary Injection of Dapsone and Penicillin, B.Vet.C.

This injection contains 33·3 per cent. powdered dapsone with 50,000 units of a 'soluble' benzylpenicillin salt per dose, in a base of liquid paraffin and soft paraffin.

All these preparations should be prepared in a sterile manner, heating the base at 150°C. for one hour and adding the antibiotic aseptically. Prepared and packed in this manner these products are very stable and are given shelf lives of up to 3 years.

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CHAPTER 25

ANTIBIOTICS
(iii) STREPTOMYCIN

STREPTOMYCIN is a narrow spectrum antibiotic which is official in all the pharmacopœias. Its salts must contain not less than 600 international units per mg. expressed as the base.

History

Streptomycin was announced in January 1944 by Schatz, Bugie, and Waksman, following a systematic examination of species of Actinomyces (since renamed Streptomyces) organisms for antibiotic production. In their laboratories at Rutgers University, New Jersey, U.S.A., they examined a considerable number of substances none of which, apart from streptothricin, were of any clinical value because of toxicity. In September 1943, cultures of a mould, *Streptomyces griseus*, were isolated from an area of heavily manured soil near farm buildings at the University Agricultural Station. It soon became apparent that their search, which had concentrated on finding an agent complementary in spectrum to penicillin and therefore active against Gram negative organisms, was ended. It was later shown (Feldmann, 1944) that, more important than its Gram negative activity, streptomycin was highly effective against *Mycobacterium tuberculosis*, and the Nobel Prize 1952 was awarded to Professor Waksman in honour of the achievement.

Following extensive research into the chemical structure of streptomycin, the compound *dihydrostreptomycin* was produced in 1946. It proved on trial to be as effective as streptomycin, though the original claim that dihydrostreptomycin was less toxic than the parent compound did not prove correct, for it was found that the compound was neurotoxic, but that the site of neural damage was different from that of streptomycin.

Manufacture

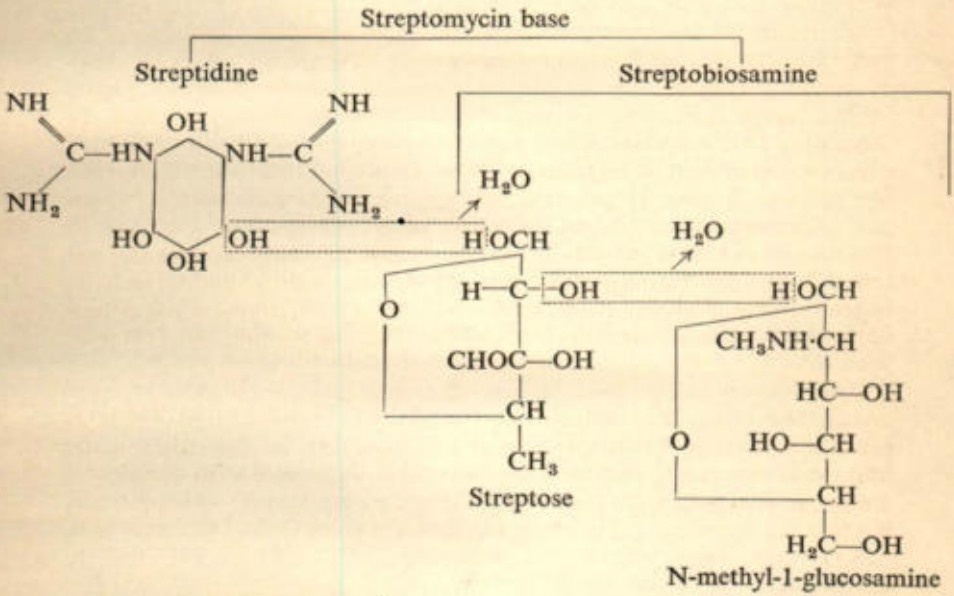
Streptomycin is now the accepted generic name for several related antibiotics produced by the deep-vat culture method using actino-phage resistant strains of *Streptomyces griseus*. (The 'phages' are virus-like organisms which attack and destroy the bacterial cultures). The strains must be sporulating ones, for non-sporulating strains produce little or no

streptomycin. The extraction and purification is a complicated process of adsorbing the base onto charcoal, precipitating, washing and removing with various solvents different combinations at successive stages, the picrate, followed by phosphotungstate, reineckate etc. until, finally, streptomycin base is obtained by chromatographic separation. The base can then be turned into the sulphate, hydrochloride, or calcium chloride complex, or, by hydrogenation, into dihydrostreptomycin.

Chemistry

Streptomycin is a white crystalline substance with possibly a slight odour and a saline taste. It is very soluble in water but only slightly so in alcohol, and insoluble in chloroform, fixed oils, and paraffins.

The structure of streptomycin is complex and consists of the hydroxylated base, streptidine, which is linked glycosidally with a disaccharide type of compound known as streptobiosamine; this compound is in turn formed from a sugar, streptose, and N-methyl-1-glucosamine:

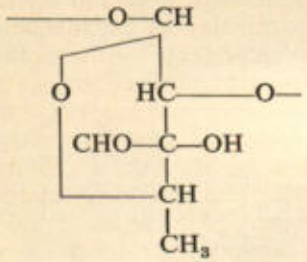


If streptomycin is subjected to acid hydrolysis, streptidine and streptobiosamine are produced, but alkaline hydrolysis produces maltol.

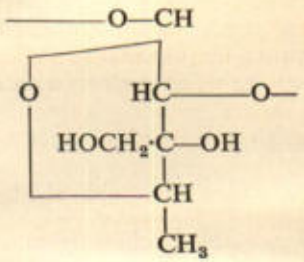
Dihydro-streptomycin base differs from that of streptomycin only in the addition of two hydrogen atoms in the streptose structure to change

the aldehyde group ·CHO at Carbon 3 into the alcohol group ·CH_2OH:—

Streptomycin



Dihydrostreptomycin



From these bases various salts can be formed. Streptomycin sulphate, hydrochloride, and calcium chloride complex, are available as well as dihydrostreptomycin hydrochloride and sulphate.

During biosynthesis, a second antibiotic is produced called mannosidostreptomycin or streptomycin B. It has a lower potency and gives streptidine, streptobiosamine, and mannose on acid hydrolysis, and maltol on alkaline hydrolysis.

Stability

Streptomycin is relatively stable when compared with penicillin, and pure dry powders will retain full potency at room temperature for at least two years.

1. *Moisture.* Streptomycin, but not dihydrostreptomycin, is hygroscopic and deliquesces in moist air. Solutions darken on exposure to light but this darkening does not appreciably affect activity and solutions at pH 6–8 will retain potency for up to one month at room temperature. Above 28°C. potency is rapidly lost. In practice, unbuffered solutions should be used within one week of preparation and should be kept in a refrigerator away from light.

2. *pH.* As with penicillin, strong acids and alkalis cause rapid deterioration. Any pH lower than pH 3 or higher than pH 8 hastens hydrolysis and irreversible destruction. When buffered with sodium citrate, aqueous solutions will keep for at least one year without appreciable loss of potency.

3. *Temperature.* Streptomycin is not as susceptible as penicillin to deterioration on raising the temperature, but nevertheless, high temperatures are deleterious and as much as 30 per cent. of a solution's potency is lost in two weeks at a pH of 6·6 and a temperature of 50°C.

4. *Oxidizing agents.* Most oxidizing and reducing agents affect streptomycin potency.

5. *Enzymes.* So far no enzyme comparable with penicillinase has been discovered, but the fact that resistant strains appear and even strains

which need streptomycin and are dependent on it for growth, is cited as indicating the elaboration of an enzyme which is capable of splitting off the streptose and glucosamine from the streptidine. This splitting at the glycosodic linkage would destroy the antibiotic activity and at the same time provide sugars for metabolic energy. The lack of an antagonistic enzyme under normal conditions is partially responsible for the intestinal activity of streptomycin, which is greatly superior to that of penicillin.

6. *Miscellaneous.* Streptomycin is inactivated by cysteine and similar sulphydryl-containing compounds but dihydrostreptomycin, not containing an aldehyde group, is unaffected. Alcohol does not affect the streptomycin series. Most salts such as sodium and potassium chlorides, sulphates, tartrates, and ammonium acetate, reduce activity of the series.

Note: A chemical incompatibility exists between the calcium chloride complex and the sulphates of streptomycin and dihydrostreptomycin. A similar incompatibility exists with this calcium complex and sulphacetamide sodium. These incompatibilities are important to remember, the former in intrathecal therapy and the latter during the treatment of eye lesions; any precipitation of calcium sulphate or calcium sulphacetamide would be extremely dangerous.

Pharmacology

The activity of the streptomycin and dihydrostreptomycin salts is almost identical. Only one feature—that of neurotoxicity, is different: this is not a difference of degree, as originally thought, but of site of toxicity.

Absorption and Administration Routes. Streptomycin is peculiar in that almost no passage across the intestinal mucosa takes place and thus systemic therapy can only be achieved by parenteral injection. The absorption of streptomycin is slower than penicillin: intravenous injections provide maximum blood levels almost immediately, but intramuscular injections take about sixty to ninety minutes to achieve maximum levels; subcutaneous injections take far longer and this route is therefore not often used. Dihydrostreptomycin should not be administered intravenously because of the greater degree of shock produced.

So far, no adequate means of slowing down streptomycin absorption rate has been discovered. This is not so important as it is with penicillin for streptomycin is slowly excreted and detectable blood levels normally persist for about eight to twelve hours following intramuscular administration.

Blood Levels. Minimum therapeutic blood levels will vary according to species and strain of organism, but in general 5·0 micrograms per ml. of serum is satisfactory. As with penicillin, it is the tissue levels which are important and these are maintained for some time after those in the blood have dropped below minimum therapeutic levels. These tissue levels are achieved rapidly, the streptomycin becoming dispersed in the tissue fluids and not entering the cells (Marshall, 1948). The recommended

interval between dosage is therefore twelve hours (Marshall, 1953), although four- to six-hourly dosing may be necessary to maintain blood levels constantly above the minimum therapeutic level. Blood levels are related but not proportional to the size of dosage.

Barriers. (1) *Blood-brain barrier.* Streptomycin diffuses very slowly into the cerebrospinal fluid unless meningitis is present, when detectable levels can be achieved, but intrathecal injections are necessary to ensure adequate therapeutic fluid levels. Dihydrostreptomycin is unsuitable for intrathecal injection and should not be used. There is, in any case, rarely any indication for intrathecal injection in animals.

(2) *Placental barrier.* Streptomycin passes the placental barrier fairly easily; fœtal blood and amniotic fluid levels achieve about 50 per cent. of that in the maternal circulation. There appears to be no neurotoxic effect on the fœtus.

(3) *Intestinal barrier.* Streptomycin is neither absorbed nor excreted in appreciable amounts through the intestinal mucosa. The extent in the cat and dog is approximately 10 per cent. of an oral dose but no appreciable blood levels are achieved (Stebbins *et al.*, 1945). This means that susceptible intestinal diseases can be subjected to maximum antibiotic concentrations.

(4) *Serous membrane barrier.* The only serous membrane crossed by streptomycin in concentrations sufficient to achieve therapeutic levels is the peritoneum. Streptomycin passes readily into normal and ascitic peritoneal fluid though at lower levels than those in the blood, but will not easily pass into the pleural cavity, synovial cavity, and pericardial sac, unless inflammatory changes are present, and even then direct injections are advisable. Adequate concentrations in the aqueous and vitreous humours of the eye are achieved following intramuscular injection, but streptomycin will not penetrate the intact conjunctiva; ulceration of the cornea provides an entrance through which the antibiotic readily penetrates. Aerosol treatment of lung infections has been used for humans; little or no streptomycin is absorbed through the lungs when this method of treatment is used.

(5) *The milk barrier.* Streptomycin is excreted in the milk in detectable and effective quantities (Hammond, 1953, reports a concentration of 6 μg. per ml. in cows milk for up to 18 hours after a single dose at the rate of 5 mg. per lb. or 11·0 mg. per kg. body weight). It is therefore of some assistance in severe mastitis of staphylococcal origin, to inject streptomycin parenterally as well as locally.

Excretion. Up to 80 per cent. of a single intramuscular or intravenous dose is excreted via the kidney. The excretion rate is maximal during the first four hours after a single dose and the majority is excreted within 12 hours. The excretion is by glomerular filtration, and tubular excretion or resorption is almost absent. Some streptomycin is excreted via the liver, and bile concentrations may reach up to 25 per cent. of the blood levels.

Toxicity. The toxicity of streptomycin has been widely advertised and is of three types, (1) a local sensitization with dermatitis, (2) a chronic and (3) an acute systemic effect. The *local toxicity* is only of significance to veterinary surgeons who frequently handle powder or solutions and may themselves become sensitized or allergic. Cross sensitization does not readily occur and dihydrostreptomycin may be used when streptomycin sensitivity has been acquired.

Systemic toxicity is an important factor in both human and veterinary medicine and has been mainly responsible for its limited use in the veterinary field. *Acute toxicity* is characterized by anaphylactoid response with nausea, vomiting, and rapid collapse with loss of consciousness. In many cases, animals will recover after several hours if kept warm and hypostatic congestion guarded against: antihistaminics injected parenterally will assist in recovery. This type of shock has been seen in dogs and cats. Dihydrostreptomycin is said to be less dangerous in this way if intravenous injection is avoided. Acute toxicity due to streptomycin has been ascribed to the presence of guanidine grouping in the molecule and also to the formation of an insoluble complex with cephalin (U.S.D. 25th Edit. p. 1331.)

Chronic toxicity is of two types, one mainly caused by streptomycin and the other by dihydrostreptomycin, though each antibiotic can cause damage of the type ascribed to the other. Streptomycin mainly attacks the cochlear division of the 8th cranial nerve, causing vertigo and, if dosage is continued, an irreversible loss of ability to balance. If dosing is decreased or stopped before symptoms intensify, recovery can take place. Dihydrostreptomycin attacks the auditory division of the 8th cranial nerve but, unlike the cochlear degeneration, no premonitory symptoms are shown and permanent deafness may result if meticulous tests for loss of hearing are not carried out. It seems therefore that dihydrostreptomycin, originally used because it was thought to be non-toxic when compared with streptomycin, is the more dangerous of the two. Both types of damage can occur in animals and large doses should not be administered for longer than three or four days. In human medicine dihydrostreptomycin is used mainly for those patients who are sensitive to streptomycin and are suffering from an acute disease not amenable to treatment with another antibiotic. Another means of overcoming the toxicity problem is to combine the two compounds, which are more or less equally active. This means that halving the individual doses almost halves the toxicity without any loss of therapeutic activity.

Action. Wherever streptomycin is mentioned in the following text this should be taken as including all the salts of streptomycin and dihydrostreptomycin unless otherwise stated.

Streptomycin is both bacteriostatic and bactericidal. It is active in the presence of blood and tissue breakdown products, including pus, but these fluids slightly reduce the antibacterial effect. Its antibacterial action

is increased with increased alkalinity. The exact method by which the bacteria are attacked is not yet known but it is thought to be due to interference in the cyclic oxidation of pyruvic acid and therefore in the respiration of the bacterial cell. In bacteriostatic concentrations the onus of destroying and removing the bacteria lies with the body's natural defences.

Antibacterial Spectrum. Streptomycin is considered to be a narrow spectrum antibiotic though it has wider powers than penicillin. In the main, it is active against Gram negative organisms but some Gram positive bacteria and the Leptospira are also affected. *In vitro*, the following organisms show sensitivity:

Organism	Disease caused
Actinomyces bovis	Lumpy jaw.
Bacterium and Salmonella species	Enteritis and septicæmias.
Brucella species	Abortion in cattle and pigs.
	Bronchitis in dogs.
Corynebacteria	Mastitis, abscesses, and septicæmias.
Erysipelothrix	Swine erysipelas, synovitis in lambs.
Leptospira	Nephritis and jaundice.
Mycobacteria	Tuberculosis and Johne's disease.
Pasteurella	Pneumonias and septicæmias.
Proteus and Pseudomonas species	Occasional pathogens.
Staphylococci	Mastitis, local sepsis.
Vibrio fœtus	Abortion in cattle.

In vivo susceptibility unfortunately does not follow the *in vitro* susceptibility, but some guidance may be taken from it. The following organisms and diseases have been reported to respond to streptomycin therapy:

Disease	Causal organism
Actinomycosis (lumpy jaw)	*Actinomyces bovis.*
Transit fever	Pasteurella species
Calf and pig scours	*Bact. coli* and salmonella species.
Mastitis	*Bact: coli* and staphylococci
Vibrionic abortion in cattle	*Vibrio fœtus*
Leptospirosis (hepatic and nephritic)	*L. icterohæmorrhagiæ*, *L. canicola*, *L. pomona* etc.
B.W.D. infections in chickens	*S. pullorum.*

Erysipelothrix infections in turkeys, various infections secondary to virus diseases, and systemic infections due to pasteurellas, coliforms, and salmonellas have also responded.

Some organisms have been proved to be resistant. They include *B. anthracis* (Anthrax), *Pfeiferella mallei* (Glanders), streptococci, rickettsiæ, viruses, and fungi.

Bacterial Resistance. Streptomycin resistance is rapidly developed by organisms subjected to sublethal concentrations. This may be achieved either by the development of resistant mutants or by the destruction of sensitive strains which leaves the field open to the rapid development of resistant strains. This development of resistant strains is common to most antibiotics, but streptomycin is peculiar in that resistance can develop within a week of starting treatment (in some cases only 3 days (Smith, 1958), though it can be delayed by the addition of penicillin, para-aminosalicyclic acid etc. Dosage should therefore be large enough to ensure rapid destruction of the organisms and administration should not be continued for longer than three or four days if response is inadequate. Resistance to streptomycin also means that an organism will be resistant to dihydrostreptomycin. Cross resistance with neomycin is shown though the reverse is not always true.

Diseases and Streptomycin Therapy. Streptomycin has not been so widely used as other antibiotics because both of its toxicity and of the rapid development of bacterial resistance. There are, however, some diseases for which streptomycin is primarily indicated. Those quoted by English (1956) are: *Bact. coli* infections in all species causing mastitis, metritis, enteritis, cystitis and septicæmias; leptospirosis; *Corynebacterium equi* infections of the horse; corynebacterial mastitis; and vibriosis.

Bovine Mastitis

Streptomycin alone is primarily indicated in mastitis due to *Bact. coli* but has also been recommended for mastitis due to other coliforms (Schalm *et al.*, 1952a) and other Gram negative organisms. Dihydrostreptomycin combined with penicillin has been recommended (Schalm *et al.*, 1952b; Bryan *et al.*, 1950; Cooper *et al.*, 1950) and is widely used for streptococcal and staphylococcal mastitis. The combination is especially valuable where mastitis is due to mixed infections or to resistant strains; the synergistic action is responsible for overcoming the resistance. English (1956) has also suggested that intraglandular injection of a penicillin/streptomycin combination may be partially effective in *C. pyogenes* summer mastitis.

When *Bact. coli* mastitis is not accompanied by systemic reactions, two intramammary injections of 0·5 G. streptomycin per quarter each day for up to four days is the treatment suggested in the Veterinary Codex, but commercially two doses of a stearate suspension in oil are recommended

at the rate of 0·25 G. dihydrostreptomycin per quarter, with a 48 hour interval between doses.

For acute systemic infections concurrent with *Bact. coli* mastitis, Schalm *et al.* (1952a) successfully used a systemic injection of dihydrostreptomycin as well as intramammary treatment. An initial dose of 5·0 G. intramuscularly with 5·0 G. into each quarter as an intramammary aqueous infusion was repeated twice daily as long as no remission of symptoms was seen. As soon as the temperature dropped and the local symptoms subsided these doses were first cut to 2·5 G. by each route and then to 1·0 G. When the temperature became normal the intramuscular dose was stopped while the intramammary infusions were continued according to the response of the udder infection. Treatment was continued for a minimum of four days, by which time 17·0 G. would have been used in those cases with mastitis in only one quarter which responded to the maximum, i.e. first dose, 5·0 G. intramuscularly and 5·0 G. intramammary followed by 1·0 G. by intramammary infusion at 12 hourly intervals, on seven other occasions. These doses were large but aimed at gaining maximum initial effect: maintenance doses were resorted to as soon as possible.

Intramammary infusions of streptomycin have also been successfully used in the treatment of *Bact. coli* mastitis in a goat (McManus, 1948).

For combined streptomycin-penicillin treatment, oily intramammary formulations are available commercially supplying 100,000 units of procaine penicillin with either 0·1 G. or 0·25 G. dihydrostreptomycin base. These should be injected daily or on alternate days and antibiotic levels maintained for five to six days, although where no response is shown after the first two doses, treatment with streptomycin should be discontinued and broad-spectrum antibiotics substituted.

Methods of application and ancillary treatments are as suggested in the chapter on penicillin.

Specific Systemic and Organic Diseases. Some diseases can be treated with streptomycin in preference to other antibiotics.

Vibriosis

This condition, which is responsible for a considerable amount of abortion during the first three months of pregnancy, is passed from cow to bull and *vice versa*, by contact and by infected semen. Streptomycin with or without penicillin has been used successfully for the treatment of cows and bulls. In females uterine and vaginal infections due to *Vibrio fœtus* have been cured by Plastridge and Easterbrooks and their colleagues (1950, 1951, 1953) using intra-uterine injections of 1·0 G. streptomycin in about 15·0 ml. sterile distilled water via a glass insemination catheter. This has been achieved irrespective of the stage of the œstrus cycle at the time of injection. Tutt (1956) used a parenteral injection of a stable buffered solution of streptomycin with good results, providing nutritional requirements where optimal. Successful treatments of bulls have been

reported (Lofthouse, 1951; Terpstra *et al.*, 1951; Flatla *et al.*, 1952; Merkt *et al.*, 1952; Edgson *et al.*, 1955) by local or parenteral antibiotic therapy. It has been contended that the recommended treatments were not always successful (Sjollema, 1952; Easterbrooks *et al.*, 1955; Adler, 1956; and Hughes, 1956), breakdowns sometimes occurring a year later. Melrose *et al.* (1957) pointed out that these breakdowns might be reinfections, especially as twelve bulls they successfully treated with cream or oil suspensions containing 2·0 G. streptomycin and 1·0 mega units penicillin were free twelve months later.

Semen from infected bulls can be rendered non-infective by diluting it 1 : 10 with a warm diluent containing 1·0 mg. streptomycin base per ml. and refrigerating for six hours after cooling (Plastridge, 1955). It was also reported by Diliello *et al.* (1957) amongst others, that optimum concentrations of antibiotic, besides destroying the vibrio also increased the number of motile sperms, probably by inactivating contaminating bacteria which are able to affect motility adversely. This latter group of workers indicated also that streptomycin was the most active antibiotic *in vitro*, but that penicillin would increase activity further: they inferred that the tetracyclines were more toxic to spermatozoa and sometimes less effective than other compounds, though workers at Weybridge and elsewhere (Report, Ministry of Agriculture 1954; Ertürk, 1956) have shown that the tetracyclines are effective *in vivo*. Vibrionic abortion in sheep has also been treated with streptomycin amongst other antibiotics, but with little success (Ryff *et al.*, 1956). Vibrionic dysentery in pigs responds moderately but not completely; Doyle (1954) recommends streptomycin on economic grounds.

Vibrionic dysentery or 'winter scours' in cattle due to *Vibrio jejuni*, previously treated with 2–3 fl. oz. (60–90 ml.) of a 5 per cent. copper sulphate solution, would probably respond to large oral doses of streptomycin, though Roberts (1957) was unable to find anything other than fluid replacement of any value.

Pasteurellosis

Pasteurella infections of animals can take the form of septicæmias which are rapidly fatal, but chronic and mild infections also occur. *Cattle* suffer from a rapidly fatal septicæmia known as 'shipping fever', 'transit fever', or 'hæmorrhagic septicæmia', and calf pneumonia due to Pasteurella organisms also exists. Both respond to streptomycin (Vigue, 1947; Handler, 1951), the adults being given twice daily injections at the rate of 0·25 G. per 100 lb. (approximately 45·0 kg.) or daily injections of 0·5 G. per 100 lb. for two or three days: calves are given twice daily injections of 0·25–0·5 G. per lb. bodyweight (approximately 0·5–1·0 G. per kg.)

Horses and *rabbits* have recovered from experimental infections with Pasteurella organisms when dosed with dihydrostreptomycin at the rate of 4–5 mg./kg. and 10 mg./kg. respectively every four hours (Goranoff *et al.*, 1956). No clinical evidence is so far available.

(Extremely good results, however, have been reported (Johnson *et al.*, 1955) from the use of tetracycline in cattle, sheep and pigs.)

Leptospirosis

Leptospirosis infections occur in all species and clinical recovery results from penicillin therapy in the case of *Leptospira canicola* and *L. pomona*, but not *L. icterohæmorrhagiæ*. Various reports (McClure, 1953; Ringen *et al.*, 1955; Simmons, 1955) indicate that a minimum of 5 mg. per lb. body weight every 12 hours eliminates *L. pomona* from the urine of *calves* and *cattle*. Penicillin does not clear the organisms from the urine. Ryley, (1955) has used streptomycin in a *sow* experimentally affected with *L. pomona*, but though leptospira were eliminated from the urine the sow aborted and the organism was isolated from a fœtus. Streptomycin in doses of 0·25 to 0·5 G. has also proved effective in stopping the excretion of Leptospira in the urine of pigs weighing about 80 lb. (Sidler, 1954). In the *dog*, though penicillin gives clinical improvement, streptomycin is superior in both *L. canicola* and *L. icterohæmorrhagiæ* infections, completely eliminating the former from the urine: 40 mg. per kg. bodyweight (approx. 20 mg. per lb.) in divided doses daily by intramuscular injection are recommended. Treatment should be continued for 4–6 days.

Actinomycosis and Actinobacillosis

A few reports of improvement following the use of streptomycin against actinomycosis (Kingman *et al.*, 1951; Redmond, 1952; Stauffer, 1953) and actinobacillosis (Stauffer, *loc. cit.*) are available. The first group of workers injected 5·0 G. streptomycin in 10 ml. water subcutaneously around the lesion on three or four alternate days, repeating the treatment later if response was slow. Ordinary intramuscular injection would probably have done as well, but it is hard to see that purulent foci within the bony matrix could be completely cured. Controlled trials are needed to clarify the position. The response of actinobacillosis would be expected to be better and more rapid.

Coli-Salmonella Group Infections

In the *foal*, *B. equirulis* (*Shigella equiruli*) causes pyosepticæmia with a purulent nephritis and joint ill. Streptomycin is the drug of choice for this infection. It is also effective against septicæmia and enteritis in the foal due to *Bact. coli* (*Escherichia coli*) if used in large doses (5·0 G. initially followed by 1·0 G. four times daily for four days were used by Bain (1954).

In the *calf*, streptomycin is reasonably active against coliform enteritis but the tetracyclines, against which resistant forms develop slowly, are preferred.

Likewise in *pigs*, streptomycin is of value in necrotic enteritis (Uvarov, 1955, Salisbury *et al.*, 1951), and *Bact. coli* scours using 0·25–1·0 G. by

mouth twice daily or 0·5–2·0 G. per pig in drinking water for two days (Doyle, 1954).

In *poultry*, streptomycin will prevent (Gwatkin, 1950) and treat (Benson, 1947) B.W.D. or 'pullorum' disease of chickens but the speed with which resistant strains develop causes this antibiotic to be avoided and the tetracyclines or, more recently, furazolidone to be preferred.

Corynebacterium Equi Infections

This organism is a frequent cause of pneumonia of foals in their first few months of life, and good clinical response is reported by Bain (1954) to parenteral streptomycin and oral chloramphenicol.

Non-Specific Systemic Diseases. Streptomycin has been used with good effect in a variety of non-specific conditions. Perhaps the most important is cystitis in dogs, which responds even more rapidly if the urine is first made alkaline (if it is not already so) with potassium citrate or acetate. Gastro-enteritis and secondary invaders concurrent with the virus infections, especially the distempers of dogs and cats, also respond well. The secondary organisms in otitis of dogs and cats are widely treated with combined penicillin and streptomycin formulations—often intramammary injections.

Miscellaneous conditions treated with streptomycin include a number of diseases of poultry, though the broad-spectrum antibiotics are replacing streptomycin. Poultry diseases include contagious coryza and chronic respiratory disease (C.R.D.) of chickens and turkeys, erysipelothrix infections of turkeys, and 'quail disease'—an ulcerative enteritis of quails. Tularæmia in dogs due to *Brucella tularensis* has also responded. Cellulitis in cats, caused by bites, responds very well both to local and parenteral administration.

Although streptomycin has been shown to benefit pigs and chickens when used as a feed supplement (Braude *et al.*, 1953), the development of resistant strains of bacteria and the greater efficiency of the broad-spectrum antibiotics has prevented streptomycin becoming popular for this purpose.

Local Use. Streptomycin is not frequently used for local applications because of the possibilities of skin sensitization.

Dosage

Suggested doses for particular diseases and species have been mentioned in the therapeutic section, but they can be varied according to the disease, larger doses being given when the organisms are known to be less sensitive or tissue reaction great enough to hinder access of the drug to the organism. Fowls require a much larger dose when estimated at the rate of mg. per kg. body weight and tolerance increases as baby chicks grow older (Huebner *et al.*, 1956). The following rates are a rough guide.

Horse and Foal:	2–5 mg. per lb. body weight every 3–4 hours.
Cow and Calf:	5–7 mg. per lb. body weight every 12 or 24 hours. (approx. 2·0–5·0 G. daily for adults and 1·0 G. daily for calves).
Sheep:	2·0–5·0 mg. per lb. body weight every 3–4 hours.
Pig:	0·2–0·4 G. per score body weight daily (5·0–10·0 mg. per kg.)
Dog and Cat:	5·0–10·0 mg. per lb. every 8–12 hours.
Fowl:	0·1–0·2 G. per bird as a single dose.
Chickens:	2·5–5·0 mg. twice daily.

All these doses are for intramuscular administration with the exception of that for chickens.

Oral dosage for the *dog* and *cat* is 0·3 to 1·0 G. per day at the rate of 15·0 mg. per lb. (33·0 mg. per kg.) body weight twice daily (Scheidy, 1951). For the *calf*, 0·5 G. daily for 2 days (Scheidy *et al.*, 1953). *Note:* All dosages are expressed in the terms of streptomycin or dihydrostreptomycin base, 1·0 G. of which is equivalent to 1·0 mega unit.

Official Preparations

The official veterinary preparations consist mainly of five powders and the injections prepared from them: streptomycin sulphate, hydrochloride, and calcium chloride complex; dihydrostreptomycin hydrochloride and sulphate. The injections should be freshly prepared, but may be kept 7 days if refrigerated; they should contain 0·25 G. in 1·0 ml. unless other strengths are specified, for at this strength they are relatively non-irritant. An intramammary injection containing 0·25 G. dihydrostreptomycin base in oil with aluminium stearate is the only other official veterinary preparation. The United States Pharmacopœia contains streptoduocin for injection which consists of equal parts of sterile powdered streptomycin and dihydrostreptomycin in vials of 1·0 G. and 5·0 G. Similar size vials are available of the British official preparations.

Also available commercially are stable buffered aqueous solutions of streptomycin containing 0·25 G. streptomycin per ml. in 1·0 and 5·0 G. vials. Combined ointments can be obtained for topical application with penicillin and streptomycin.

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CHAPTER 26

ANTIBIOTICS: BROAD SPECTRUM
(iv) OXYTETRACYCLINE

THIS antibiotic is one of the most important and widely used antibiotics in veterinary medicine. It has broad spectrum antibacterial action both *in vitro* and *in vivo*, and is official as the base and as the hydrochloride both in Great Britain and America.

History

Oxytetracycline was discovered as the result of the co-ordinated research of a team of eleven workers employed by an American commercial organization. In the course of their investigation they examined approximately 100,000 soil samples submitted to them from all parts of the world, finding 75 antibiotic producing moulds. Amongst this number was a previously unidentified species of mould *Actinomyces rimosus*, from which a broad spectrum antibiotic was obtained and named Terramycin. This discovery was announced in 1950 (Finlay *et al.*).

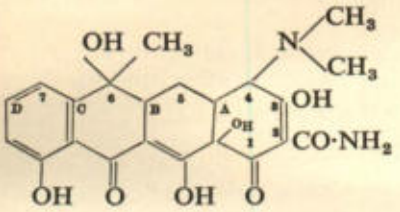
Manufacture

Oxytetracycline is manufactured by the normal deep culture fermentation methods; approximately 4½ lb. (about 2·0 kg.) is isolated from each 1000 gals. of fermentation broth, or about 1 cwt. (50·0 kg.) from one 25,000 gal. fermentation. Purification is a complex sequence of solution and extraction of base and salts from different solvents following kieselguhr filtration. A crystalline base or the hydrochloride is finally obtained, the former containing not less than 96 per cent. of pure base in the official B.P. form, whilst the hydrochloride of the B.Vet.C. must also contain not less than 96 per cent. of the salt.

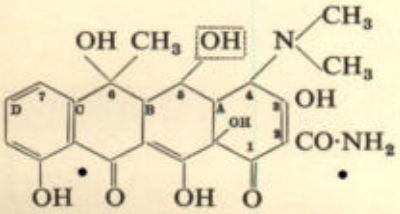
Chemistry

Amphoteric oxytetracycline (oxytetracycline dihydrate) base and its hydrochloride are yellow, odourless crystalline powders with a bitter taste. The base is only slightly soluble in water but the hydrochloride is readily soluble, though some turbidity may result from the release of oxytetracycline base: buffering with sodium glycinate overcomes this. Both are readily soluble in dilute hydrochloric acid, and fairly soluble in methyl and ethyl alcohol, but insoluble in chloroform and ether.

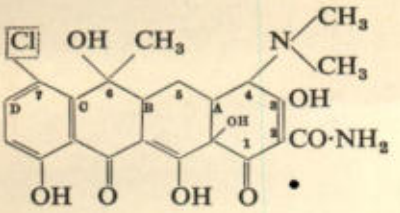
The *structure* of oxytetracycline (ii) contains tetracycline (i) as a nucleus which is also the basis of chlortetracycline (iii).



Tetracycline (i)



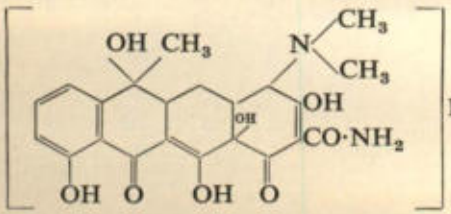
Oxytetracycline (ii)



Chlortetracycline (iii)

From these diagrams it can be seen that oxytetracycline consists of the tetracycline nucleus with a *hydroxyl group* instead of a hydrogen atom at carbon 5 in benzene ring B, whilst chlortetracycline contains a *chlorine* atom in place of the hydrogen atom attached to carbon 7 in ring D.

All three compounds are used as hydrochlorides, which may be represented graphically as follows:



Tetracycline hydrochloride and similarly oxytetracycline and chlortetracycline hydrochlorides.

As with the other two members of the series, oxytetracycline is amphoteric and will form salts with either acids or bases.

Stability

Oxytetracycline is very stable when compared with chlortetracycline and penicillin, but solutions cannot compare in stability with those of the polymyxins and neomycin.

1. *Moisture.* In the dry state this antibiotic is stable for at least two years at room temperature. When in solution, however, the situation is not quite so satisfactory for, though unbuffered 1 per cent. solutions at a pH of 2·5 will maintain potency for at least 30 days at 25°C., the official U.S.P. parenteral injection, buffered with sodium glycinate and having a pH of approximately 9·0, loses 2 per cent. of its potency (100 mg. per ml.) in 2 hours and 8 per cent. in 24 hours at room temperature. Up to 8 per cent. activity is lost in 3 days during refrigeration (Armstrong *et al.*, 1952): four days is therefore as long as solutions should be kept and even so they should be refrigerated. Potency is unaffected by the progressive darkening which occurs. Commercial intravenous and intramuscular injections may be kept refrigerated for 2 days and 4 days respectively.

2. *pH.* Oxytetracycline is relatively stable in acid solution especially below pH 2·5., but neutral and particularly alkaline solutions deteriorate rapidly. Buffering oxytetracycline with sodium glycinate (to give an alkaline pH.) is aimed not at maintaining potency but in maintaining solution, for hydrolysis and deposition of the base occurs in acid solutions of the hydrochloride; this necessary alkalinity is detrimental to stability.

3. *Temperature.* Solutions of oxytetracycline are no exception to the rule that their stability, though related closely to pH, is also markedly affected by temperature. At pH 2·5 and room temperature unbuffered solutions are quite stable but at the same pH and 37°C. the half-life of the antibiotic is about 5½ days. (Half life is a term coined by atomic scientists to indicate the period during which half the radioactivity of an element was lost. This was necessary because rate of activity loss decreased with loss of activity, so that half the activity was lost in 5½ days; complete loss may not follow for several weeks, months, or even years. The same principle can be applied to antibiotic potency.).

The *dry* powder will withstand heating for 4 days at 100°C. without loss of potency (Antibiotics. Pharm. Press. 2nd Edit. P: 67) and only 5 per cent. potency loss occurs after 4 months at 50°C.

4. *Oxidizing agents, enzymes, etc.* The tetracyclines appear to be stable in most respects other than moisture, pH and temperature.

Pharmacology

The pharmacology of the base and salts of oxytetracycline is fundamentally the same. The relative insolubility of the base makes it unsuitable for parenteral injection; but its less bitter taste makes it more suitable for oral administration.

Absorption and Administration Routes. Oxytetracycline hydrochloride may be administered by any of the normal routes. It is readily absorbed

from the intestines by all mammals but intestinal absorption in poultry is restricted. Effective blood levels are achieved in 2 to 4 hours. By the intravenous route, maximum levels are achieved within 30 minutes, but intramuscular dosage delays peak blood levels for about two hours and levels are not so high though maintained for a longer time. *Note* that commercial intramuscular injections should not be given intravenously, but intravenous formulations may be given intramuscularly. Oily injections intended for subcutaneous injection in poultry should not be used as parenteral injections in mammals. Oxytetracycline is very effective and suitable for topical application.

Blood Levels. In human medicine, 0·5 to 1·0 mg. per ml. serum has been accepted as adequate for most purposes in the treatment of infected adults. (Kranz and Carr, 1951). It has been assumed that this level is adequate in animals also, and this is borne out by clinical experience, although, owing to assay difficulties, accurate blood and tissue level estimations are not possible. These levels are easily maintained by single daily intramuscular doses in cattle (Yoder *et al.*, 1954), dog and horse (Gratzl *et al.*, 1953); other species follow the same pattern.

Barriers. Oxytetracycline is most useful in that it readily disperses throughout the body, attaining therapeutic levels in most tissues and fluids within a short time.

1. *Blood-brain barrier.* Oxytetracycline was originally thought to pass the blood-brain barrier quite easily but, though some will pass the barrier normally, therapeutic levels will only appear in the cerebrospinal fluid when the meninges are inflamed or damaged. Intrathecal injections should therefore be used to initiate treatment.
2. *Placental barrier.* The placenta is readily passed by oxytetracycline and concentrations in the fœtal blood may reach those of the maternal circulation, although it is usually somewhat lower, sometimes even as low as 25 per cent.
3. *Intestinal barrier.* Absorption from the intestines is reasonably fast but not complete, and in man as high a fæcal concentration as 2·5 mg. per gramme have been assayed in an active form (Herrell *et al.*, 1950). These quantities are several times greater than would be expected from similar doses of chlortetracycline or chloramphenicol.
4. *Serous membrane barriers.* Therapeutic levels in pleural and peritoneal fluids can be achieved readily, even from oral dosage, though initial levels should be established by parenteral administration either by intraperitoneal or intravenous injections or both if severe and acute inflammations are present.
5. *Milk barrier.* Oxytetracycline readily diffuses into the milk and therapeutic milk levels can be achieved by single intravenous doses (Schipper *et al.*, 1953), but intramuscular dosage is not satisfactory and parenteral administration is not a substitute for local intramammary

treatment, especially as milk levels drop sharply after the first milking. No irritation results from contact of the antibiotic with mammary tissue (Simon *et al.*, 1953).

Excretion. The main excretory routes of oxytetracycline are the urinary system and the intestinal route via the biliary system.

The antibiotic appears in the urine within an hour of administration (usually 30 minutes) and reaches a maximum in about four hours in man (Schoenback *et al.*, 1950; Bliss *et al.*, 1950). About 15 per cent. is excreted in the first 24 hours but as much as 50 per cent. may ultimately be recovered in an active form. High concentrations—up to 400 mg. per ml.—may be reached (Welch *et al.*, 1950; Welch, 1950) and will persist for at least 24 hours following single intravenous or intramuscular doses (Schipper *et al.*, 1953). Concentration of oxytetracycline also occurs in the bile, and levels up to eight times those of concurrent serum levels may be achieved (Herrell *et al.*, *loc. cit.*). Along with chlortetracycline, oxytetracycline is therefore valuable in treating liver infections. The antibiotic eliminated in the bile serves to swell that already in the intestines and some may be reabsorbed to begin the cycle again.

Toxicity. Acute toxicity is not common with oxytetracycline. Oral therapy in ruminants may cause indigestion during the first few days of treatment, but animals soon become acclimatized and symptoms, including diarrhœa, should slacken within a few days. In small animals, nausea, vomiting, and diarrhœa, with lethargy, are the main signs, but toxicity normally results only from large doses and these symptoms are not common. In man, rapid proliferation of yeasts and moulds frequently follows oral administration, but changes of this type are not reported in the veterinary field yet. (This increase in fungi is probably due to the elimination of the organisms which normally overgrow them or possibly restrain them by antibiotic production).

Action. Oxytetracycline is bacteriostatic at low therapeutic levels but in higher concentrations may be bactericidal. The effect, as with all antibiotics, must also depend on the sensitivity of the organism. The method of action is uncertain but is considered to be due to interference with intracellular phosphorylation mechanisms (Miura *et al.*, 1952). The action is not appreciably affected by blood and tissue breakdown products, but *in vitro*, tests by Price *et al.* (1955–56) have shown that most antibiotics are less effective against mastitis organisms in milk media. Oxytetracycline is one of these antibiotics; penicillin is far less affected than the others.

Oxytetracycline is synergistic with polymyxin, and most formulations for topical application make use of this phenomenon.

Antibacterial Spectrum. Oxytetracycline is a broad-spectrum antibiotic, both *in vitro* and *in vivo*, and is active against a large number of Gram

positive and Gram negative organisms. Species of streptococci, staphylococci (micrococci), anthracoids, Pasteurella, Brucella, corynebacteria, Erysipelothrix, coliforms, and salmonellas, are sensitive. Some rickettsiæ and the larger viruses are also affected and activity against other organisms such as Pseudomonas, Proteus, and Klebsiella species is useful but less than other antibiotics such as polymyxin. Though it is effective against some protozoa and even has some activity against certain helminths, oxytetracycline has no activity against yeasts, moulds, and other fungi; this fact is of considerable importance in human medicine, for proliferation of yeasts and fungi has frequently followed broad-spectrum antibiotic therapy and has necessitated further treatment to overcome these secondary invaders. Nystatin (another antibiotic) has prevented this happening when it has been combined with broad-spectrum antibiotics. Such a situation has not so far been reported in animals but clinicians should bear it in mind if broad-spectrum antibiotics are used for prolonged periods.

Bacterial Resistance. It was originally hoped that bacteria would not develop resistance but that hope has not been fulfilled and resistant strains are appearing. Smith and his colleagues (1956, 1957) have reported resistant *Bact. coli* (*Esch. coli*) strains in calves with white scours on two farms where chlortetracycline supplements had been fed; a similar situation was found in poultry and pigs but was more wide-spread, especially in pigs. Diseases due to tetracycline resistant *Bact. coli* were not uncommon in piglets weaned with oxytetracycline supplemented milk and where the sows feed was also supplemented.

So far no reports on *in vivo* resistance of mastitis organisms has been published.

Organisms found resistant to any antibiotic containing the tetracycline nucleus will prove to be resistant to the rest of the group though individual variations of sensitivity do occur. This was clearly demonstrated by Barr *et al.* (1955) who reported five organisms isolated from calf scours which showed cross resistance to the tetracycline group. Tetracycline itself may occasionally prove effective where the chloro- and oxy- derivatives have failed, but in principle, where one tetracycline has failed, further treatment should be with non-tetracycline antibiotics or sulphonamides (B.P.C. 1954, Addend. 1957).

Diseases and Oxytetracycline Therapy. The tetracyclines have similar antibacterial spectra and are used for practically the same purposes. There are, however, differences in degree of action and also in methods of administration.

The diseases which have responded to oxytetracycline are very numerous: some of the more important ones are mastitis due to *Bact. coli*, streptococci and staphylococci, transit fever, white scour in calves and enteritis in pigs, strangles, actinomycosis and actinobacillosis, infectious keratitis in cattle, otitis, and secondary invaders in the virus

diseases of small animals. Most of the common bacterial diseases of poultry also respond.

Mastitis

Acute streptococcal mastitis should be treated by penicillin in preference to other antibiotics (Wilson, 1954; English P. B., 1956) unless the organism is insensitive, which is not a common occurrence. Oxytetracycline has only one advantage—that of speed, for one injection of about 450 mg. combined with about 150,000 units of polymyxin (i.e. one tube of a commercial intramammary injection) suffices where two injections of procaine penicillin might be required. It is doubtful whether the expense justifies its use and the possibility of the development of resistant strains must be borne in mind. Chronic streptococcal mastitis can often be treated successfully with oxytetracycline.

Staphylococcal mastitis is commonly treated with combined penicillin and streptomycin intramammary injections but in acute and severe cases oxytetracycline both locally and systemically is frequently effective. Barnes (1955) found that about 25 per cent. of staphylococcal mastitis cases responded. Two or three intramammary injections at 24 hour intervals may be needed, though in very severe cases injections have been given at 12 hourly intervals.

C. pyogenes mastitis accompanied by severe systemic disturbances can often be alleviated by parenteral oxytetracycline, though the influence on the local condition is not appreciable.

Bact. coli mastitis, though not common, responds favourably to local oxytetracycline and polymyxin therapy, with parenteral therapy where there is systemic involvement. Three intramammary injections are usually sufficient (Tunsmeyer, 1952).

Mastitis due to other organisms such as Klebsiella (Barnes, 1954), Pseudomonas, and Proteus can be favourably influenced by an oxytetracycline-polymyxin combination.

In the case of Klebsiella infections Easterbrooks *et al.* (1956) suggested that sulphadimidine and streptomycin be tried before resorting to the tetracyclines or neomycin; they also indicated that early treatment was vital. White (1957) stresses the need for rapid sensitivity tests in view of the number of strains and differences in drug sensitivity.

Specific Systemic and Organic Diseases.

Strangles

Farquharson *et al.* (1953) treated two cases of strangles, one complicated by abscess formation whilst the other was a simple uncomplicated case. The former responded to four daily intravenous injections of 1·0 G. of oxytetracycline in conjunction with surgical drainage of the abscesses. The second was a yearling thoroughbred which responded to the same dose given for two days only; recovery was uneventful in spite of a

concurrent attack of colic. Treatment should be given early and in relatively large doses in view of the *in vitro* resistance of *Str. equi* (Rahman, 1957).

Anthrax

Over 200 cases of this septicæmic disease which followed vaccination in cattle and horses have been treated by Bailey (1953, 1954). The cases were treated in three groups; penicillin, oxytetracycline, and a combination of the two were used in the respective groups. Those treated solely with oxytetracycline appeared to respond more rapidly and more frequently.

Pasteurellosis

Transit fever, and hæmorrhagic septicæmia of calves respond very well to oxytetracycline. Hawley (1952) obtained 96 per cent. recoveries from about 4500 calves treated with one or sometimes two treatments. Cromley *et al.* (1951) obtained equally good results in 124 cases using oxytetracycline at the rate of 1·0 mg. per lb. (2·2 mg./kg.), but Farquharson *et al.* (1953) were not successful although their cases were in many instances chronic and debilitated following protracted and unsuccessful treatment.

Experimental fowl cholera in young chickens due to *Past. aviseptica* inoculation has responded to oxytetracycline given intramuscularly (Smith, 1955). Good results were obtained by single intramuscular injections of an oily suspension at the rate of 25·0 mg./kg. bodyweight given six hours after inoculations. It was more effective in older birds, giving good results on injection 24 hours subsequent to culture inoculation. It was also pointed out that other antibiotics and sulphonamides were less effective and furazolidone ineffective. Sulphonamides were effective in controlling the disease when administered prophylactically, beginning before inoculation: sulphamerazine and sulphadimidine were used at the rates of 0·2 per cent. in the mash or 0·1 per cent. in drinking water.

Leptospirosis

All tetracycline derivatives are excreted in the urine and bile in high concentrations. It would therefore be expected that *L. icterohæmorrhagiæ* and *L. canicola* infections would be highly susceptible to tetracycline treatment. This is confirmed by Dykstra (1954) who indicated, however, that early treatment was necessary in view of the structural damage which these organisms cause.

In *cattle*, success is not invariable for though Cady *et al.* (1953) treated sixteen cases successfully and found intravenous oxytetracycline superior to other antibiotics, Ringen *et al.* (1955) found that, although the numbers of Leptospira in the urine could be reduced, complete elimination was not possible with single daily doses of 1 to 2 mg./kg. given intramuscularly for five days. Cady used intravenous injections of 2·0 G. followed in 24 hours by 1·0 G. followed by a further 1·0 G. two days later, and it is possible that the route of administration and dosage are responsible

for these different findings. Bryan (1955) also found that neither chlortetracycline alone nor streptomycin plus oxytetracycline were of any use in experimental treatment of chronic bovine leptospirosis, whereas McLure (1953) reported the elimination of Leptospira from the urine with chlortetracycline. In cattle, high dosage with intravenous administration is indicated. *Leptospira pomona* carriers in *pigs* have been cleared by oxytetracycline in the food at the rate of 500 G. per ton (Baker *et al.*, 1957). The situation needs clarifying, but it would appear that in *small animals* the tetracyclines, and in particular oxytetracycline because of the higher levels achieved when compared with chlortetracycline (U.S.D. 25th Edit. 1955 p. 953), are superior to other antibiotics but should be given as early after infection as possible and in maximum doses.

Coli-Salmonella Group Infections

White scour in calves was shown by Kafka (1951) and Pearson (1954) to respond to two doses of up to 0·5 G. orally given with an interval of 24 hours. As little as 100 mg. each day for three days 'was highly successful' (Kafka). Prophylactically, 0·25 to 0·5 G. give on each of the first and second days of life will give 100 per cent. protection against sensitive strains. Smith (1957) however, has pointed out that resistant strains are becoming increasingly common. It has been noticeable that in Scotland, at least, oxytetracycline is not giving results comparable with the excellent results obtained prior to 1957, and veterinary surgeons are resorting to the symptomatic type of treatment used prior to the advent of broad-spectrum antibiotics.

Enteritis in pigs has also responded favourably to oral doses of 50–100 mg. for suckling pigs given three times at intervals of 12 hours, but this necessitates handling and takes a great deal of time as does the intramuscular injection of 50 mg. used successfully by Farquharson *et al.* (1953). Schipper and his colleagues (1956) therefore gave 2·0 g. to the sows by intramuscular injection which resulted in the piglet scours stopping within 12 hours. They later found that 1·0 G. intramuscularly was sufficient but neither oral dosing of the sow with oxytetracycline nor parenteral injections of streptomycin or penicillin or both were of any value. In some cases, extreme debility of the piglets prevented them from suckling and therapeutic doses were therefore not taken in. It would be advisable in these cases to give an intramuscular injection to each severely debilitated piglet.

S. pullorum infection in chickens has been satisfactorily treated (Schildmeyer, 1955) by medication of the drinking water at the rate of 10·0 G. in 5·0 litre (10·0 G. in 8¾ pints approx.) for three days. There were no losses, and treated chicks grew much more rapidly and were much livelier than untreated controls.

Heavy losses in turkeys due to Salmonella infection showed a marked decrease following medication of the food for five days at the rate of 250·0 G. per ton, and the drinking water for three days at the rate of approximately 2½ oz. (710·0 G.) in 10 gal. (45·5 L.). Food consumptions

returned to normal in 4–5 days (Lukas *et al.*, 1954). Thirty species of salmonellæ were isolated during this work but over 30 per cent. of the uncomplicated salmonella cases were due to *Salm. typhimurium*. Either chlortetracycline or oxytetracycline were equally effective (Lukas *et al.*, 1954). In Great Britain, furazolidone is preferred for treating salmonellosis in poultry (Blount, 1955).

Fusiformis Infections

Calf diphtheria is now rarely seen in Great Britain following the use of sulphapyridine and sulphadimidine, but Fuechsel (1952) reporting on over fifty cases preferred oxytetracycline before other treatments.

Foot rot in sheep responds to many treatments providing adequate preparation of the feet is effected before the therapeutic is applied. Chloramphenicol aerosol sprays have been widely used, but oxytetracycline is also effective when applied topically in the form of an ointment (Harriss, 1955). It is significant that Miss Littlejohn (1955) achieved a 77 per cent. recovery in 114 sheep after one immersion in 10 per cent. formalin for 1–1½ minutes, whilst the remainder cleared up after one or two further treatments; the economy was appreciable. Foul-in-the-foot in cattle has also responded following intravenous administration of oxytetracycline.

Actinomycosis and Actinobacillosis

Oxytetracycline has been used in both these conditions with favourable responses. Piper (1953) reported good results in actinomycosis following the intravenous administration of 2·0 G. daily for four days when combined with penicillin and streptomycin. Farquharson reported one case of actinobacillosis which had failed to respond to other treatment and yet made a gradual recovery after three doses of 2·0 G. administered intravenously at intervals of 24 hours. In both types, oxytetracycline should only be used after normal therapy has failed—for economic reasons and because of the possibility of creating tetracycline resistance, though as yet there is no evidence of this arising.

Anaplasmosis

Miller *et al.* (1953) reported the action of tetracycline derivatives against the protozoan infection, anaplasmosis. In conjunction with Splitter (1953), Miller showed that the normal maximum dose of 5 mg. per lb. body weight daily for about a fortnight eliminated the parasite completely, but further stated (Miller, 1953) that treatment must be commenced before anæmia was so advanced as to make recovery virtually impossible. This initial work has been substantiated (Oglesby, 1954; Farber, 1955; Brock *et al.*, 1957; Pearson *et al.*, 1957). Oxytetracycline given in 2·5 G. doses intravenously to 10 infected cattle as soon as a temperature rise occurred was responsible for complete recovery in each case. A further animal with anæmia and ruminal atony showed no response (Farber, 1955). Pearson *et al.* (1957) also showed that tetracycline in daily intramuscular

doses at the rate of 5 mg. per pound body weight, when continued for ten days, eliminated infection from 30 carrier cattle.

Feline Influenza

Known in the U.S.A. as feline pneumonitis, this disease is caused by a virus. This virus is susceptible to oxytetracycline action both experimentally in mice (Kneeland *et al.*, 1950), and in cats (McKercher, 1953).

Virus Pneumonia of Pigs

Börnfors *et al.* (1955) indicated that the tetracyclines, penicillin, and sulphadimidine, were beneficial in virus pneumonia probably by reducing secondary infection. They continued their work and in 1956 (Lanneck *et al.*) published findings showing that prophylactic doses of tetracycline and oxytetracycline at the rate of 100 mg./kg./day would protect pigs from intranasal challenge with infected material and also infection from natural contact. They also showed that under field trial conditions tetracycline at 50 mg./kg./day would give complete protection against the virus disease. Later in the year further details were published indicating that tetracycline would not eliminate nor even moderate established experimental or natural infections (Börnfors *et al.* 1956).

Poultry Diseases

Blue comb of turkeys has been successfully treated by medication of the feed (100 p.p.m. in the mash) and drinking water (5 p.p.m.). This gave results within 48 hours, when mortality ceased. (Peterson *et al.*, 1951).

C.R.D. (Chronic respiratory disease) in chickens, which is thought to be due to a pleuropneumonia-like organism (P.P.L.O.) and similar to, if not the same as, aerosaccitis of turkeys responds well to oxytetracycline therapy. In the former disease 2·0 ml. of a 2·5 per cent. oil suspension of oxytetracycline was adequate when given subcutaneously and eliminated symptoms within 7 days (Carson *et al.*, 1954). In experimental aerosaccitis, however, 1 part of oxytetracycline in 630 parts of mash was required prophylactically, though less might be required in the field (DeVolt *et al.*, 1956). *Infectious sinusitis* in turkeys, also related and possibly caused by the same organism as C.R.D., responds to injection of the mineral oil suspension directly into the infected sinus. It does not respond to oral medication. *Contagious catarrh* or coryza is also susceptible to subcutaneous doses of oily suspensions, 2 ml. being adequate for pullets but 4 ml. is required in cockerels.

Erysipelothrix infection in turkeys, shown experimentally to be susceptible to oxytetracycline and benzathine penicillin, along with penicillin and streptomycin combinations, responded without interference with the development of immunity, (Moynihan *et al.*, 1954). Smith (1956) confirmed these findings and showed that oxytetracycline at the rate of 100 mg./kg. as an oil suspension, or benzathine penicillin at the rate of 160,000 units/kg. in single doses, were both highly effective experimentally.

Infectious synovitis of turkeys has also been shown experimentally to be susceptible to parenteral treatment with concurrent food medication.

Non-Specific Conditions

Oxytetracycline is very useful in all species as an eliminator of the secondary invaders which are usually found in virus diseases. This antibiotic has therefore been widely used either orally or parenterally in the treatment of equine influenza, virus pneumonia of pigs, infectious panleucopenia of cats (cat distemper), and the distemper complex of dogs (including *Brucella bronchisepticus* infections).

Pneumonia or bronchitis in all species and tonsillitis in dogs usually respond. Cystitis in small animals, and metritis in cattle, mares, dogs, and cats, all respond to oxytetracycline therapy following local/or parenteral and oral administration.

Fistulous withers in horses has responded (Landon, 1952) but surgical treatment is preferred wherever it is possible to operate (Danks, 1954). Post-operative therapy with oxytetracycline is beneficial in most cases.

Oxytetracycline has been used successfully to restrict infections following abdominal surgery. In the antibiotic sterilization of bulls semen, Easterbrooks (1952) has reported that 20 μg. per ml. of diluted semen was adequate and gave good results, whilst Stallcup *et al.* (1953) showed that ten times this quantity has no spermicidal effect. (DiLiello *et al.*, 1957, have inferred that the tetracyclines are not as harmless as penicillin and streptomycin.)

Topical Application

The two main conditions for which oxytetracycline is effective externally is in the treatment of infectious keratoconjunctivitis (New Forest disease) in cattle and sheep, and external otitis in the dog. Lamellæ containing, in addition, polymyxin and a local anæsthetic are used in the former and an ointment or intramammary preparation in the latter cases. In both these types of cases the additional polymyxin is of some value: in *otitis externa* in the dog *Pseudomonas pyocyanea* frequently assumes pathological propensities.

Oxytetracycline is also useful in many pyogenic skin infections, and in infected wounds or burns.

Foot-rot in cattle and sheep is mentioned earlier in the chapter.

Dosage

Daily doses for animals (excluding poultry) can be divided into two groups, the maximum recommended doses being:

Intramuscular and Intravenous:

1. Horse, Cow, Sheep, Pig: 2 mg. per lb. (4·4 mg./kg. body weight).
2. Foal, Calf, Lambs, Piglets, Dogs and Cats: 5 mg. per lb. (11·0 mg./kg. body weight).

Injections should be diluted to 25 mg./ml. and 5 mg./ml. for intravenous and intramuscular injection respectively.

Oral:

Horse, Cow, Sheep, Pig: (over 100 lb.)	5 mg. per lb. (11·0 mg./kg. body weight).
Foal, Calf, Lamb, Pig, Dog and Cat: (under 100 lb.)	25 mg. per lb. (55 mg./kg.) body weight (increased to 50 mg. per lb. or 110 mg./kg. in severe acute conditions.)

All daily doses should preferably be divided into two or three doses given at regular intervals, but it is interesting to see that Gratzl and Jaksch (1953), following extensive pharmacological investigation, made the following recommendations:

Horses:	5 mg./kg. intramuscularly once daily.
Cattle:	10 mg./kg. intramuscularly every 48 hours.
Dogs:	5–20 mg./kg. intravenously every 24 hours. 10–20 mg./kg. subcutaneously every 24 hours. or 25–50 mg./kg. orally every 8–12 hours.

Miscellaneous doses:

Cattle:	Intramammary injections:	15·0 G. tubes containing 60 mg./G. at 12–48 hour intervals.
	Intra-uterine therapy:	½–2 G. repeated in 36–48 hours.
Mink:	Orally:	20–30 mg. daily.

Feed supplements for all species as short term prophylaxis and therapy, should provide 50–100 G. oxytetracycline per ton of feed. Supplementation should normally not be continued for longer than one week.

Official Preparations

The British Veterinary Codex recognizes only the hydrochloride powder; the British Pharmacopœia recognizes additionally the dihydrate and tablets containing 0·25 G. of this, and the oxytetracycline base. The United States Pharmacopœia, however, recognizes formulations which are available in Great Britain only as commercial products. These include an oral suspension of oxytetracycline base, various sized capsules, an amino-acid buffered injection, and an ophthalmic solution, all containing the hydrochloride.

Commercially, intravenous injections stabilized with ascorbic acid, intramuscular injections stabilized with magnesium chloride and containing a local anæsthetic, intramammary formulations, topical and ophthalmic ointments, and lamellæ, all containing polymyxin B. additionally*, as well as capsules, tablets, powders for oral administration, and feed supplements are all available for veterinary use.

* Polymyxin has lately been omitted from many of these preparations.

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CHAPTER 27

ANTIBIOTICS: BROAD-SPECTRUM

(v) CHLORTETRACYCLINE

CHLORTETRACYCLINE was the first of the tetracycline group and the second broad-spectrum antibiotic to be discovered. It is official in the U.S.P. as Chlortetracycline Hydrochloride and in the British Veterinary Codex, 1953, as Aureomycin Hydrochloride.

History

Further work into the antibiotic producing potentialities of the Streptomycetes following the discovery of streptomycin resulted in the announcement by Duggar in 1948 of a new species of actinomycete *Streptomyces aureofaciens* and a new antibiotic, given the name Aureomycin. The fungus was so named because of the intense yellow colour of cultures; the commercial name of Aureomycin refers directly to the golden-yellow of the antibiotic.

Manufacture

Chlortetracycline is manufactured by deep-culture fermentation as with most other antibiotics, using a strain of mould obtained by mutation following ultra-violet irradiation.

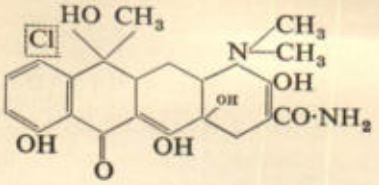
There are several methods of extracting and purifying the substance but the principles are much the same as for oxytetracycline extraction. Use is made of the amphoteric character of the base and the different solubilities of base and salts in various solvents; use is also made of the selective adsorption of base and salts by exchange resins. The final extraction and crystallization is carried out aseptically so that a sterile crystalline salt or base is obtained.

Chemistry

Chlortetracycline base is a golden-yellow crystalline amphoteric compound sparingly soluble in water and with a bitter taste. The hydrochloride is similar in appearance but with a strong bitter taste; it is fairly soluble in water (1 : 75) but only slightly soluble in alcohol and almost insoluble in other organic solvents.

The structure of the compound is based on the tetracycline nucleus, the hydrogen atom attached to carbon 7 in the nucleus being replaced by a chlorine atom. This substitution is said to be responsible for the instability

of this compound when compared with tetracycline and oxytetracycline. This base, in common with tetracycline and oxytetracycline, will form



Chlortetracycline.

salts with both acids and bases. The hydrochloride is recognized by most pharmacopœias and a calcium salt appears in New and Non-official Remedies 1950 (N.N.R.) specifically intended for oral administration.

Stability

Had chlortetracycline been more stable (and less irritant on injection) its therapeutic importance would have been considerably greater.

1. *Moisture.* Chlortetracycline hydrochloride is stable in dry air, and in moisture free containers protected from light is stable for at least seven months at room temperature. Solutions in water having a pH of 2·5 are relatively stable but cannot be administered. When buffered to neutrality or alkalinity for administration, solutions deteriorate very rapidly losing about 12 per cent of their potency in 30 minutes at 25°C., 20 per cent in 1 hour and 40 per cent in 2 hours (Harned *et al.*, 1948). Solutions must therefore be freshly prepared, for though refrigeration of a solution will maintain potency for slightly longer periods it is of no clinical significance.

Chlortetracycline borate, used for eye infections as a solution, is stable as a dry salt when kept in air, but even this is very unstable in solution.

2. *pH.* Acid solutions are comparatively stable and at pH 4 will keep in a refrigerator for 2 weeks. At pH 8 the intravenous injection potency is rapidly lost. When buffered with sodium borate (chlortetracycline borate eye drops) solutions have approximately pH 7·5; these solutions are inert after 24 hours (Braley *et al.*, 1948) but will keep for several days when refrigerated.

3. *Temperature.* Solutions are susceptible to temperature changes and whereas dilute solutions at pH 2·5 will remain stable for several hours at room temperature, at 37° they will lose up to 15 per cent. potency in 5 hours and 50 per cent. in 24 hours.

Oxidizing agents, enzymes, etc. Chlortetracycline is similar to other members of the group in its stability under conditions other than those mentioned above.

Pharmacology

In many respects chlortetracycline has a pharmacology similar to oxytetracycline but differs materially in one or two instances.

Absorption and Administration Routes. Only biological tests are available for estimating blood, tissue and body fluid levels; as chlortetracycline deteriorates rapidly in solution no absolute figures but only relative values can be obtained by these methods.

Following oral administration of single doses, maximum blood levels are achieved in about the same time as those for oxytetracycline (Welch, 1950)—2 to 8 hours—and detectable levels may remain for as long as 24 hours. Increase in dosage is not followed by commensurate increase in blood levels, but levels are maintained for a longer period. Intramuscular injection is painful and is not recommended. Intravenous administration is permissible but care must be taken not to allow perivascular leakage, for irritation locally and thrombophlebitis may result. Small intravenous doses—as low as 25 mg. in man—are sufficient to provide satisfactory blood levels which can then be maintained by oral dosage. Maximum levels may be achieved in as short a time as five minutes and detectable levels persist for up to twelve hours after a single dose. Chlortetracycline has also been administered by intraperitoneal injection. Chlortetracycline is suitable for topical applications and is extremely effective when used against susceptible infections.

Blood Levels. In man, blood levels of 2·0–4·0 mg, are considered to be 'therapeutically effective' (Extra Pharm. 23rd Edit. 1952 p. 104) but it has been shown (Brit. Pat. 654215, 660511) that 0·03 μg. is effective against a heavy experimental inoculation of pneumococci. Blood levels are maintained for approximately the same time as similar doses, by the same route, of oxytetracycline (Welch, *loc. cit.*).

Barriers. Chlortetracycline rapidly diffuses into most tissues and fluids and is thought to diffuse into the intracellular water of tissues. The remarkable effect on rickettsiæ is probably due to this diffusion, in this case into the intracellular fluid of endothelial cells.

1. *Blood-brain barrier.* Confusion exists concerning the diffusion into the cerebrospinal fluid. It appears that some diffusion takes place, but that the concentrations increase in meningitis. This follows the pattern of oxytetracycline.

2. *Placental barrier.* Diffusion of chlortetracycline across the placental barrier takes place readily and, as with oxytetracycline, appreciable quantities can be detected in the fœtal circulation.

3. *Intestinal barrier.* Absorption from the intestines is rapid but incomplete and therapeutic concentrations in the fæces are easily obtained. The detectable levels may not be quite so high as those given by similar doses of oxytetracycline but that is due in part at any rate, to the instability of solutions of chlortetracycline and the consequent inaccuracy of tests.

4. *Serous membranes.* The peritoneum and pleura offer little resistance and detectable quantities appear in peritoneal and pleural fluid within a relatively short time of administration. Intraperitoneal injection has been

used for administration, though Chivers (1952) has stated that chlortetracycline causes irritation when given by this route as well as by intramuscular or subcutaneous injection. There is no information on diffusion into the humours of the eye nor across the sinovial membrane.

5. *Milk barrier.* Chlortetracycline diffuses into the milk in concentrations equal to or higher than those in the blood (Schipper *et al.*, 1952), and combined intravenous and local treatment has been recommended in acute mastitis cases (Easterbrook, 1950; Lower, 1950; Bell *et al.*, 1951). There is normally no irritant action on the mammary tissue.

Excretion. As with the other tetracyclines, the main excretory routes are the urinary system, the biliary system, and the intestines. Higher concentrations of chlortetracycline than are given by equal doses of oxytetracycline are often found in the bile (also lungs and spleen) but urinary and fæcal concentrations are usually lower (Welch, 1950).

Urinary excretion is from 9–15 per cent. of a single oral dose during the 24 hours subsequent to dosing, but up to 25 per cent. of the total dose may be recovered following repeated dosing (compared with 50 per cent. for oxytetracycline). These discrepancies have not been accounted for, oxytetracycline is therefore preferred for urinary infections.

The higher biliary excretion makes chlortetracycline preferred before oxytetracycline for liver infections of which *Leptospira icterohæmorrhagiæ* may be quoted as an example.

Details are quoted in Antibiotics (Pharm. Press, 2nd Edit., 1952, p. 184) showing that the excretion of chlortetracycline by the udder persists for 48 hours and the observation is made that the udder probably provides one of the main means of excretion.

Toxicity. Chlortetracycline is slightly more irritant than the other tetracyclines when administered orally, and pigs, cats, and dogs may show signs of nausea, may vomit, and may suffer from diarrhœa. Administration may be either in milk or followed by milk, which seems to lessen the incidence of these symptoms. Ruminants have been shown to suffer gastro-intestinal upsets following oral administration, but as with oxytetracycline this is not of any permanent clinical significance, though repeated small doses are less troublesome in this respect than single large doses, (Kanegis *et al.*, 1950; Turner *et al.*, 1952; Hardie *et al.*, 1954; English, 1956).

The reference made to fungal growth during the use of oxytetracycline also applies to chlortetracycline, and a fungistatic compound such as the antibiotic nystatin has been used to overcome this trouble in man.

Action. Chlortetracycline is normally bacteriostatic but in higher concentrations and used against the more sensitive bacteria it may also be bactericidal. The method of its bacteriostatic action is still unknown but is probably the same method used by the other tetracyclines and suspected of being related to an interference with phosphorylation. Though a decrease in antibacterial effect due to antagonism by blood and tissue

fluids has been reported by Jones (1954), this is of little clinical significance; indeed, the activity *in vivo* is said to be greater than would be anticipated following *in vitro* tests (Klein *et al.*, 1950).

There has been reported a shortening of blood coagulation time following the administration of chlortetracycline to some animals (Macht *et al.*, 1949; Innerfield *et al.*, 1951).

Antibacterial Spectrum. A broad-spectrum antibiotic, chlortetracycline is active against a wide variety of organisms including Gram positive and Gram negative bacteria; rickettsial activity is particularly good and it has some antiviral activity. Some protozoa are also affected. It has negligible effect on *Myco. tuberculosis*, yeasts, and moulds; Proteus and Pseudomonas species are mostly insensitive, the occasional strains are susceptible to higher concentrations than are normally used.

As with other broad-spectrum antibiotics the danger of yeast and mould proliferation can be troublesome.

Bacterial Resistance. Chlortetracycline insensitivity is being met increasingly in clinical practice and resistance follows the pattern of oxytetracycline resistance (*q.v.*) It should be remembered that cross resistance exists within the tetracycline group. Where resistance to one of these broad-spectrum antibiotics exists it is always wiser to use a narrow-spectrum compound to which the organism has a specific sensitivity rather than to rely on larger doses of a related antibiotic.

Diseases and Chlortetracycline Therapy. There is little difference between the disease coverage of chlortetracycline and oxytetracycline, but whereas the latter antibiotic is more effective in the urine and fæces because of its greater concentration, the former antibiotic creates higher concentrations in the lung and spleen and is therefore more effective in pneumonias and septicæmias. Differences exist in degree of effect in some cases, and in administration methods.

Specific diseases which respond to treatment with chlortetracycline include pasteurellosis, strangles, leptospirosis, calf diphtheria, vibriosis in cattle, and infectious feline influenza. Non-specific diseases include mastitis, metritis, gastro-enteritis including calf and pig scours, and secondary infections in virus diseases. As with oxytetracycline, most of the common bacterial diseases of poultry respond to chlortetracycline treatment.

Mastitis

Following intramammary infusion of 400 mg. (one ¼ oz. intramammary tube) chlortetracycline, adequate antibacterial levels of 4 μg. per ml. are maintained for 48 hours, even with regular 12 hourly milkings (Kanegis *et al.*, 1953).

Chlortetracycline is of most value as a treatment for penicillin resistant streptococcal mastitis and for staphylococcal mastitis; it is of value for the systemic effects of corynebacterial mastitis, though it has little effect

on the condition in the udder. Chivers (1952) reports such an effect in a cow which was moribund at the commencement of treatment but was considerably improved by the second day of systemic treatment; the cow lived, but there was little effect on the udder infection.

Streptococcal mastitis. Penicillin is preferred for all routine purposes but where resistance to penicillin is encountered, in chronic cases, and in acute severe cases with systemic involvement, chlortetracycline is equally effective with the other tetracyclines. In acute cases, Lower (1950) reported favourable results from intravenous injection of 5·0 G. chlortetracycline in conjunction with local udder infusions. One intramammary injection of 400 mg. is frequently sufficient but this may be repeated 48 hours later, and again 2 days later if necessary.

Staphylococcal mastitis has responded well to chlortetracycline intramammary injection (Slanetz *et al.*, 1950; McCulloch *et al.*, 1949; Packer, 1950; Wilson, 1954; Edwards, 1954), but Schalm (1950) showed that the 70 per cent. of quarter recoveries reported by Packer, the 85 per cent. reported by McCulloch *et al.* (*loc. cit.*), and the 96 per cent. of quarters freed of infection by Slanetz *et al.*, were not to be expected every time, and that penicillin will often give results as good as those achieved by chlortetracycline. With the increase of mastitis due to penicillin resistant strains the importance of chlortetracycline and the other members of the group will increase, though increasing amounts of penicillin with dihydrostreptomycin are being used where resistance occurs. Coliform infections will sometimes respond to chlortetracycline but Pseudomonas infections are generally resistant (U.S.D., 25th Edit., 1955).

Klebsiella mastitis shows good clinical response to chlortetracycline (Buntain *et al.*, 1953), and Easterbrooks *et al.* (1956) have confirmed that a proportion of cases will respond, though they recommend sulphadimidine sodium intravenously initially, continued by oral therapy; streptomycin was suggested as a secondary treatment where this failed. *In vitro* tests showed that tetracycline, neomycin, and chlortetracycline, were active against two strains isolated, whilst oxytetracycline was slightly less active than chlortetracycline.

The action of chlortetracycline in mastitis thus parallels that of oxytetracycline quite closely, but commercial intramammary injections of oxytetracycline also contain polymyxin B and therefore have far greater activity in *Bact. coli* and Pseudomonas infections. [Note: Polymyxin has since been omitted following reformulation in 1958.]

Specific Systemic and Organic Diseases. Most of these diseases respond in a similar way to oxytetracycline but with some small variations in degree of response.

Strangles

Rahman (1957) reports 'moderate resistance' to both chlor- and oxytetracycline of all 20 strains of streptococci isolated from cases of strangles and rhinitis but tested *in vitro*. In general, penicillin is preferred due to the

greater sensitivity of *Strep. equi* to that antibiotic (0·03 μg.* average as against 19·2 μg. for chlor- and 18·3 μg. for oxy-tetracyclines) but nevertheless clinical response has been reported (Sheetz, 1951).

Anthrax

Although chlortetracycline has been shown to be effective *in vitro* against *B. anthracis* no clinical reports are available. However, in view of the good clinical reports on oxytetracycline treatment (*q.v.*) and the highly successful experimental use of tetracycline in sheep (Johnson *et al.*, 1955), it is probable that chlortetracycline will be equally effective.

Pasteurellosis

Chlortetracycline is recommended by the manufacturers for the treatment of transit fever in cattle and horses and good results have been reported from intravenous injection (Lower, 1950; Chivers, 1951 and 1952). Rahman (1957) gave some interesting details on the action of chlortetracycline against *Pasteurella septica* in mice and *in vitro*. On its showing *in vitro* (a potency of 45·3 compared with penicillin taken as 1) it was comparatively ineffective, but *in vivo* (a potency of 0·058 compared with penicillin taken as 1) chlortetracycline proved to be the most effective antibiotic in common use. These figures were far superior to those of oxytetracycline with 31·7 *in vitro* and 0·25 *in vivo*.

Fowl cholera responded experimentally (Prier, 1950) and chlortetracycline, as well as oxytetracycline, has been used successfully in the field, though Blount (1955) indicated that furazolidone was preferable to any antibiotic for this and for the Salmonella group of diseases in poultry; Smith (1955) was unable to show that furazolidone had any curative effect at all.

Leptospirosis

Bovine leptospirosis has been successfully treated with chlortetracycline and the organism entirely eliminated from the urine (McLure, 1953). The effect was superior to that of either penicillin or streptomycin. Bryan (1955) on the other hand has indicated that chlortetracycline alone was not effective experimentally in chronic *L. pomona* infections in cattle.

In *pigs*, various reports (Ferguson *et al.*, 1956; Howarth, 1956) indicate that a daily oral intake of about 1·5 G. per animal (7·5 mg./lb. bodyweight) will eliminate *L. pomona* infection from breeding sows.

In *dogs*, both *L. canicola* and *L. icterohæmorrhagiæ* infections respond to chlortetracycline (Brunner *et al.*, 1950; Heuer, 1953; English, 1956).

Doses of chlortetracycline in this disease need to be high and should be given early to prevent structural changes in the liver and kidneys.

Coli-Salmonella Group Infections

Many reports and wide clinical usage have indicated the usefulness of chlortetracycline in the treatment of white scours in calves, and enteritis

* Concentration in μg. per ml. giving 50 per cent inhibition following overnight incubation.

in pigs and dogs (Lower, 1950; Konde, 1951; Bortree *et al.*, 1952; Chivers, 1952) either by intravenous injections or by oral administration; prophylaxis in calf scours is achieved in the same way as with oxytetracycline, dosages for this purpose and for treatment being 5 mg. per lb. bodyweight (11 mg. per kg.). *Bact. coli* resistance is, however, becoming much more common and has been attributed, in part at least, to medicated supplements (Smith and colleagues, 1956, 1957).

In *calves*, infections with *Salmonella dublin* have responded very satisfactorily (Ben David, 1953) to oral dosage with chlortetracycline.

In *foals*, septicæmic infections with *B. equirulis* (*Shigella equirulis*) have responded well to intravenous injections of chlortetracycline (McCollum *et al.*, 1951; Doll *et al.*, 1951 a, and b) prophylaxis is achieved by a single dose at the daily curative rate of 5 mg. per lb. (11·0 mg. per kg.) bodyweight. However, as streptomycin is effective and the drug of choice (English, *loc. cit.*) the broad-spectrum antibiotic should only be used in streptomcyin resistant cases.

In *poultry*, experimental evidence indicates that Salmonella infections will respond to chlortetracycline, up to 600 mg. per kg. being satisfactory against *S. pullorum* if used early (Gerriets, 1957). Nevertheless, as with other poultry diseases, furazolidone in mashes will give very good and economical control of salmonellosis (Blount, 1955; Wilson, 1955; Gordon *et al.*, 1955, 1957) and chlortetracycline, along with other antiobitics, is used mainly for other purposes.

Listeriosis

This disease is typified mainly by meningitis which causes circling in cattle and sheep. The organism implicated is *Listeria* or *Erysipelothrix monocytogenes* which is susceptible *in vitro* to chlortetracycline but not other broad or narrow spectrum antibiotics including oxytetracycline, according to Zink *et al.* (1951). Over 60 per cent. recoveries in cattle have been reported but no effect is exerted on the disease in sheep: intravenous injections at the daily rate of 5 mg. per lb. (11·0 mg. per kg.) should be continued for 4 days (Gray *et al.*, 1953).

Clostridial Diseases

It has been shown (Long *et al.*, 1950) that *Cl. tetani* is susceptible *in vitro* to concentrations of 0·1 μg. per ml. of chlortetracycline. So far no reports are available on clinical use, but it must be remembered that it is the toxin of this organism which is the lethal factor: this toxin is elaborated by the organism at the site of infection so that local dressing of the wound is of prime importance. The wound may not always be apparent, though tetanus infected wounds heal very slowly, and large oral or parenteral doses may be the only way of eliminating the bacterial focus.

Cl. septique infections of the head and sinuses of two steers following dehorning were treated by Chivers (1952). One animal was given 1·5 mega units in oil daily but died on the sixth day; the other animal, given

chlortetracycline intravenously at the rate of 4·0 mg. per lb (8·8 mg. per kg.) bodyweight as a single dose once a day, was considerably improved two days after treatment commenced and was completely normal when treatment was ended on the third day.

Experimental evidence (Percival *et al.*, 1953) in sheep indicates the activity of chlortetracycline against *Cl. chauvæi*. The clinical application can only be of prophylactic importance for there were 20 per cent deaths and severe lameness occurred in 100 per cent. of the experimental animals when chlortetracycline was injected intravenously at the rate of 5 mg. per lb. in single daily doses for four days, commencing 24 hours after inoculation of cultures. Severe lameness resulted in 20 per cent. and there were no deaths when the first antibiotic dose was given at the same time as the inoculation.

It must be remembered that rapidly acting toxins are the lethal factors with many of the clostridia and that vaccination as prophylactic treatment cannot satisfactorily be replaced by curative treatment either with antibiotics or antitoxic sera.

Pfeifferella Infections

Chlortetracycline has a marked *in vitro* effect against *Pf. mallei* which causes glanders, a severe and fatal disease of horses and man (Sîrmon *et al.*, 1956). *In vitro* and *in vivo* tests on guinea pigs (Nemoto *et al.*, 1954) showed that chlortetracycline was the most active antibiotic *in vitro* and, with oxytetracycline and dihydrostreptomycin, was able to protect the experimental animals from the disease. Clinical reports are not available.

Feline Influenza

In experiments on kittens McKercher (1953) showed that the oxy- and chlor-tetracyclines were equally effective against the virus of 'cat flu' either by oral or parenteral administration but dosages near the maximum were required.

Canine Coccidiosis

Good clinical responses have followed the oral administration of chlortetracycline at the rate of 25 mg. per lb. (55·0 mg. per kg.) body weight but complete elimination of the oospores of *Isospora bigemia* only occurred after a further period of varying length (Altman, 1951). The improvement has been ascribed to the reduction of secondary invaders and the consequent revitalization of the alimentary mucosa (Jones, 1954).

Poultry

The effects in pasteurellosis (fowl cholera) and salmonellosis have already been mentioned (*q.v.*).

Infectious sinusitis in turkeys has responded to chlortetracycline amongst other antibiotics (Prier, 1950; Zander, 1955), also *Chronic Respiratory*

Disease (C.R.D.) of chickens (White *et al.*, 1953), but for the former disease, at least, it is recommended that different antibiotics should be used in succession as the response to each slows down (Blount, 1955; Wilson, 1955).

Non-Specific Conditions. Chlortetracycline has proved of value in the treatment of non-specific enteritis, especially that associated with virus diseases. In virus diseases generally this antibiotic is quite effective in eliminating or reducing secondary bacterial infections. This is of particular value in the canine distemper—hepatitis complex and in the complications of cat distemper or infectious panleucopenia.

Metritis in cattle responds well to chlortetracycline (Lower, 1950). The soluble 0·5 G. tablet has proved valuable in the treatment of retained placentæ (Beattie *et al.*, 1952; Easterbrooks *et al.*, 1955). The latter workers recommended the insertion of 0·5 G. every 48 hours from parturition until the placenta sloughs naturally; they found a decreased incidence of metritis and no impairment of fertility when the antibiotic was used in this manner. This is in accord with the effects achieved by oxytetracycline.

Vibrio fœtus infection has been found to respond to chlortetracycline (Report: Min. Ag. Fish., 1954) but its value relative to streptomycin is contested. Though good results were reported by Easterbrooks *et al.* (1955b) following intra-uterine aqueous injection of 0·5–1·0 G. of chloramphenicol and the three tetracyclines, they preferred streptomycin because of its low cost, equal efficiency, and lack of side effects when injected at any time during the œstrus cycle.

Other non-specific conditions such as pneumonia, tonsillitis, bronchitis (including kennel cough), and cystitis, have frequently responded satisfactorily in all species.

Topical Application. Chlortetracycline has been used successfully in eye conditions as an ointment or a solution of chlortetracycline borate; the latter is used owing to the acidity and irritant effect of the hydrochloride. It is of value in most ocular lesions, penetrating only when the conjunctiva is damaged: it causes less retardation of healing than streptomycin.

As a topical ointment, sometimes in conjunction with systemic therapy, chlortetracycline is useful in otitis externa, burns and wounds, abscesses, and other forms of pyogenic infections.

Miscellaneous. Chlortetracycline is widely used as feed supplements for encouraging growth in pigs, poultry, and sometimes in calves. Braude *et al.* (1953) suggest 90–20·0 G. per ton for pigs, 1·0–10·0 G. per ton for poultry, and 50·0–100·0 mg. per head per day for calves. Commercial supplements contain not less than 3·6 G. per lb. and also contain the vitamins elaborated during fermentation.

Daily doses of 1·0 G. chlortetracycline have removed 86 per cent. of ascarids from cats (Brown, 1953).

Dosage

Intravenously:	all species 2–5 mg. per lb. bodyweight. (4·4–11·0 mg. per kg.)	
Orally:	Foals and calves:	10·0 to 25·0 mg. per lb. bodyweight.
	Pigs (in food):	1·25 to 2·5 G. per 100 lb. bodyweight.
	Dogs and cats:	10·0–25·0 mg. per lb. bodyweight daily (22·0–55·0 mg. per kg.) in 2 equal doses.
Intramammary:	Cattle:	One or two ¼ oz. tubes per quarter, repeated every 48 hours if necessary.
Intra-uterine:	Cattle:	One 0·5 G. tablet every 48 hours.

In all cases dosage should be continued for at least 24 hours and preferably 48 hours after temperatures are normal and symptoms have disappeared, though doses may be cut by 50 per cent. during the post-febrile period. Daily doses in large animals *may* be split into two equal and equally spaced doses. In small animals this should always be observed.

Official Preparations

The British Veterinary Codex recognizes only one form—Aureomycin Hydrochloride Powder. It must contain not less than 900 units per mg.

The United States Pharmacopœia recognizes—Chlortetracycline Hydrochloride with a potency of not less than 900 units per mg.; capsules containing not less than 85 per cent. of the labelled concentration are available in 50, 100 and 250 mg. sizes; an injection suitably buffered, usually with sodium glycinate; and an ophthalmic powder for making solutions consisting of chlortetracycline hydrochloride with sodium chloride and borax to buffer the compound and form the less irritant borate.

Commercially available in Gt. Britain are 50·0 mg. and 250·0 mg. capsules, 0·5 G. soluble tablets and a soluble tinted powder for oral administration, an intramammary ointment in 7·1 G. tubes containing 400 mg. chlortetracycline hydrochloride, a 3 per cent. ointment and an ophthalmic ointment containing 10·0 mg. chlortetracycline hydrochloride per gramme (1 per cent.). Feed supplements are also available.

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CHAPTER 28

ANTIBIOTICS: BROAD-SPECTRUM

(vi) CHLORAMPHENICOL

THIS antibiotic is notable because it was the first to be synthesized and manufactured synthetically. It is official in the United States and British Pharmacopœias and in the British Veterinary Codex. Samples must contain not less than 90 per cent. of the pure substance.

History

The discovery of chloramphenicol was reported in 1947 by Ehrlich *et al.* following intensive study of the organisms isolated from about 6000 soil samples by Burkholder, a botanist at Yale University. A new species of actinomycete, named *A. venezuelæ* after the origin of the soil sample from which it was cultured, was found to produce a highly active antibiotic to which was given the trade name of Chloromycetin by the commercial concern in whose laboratories the work was done. In 1949 the chemical structure and the chemical synthesis were announced along with manufacturing methods, making chloramphenicol the first antibiotic to be manufactured synthetically on a commercial scale.

Manufacture

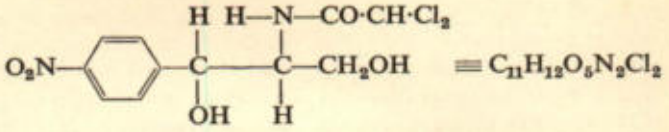
The biosynthesis from *Streptomyces venezuelæ* used initially was similar in principle to that used for the manufacture of other antibiotics. Later the compound was manufactured by chemical synthesis involving 10 major reactions achieved in about 30 stages, and commencing with a complex compound paranitrobromoacetophenone. Other methods have been published.

Chemistry

Chloramphenicol, whether manufactured synthetically or biosynthetically, is a white, but sometimes slightly grey or yellow, fine crystalline powder. It has a bitter taste and is only slightly soluble in water (1 : 400) but soluble in most of the organic solvents.

The *structure* of chloramphenicol is relatively simple, the compound being a derivative of nitrobenzene and of dichloroacetic acid. It is unique, in chemicals of natural origin, in having this aromatic nitro-grouping in

its molecule. Defined as D-(-)-threo-2-dichloroacetamido-1-p. nitrophenyl-1:3-propanediol, chloramphenicol appears graphically as:



$\equiv C_{11}H_{12}O_5N_2Cl_2$

There are four stereoisomers of chloramphenicol but only the D-threo form has antibacterial activity, so that in the formation of derivatives such as the palmitate and cinnamate esters the stereochemical configuration of the propanediol side chain must be retained. The paranitrophenyl group may, however, be changed to the ortho- or meta-nitro compounds or even be replaced by halogens without eliminating the antibacterial effect, though there is some reduction. It is thus the propanediol D-threo stereoisomer which is vitally concerned with the antibacterial activity. The aromatic nitro-group is important in that it represents the possibly toxic portion of the molecule whilst having only a slight effect on the antibacterial properties. It has also been suggested that the —CO·NH group may be implicated in the depression of bone marrow hæmopoiesis.

Stability

Chloramphenicol is more stable than either oxy- or chlor-tetracycline, and the dry powder is stable in air but should be kept in tightly closed light proof containers.

1. *Moisture.* Aqueous solutions in distilled water will keep for at least one month at normal room temperatures. An aqueous solution is unaffected after boiling for five hours, providing pH 9 is not exceeded.
2. *pH.* Solutions are relatively stable between pH 2 and pH 9, but strongly alkaline solutions cause rapid decomposition.
3. *Temperature.* The powder and solutions are heat stable and solutions will withstand boiling for at least 5 hours.
4. *Oxidizing agents.* The secondary hydroxyl group is easily oxidized so that the addition of any oxidizing agent is contra-indicated. The nitro-group can be reduced to an amino-group so that reducing agents are likewise contra-indicated.
5. *Enzymes.* Besides oxidation of the hydroxyl group and reduction of the nitro-group, a third weakness exists in the chloramphenicol molecule which lays it open to enzyme activity. This is the dichloroacetyl side chain which is readily hydrolysed (U.S.D., 2nd Edit., 1955, p. 281). However, no specific antichloramphenicol enzymes comparable with penicillinase have been reported.
6. *Miscellaneous.* Monohydrogen phosphate ions, acetic acid, and citrate buffers all assist destruction of the antibiotic by catalytic action.

Pharmacology

Most of the pharmacological information available refers to man and dogs.

Absorption and Administration Routes. Following *oral* administration, chloramphenicol is rapidly and almost completely absorbed, giving very high maximum blood levels about 2 hours after a single dose. Blood levels are proportional to the dose and far exceed those attained by the tetracyclines with similar dosage. Following *intravenous* and deep *intramuscular* injections therapeutic blood levels are achieved rapidly. The absorption *per rectum* is also sufficient to provide therapeutic concentrations in the system.

Blood Levels. Maximum blood levels take from 2–4 hours to develop. Therapeutic blood levels are given as 5–10 μg. because of the adsorption by serum proteins of a proportion of the circulating antibiotic, shown to occur by Glazko *et al.* (1949) and Smith *et al.* (1948); the latter group estimated that as much as 45 per cent. of the chloramphenicol in the circulation was bound to protein. Blood levels are proportional to the size of the dose and the period during which the level remains over a given concentration also varies according to dose size; at any given dose the concentration is always maintained longer than the concentration given by similar doses of the tetracyclines: this applies in man to single or multiple doses of 1·0 G. In dogs, this maintenance of levels may be related to the fact that inactivated chloramphenicol, when excreted into the intestines is hydrolysed back into an active form (Glazko and co-workers, 1950a, 1950b) and can then be reabsorbed.

Barriers. Though the diffusion of chlortetracycline is both rapid and widespread, chloramphenicol is distributed quite as rapidly and diffuses throughout the tissues more widely.

1. *Blood-brain barrier.* Chloramphenicol diffuses readily into the spinal fluid reaching levels between $\frac{1}{4}$ and $\frac{1}{2}$ of the blood levels.

2. *The placental barrier.* The antibiotic passes across the placenta and achieves fœtal cord levels of up to $\frac{3}{4}$ of those in the maternal circulation.

3. *Intestinal barrier.* So efficient is absorption of chloramphenicol from the intestines that for all normal purposes in small animals oral dosage is sufficient. In large animals oral dosage frequently suffices but initial levels are often established by intramuscular injections. Fæcal concentrations are appreciable but below those of oxytetracycline in man and presumably in carnivores; no information is available on the fæcal content of chloramphenicol in the herbivores, although concentrations expected would be well above those which depress ruminal fermentation in cattle.

4. *Serous membranes.* Appreciable quantities pass into the pleural cavity and into the peritoneal cavity. Chloramphenicol will diffuse into the aqueous and vitreous humours of the eye (B.Vet.C., 1953) following oral administration. It will penetrate the intact cornea and does not delay corneal regeneration (Magrane, 1951; Leopold, 1951).

5. *The milk barrier.* Chloramphenicol is excreted in the milk (B.Vet.C.) but mastitis therapy is surer by local infusion, supported by oral or parenteral administration in severe acute cases.

Excretion. The major part of any one dose is excreted in the urine, detectable quantities appearing within 30 minutes of administration. Part is excreted in a hydrolysed or conjugated form and only 10 per cent. is active: concentrations are below those of oxytetracycline and, except in high dosage, lower than those of chlortetracycline. Bile concentrations are also quite high but fæcal levels are below those of oxytetracycline and in general about the same as chlortetracycline.

Toxicity. So far no toxic effects other than those normally associated with broad-spectrum antibiotics have been recorded. Occasional nausea and vomiting may occur in dogs and cats but this is far less common than with the tetracyclines (English, 1956). In large animals, some interference with gastro-intestinal flora occurs but is of no more significance than with other similar antibiotics.

In man the occasional occurrence of blood dyscrasias due to suppression of bone marrow function following prolonged administration has brought this antibiotic into temporary disrepute. Intense investigation has shown that this is not to be feared when the antibiotic is used correctly, although blood tests should be carried out when administration is continued for more than two weeks.

In animals, studies on monkeys over a period of 15–22 months (Saslaw *et al.*, 1955) did not result in one drug induced dyscrasia, and Reutner *et al.* (1952) were unable to produce changes in the hæmopoiesis of dogs to which daily doses as large as 200 mg. per kg. bodyweight were given over a period of a month.

Action. Chloramphenicol is highly bacteriostatic and can be bactericidal. Its mode of action is unknown but its effect is reduced by adsorption onto serum proteins.

Antibacterial Spectrum. The most important aspect of the antibiotic effect of chloramphenicol is its action against all rickettsiæ: in addition, it is active against both Gram positive and Gram negative bacteria and against some viruses: spirochætes including leptospiræ are sensitive only to relatively high concentrations.

In vitro studies have shown that the blood levels of 5·0–10·0 μg. per ml. are adequate for controlling:

B. anthracis	Pasteurella species
Bact. coli-Salmonella group	*Proteus vulgaris*
Brucella species	*Ps. ærogenes* (*pyocyanea*)
Corynebacterium species.	Staphylococci and Streptococci.
Erysipelothrix species	

Clinical response does not follow entirely according to this list.

Bacterial Resistance. Resistance to chloramphenicol develops in a 'stepwise fashion', the maximum increase in one step recorded up to 1951 being eightfold compared with as much as one thousandfold with streptomycin (Meads *et al.*, 1950; English *et al.*, 1951). In clinical investigations the increments of resistance have occurred at irregular and unpredictable intervals during treatment. In general, the number of strains of susceptible species which do not respond is very small. Of eighty-eight strains of organisms isolated from diseased animals and birds, and representing fifteen different species, not one strain showed resistance (Rahman, 1957). Resistance to the tetracyclines does not mean that there will also be resistance to chloramphenicol as suggested by artificial resistance created *in vitro* (Herrell *et al.*, 1950), for Rahman (*loc. cit.*) showed that 50 per cent. inhibition of *C. equi* was achieved by 7·7 μg. (10·6 maximum) per ml. of chloramphenicol, but as much as 36·3 μg. (80·2 maximum) per ml. of chlortetracycline and 58·9 μg. (86·7 maximum) per ml. of oxytetracycline were required.

Diseases and Chloramphenicol Therapy. Chloramphenicol has not been widely used systemically in veterinary medicine in Great Britain, though local use has been quite extensive. The reasons for this are varied: chloramphenicol was the first of the broad-spectrum antibiotics to be available in the veterinary field and was relatively expensive; it was at first available only in capsule form because of the lack of a suitable injection solvent; this restricted its use to small animals. The great difficulty of giving capsules to cats and dogs further restricted its appeal. Following the introduction of an intramuscular injection it was generally found to cause tissue reaction and necrosis (English, 1956) though this was not an invariable occurrence (Eads *et al.*, 1955). A new formulation for intramuscular injection has been recently introduced which may make this form of administration more popular where chloramphenicol is concerned. In Great Britain, until its use for bovine keratitis and foot rot in sheep became widely accepted, the antibiotic was not strongly publicized and its possibilities were relatively unknown; finally came the very widely publicized possibility of blood dyscrasias following its use; this has not materially affected its acceptance in the veterinary field.

Chloramphenicol has been shown to be of value in transit fever, calf scours, Salmonella infections (for which it is probably the most useful antibiotic), various secondary invaders in virus diseases, kennel cough, infectious bovine keratitis, and foot rot in sheep. It has also been used in conjunction with dapsone as an intramammary injection and very recently an intramammary injection of chloramphenicol alone has been marketed.

Bovine Mastitis

Chloramphenicol has not been widely used in mastitis because of difficulties in finding a suitable vehicle. However, a preparation containing both chloramphenicol and a synergistic sulphone-dapsone, is official in the

Veterinary Codex and has been available commercially for some time; a suitable vehicle for chloramphenicol alone has been found and reports on its use should become available. Its rapid and facile diffusion make chloramphenicol suitable for intramammary injections and it appears to be about equal to penicillin in activity against streptococcal mastitis. It has been reported to be very effective against staphylococci and coliforms which cause mastitis (Hop, 1954). In conjunction with dapsone, Wilson (1954) reported that chloramphenicol was more active against *Bact. coli* mastitis than either chloramphenicol alone, chlortetracycline, or penicillin.

Specific Systemic and Organic Diseases

Pasteurellosis

Spectacular results with chloramphenicol in the treatment of transit fever (hæmorrhagic septicæmia, shipping fever) are reported by Eastman *et al.* (1952), for 10·0 G. intravenously brought the temperature of an 800 lb. bull down 6°F. in 18 hours; a further 10·0 G. returned the animal to normal 24 hours later. As little as 2·0 G. orally in a single dose brought about recovery of a heifer. The majority of the animals recovered in 24 hours.

There is a large variation in the sensitivity of Pasteurella strains to drugs (Neter *et al.*, 1950, 1951). In addition to this strain sensitivity, large differences between *in vitro* and *in vivo* susceptibility have been reported (Rahman, 1957), so that variable results might be expected. Chlortetracycline was suggested as the most potent antibiotic in pasteurellosis (Rahman, *loc. cit.*).

Contagious Bovine Pleuropneumonia

Newton (1954) used intravenous and intramuscular injections of chloramphenicol successfully in controlling excessive reactions to vaccination. Good results were also obtained by Hyslop *et al.* (1957) in preliminary trials, but its use in the field has not yet been attempted by these workers.

Fusiforms Infections

Calf diphtheria has been successfully treated by single daily intramuscular injections given at the rate of 2·0 mg. per lb. (4·4 mg. per kg.) bodyweight for 2–3 days combined with local cleansing and dressing with chloramphenicol (Sheriff, 1956). Previously the best, but very slow, recovery had been achieved following prolonged treatment with triple sulphonamide compounds combined with high dose penicillin injections.

Foot rot in sheep has provided chloramphenicol with one of its greatest successes in veterinary medicine. Stewart (1954a and b) first reported its efficacy, recommending 10 per cent. chloramphenicol in propylene glycol and showing that lower concentrations were less effective; results of 81–100 per cent. recoveries were obtained with one or occasionally two applications of the 10 per cent. solution, whereas only 50 per cent. of cures

were effected by the 5 per cent. spirit solution. These results were later confirmed in Great Britain by Sambrook (1955), Penny (1955), Harris (1955a), and Baxter *et al.* (1956). Both Baxter and Smyth and Harris were concerned at the high cost of the treatment when it was marketed following the experimental trials of previous workers; the former group of workers investigated a 5 per cent. chloramphenicol tincture with dapsone and found it almost as effective as the 10 per cent. tincture, though they pointed out that *Strongyloides papillosus* was not involved in the cases treated in their trial. In spite of the very good results, many still prefer cheaper if less effective methods, though some doubt as to the uselessness of other preparations such as 10 per cent. formalin has resulted from Miss Littlejohn's (1955) work. Harris (1954b) showed that oxytetracycline 5 mg. with polymyxin B sulphate 10,000 units per gramme in an ointment was found to be very efficient and cheaper than the chloramphenicol treatment. The efficacy of all treatment depends on efficient paring of the hoof, dry conditions, segregation of 'clean' and affected sheep, and the use of 'clean' ground after treatment: these details are aimed at applying the treatment directly to infected tissue, allowing it to heal efficiently and preventing reinfection.

Chloramphenicol may be applied after paring the feet, either by painting the lesions using a stiff brush, or by using an ærosol spray. Animals should be kept on concrete or wooden floors until the tincture has dried and then turned onto fresh pasture on which no sheep have grazed for at least two weeks, but preferably longer. All feet should be reinspected and, if necessary, retreated at 14-day intervals—one, two, or with very severe and chronic lesions, three treatments may be required.

Virus Pneumonia

This condition was reported by Penny (1954) to respond clinically to chloramphenicol injected twice daily; this treatment was subsequently reported by Pugh (1956) to be no more effective than sulphadimidine therapy, although it was quite effective against secondary invaders. No work comparable with that of Börnfors and Lanneck (1955, 1956) using the tetracyclines has so far been reported, and the tetracyclines (*q.v.*) are consequently preferred for prophylaxis and treatment, even though they too have no effect on the established virus but will depress secondary infection and will prevent infection of susceptible animals.

Coliform-Salmonella Infections

In *white scour* in calves the clinical response is variable. Eastman (1952) reports four recoveries in twenty-four hours whilst two died within forty-eight hours; one relapsed and died 2 months later and one showed no change either way. Smith (1957) reports excellent results from chloramphenicol on farms where sulphonamides, streptomycin, and the tetracyclines have created resistance in the indigenous *Bact. coli*, but later chloramphenicol resistant strains were also isolated.

Scouring in *pigs* was also shown to resist the tetracyclines but, in many instances, to respond to streptomycin or chloramphenicol. These cases were considered to be *Bact. coli* infections (Smith, *loc. cit.*).

In *salmonellosis*, response is also varied, but Rahman (1957) has expressed the opinion that chloramphenicol is the best agent against Salmonella infections. However, furazolidone is preferred in poultry (Blount, 1955), but clinical reports do indicate that chloramphenicol is relatively successful in mammals. Brennan *et al.* (1954) used 12–16 mg. per lb. (26·4–35·2 mg. per kg.) body weight intravenously in calves affected with *S. dublin* with good results, and Schaaf (1953) obtained good clinical, but less successful bacteriological, cures when 20 of 25 cows responded to one intravenous injection and a further three with repeat injections. The variation of susceptibility is emphasized by a steer which died in spite of combined streptomycin and chloramphenicol treatment (Arnold *et al.*, 1954).

Non-Specific Systemic Diseases. Good results from the use of chloramphenicol have been reported in most virus diseases of small animals, the distemper complex in dogs (Toosey, 1951), infectious feline panleucopenia (Schirmer *et al.*, 1951; Wright, 1953; Kirk, 1953; and Jenson, 1954) and infectious feline influenza (cat 'flu) (Schirmer, *loc. cit.*). In none of these conditions is response likely to be an antiviral action. Kennel cough and tonsillitis in dogs, frequently due to *Brucella* (*Hæmophilus*) *bronchiseptica*, whether concurrent with distemper or not, frequently, and in some cases with spectacular effects, responds to chloramphenicol when administered as capsules or as a palmitate suspension. Expense limits its prophylactic use, which would be its best indication.

Metritis in dogs (Eastman *et al.*, *loc. cit;* Schirmer, *loc. cit.;* and Heney, 1951) and in cattle (Eastman, *loc. cit.*) has responded to local treatment and, in some cases in bitches, to oral therapy at the daily rate of 15 mg. per lb. (33·0 mg. per kg.) body weight in divided doses.

Vibriosis in cattle has responded clinically to intra-uterine injection in propylene glycol, but workers at Weybridge indicated (Report on Animal Health Services, 1954, Ministry of Agriculture and Fisheries) that chloramphenicol was least effective of all the antibiotics tried (chlortetracycline, penicillin, streptomycin).

Cystitis and other urinary infections respond to chloramphenicol oral treatment, but leptospirosis is in the main resistant, although some cases will respond.

Local Application. Infectious bovine keratitis due to a Rickettsia responds very well and is considered by some (English, 1956) to give the best results. It is effective when applied as an ointment in cattle (Faull *et al.*, 1951; Hall-Patch, 1951; Jackson, 1954) and sheep (Riley *et al.*, 1953) if applied once or twice daily for 7–10 days. Animals under treatment should be housed and in darkness if possible.

Other eye conditions, wounds, pyogenic infections, and external otitis, have all responded to local therapy, either with a 1 per cent. eye ointment or a 0·1 per cent. to 0·2 per cent. saline or borate buffer aqueous solution.

Dosage

Oral administration:

Calves and Foals:	0·5 G. two or three times daily.
Piglets and Lambs:	0·25 G. two or three times daily.
Dogs:	Up to 75·0 mg. per lb. (165·0 mg. per kg.) body weight daily in three equal and equally spaced doses.
Cats:	0·25 G. once or twice daily.

Capsules or a palmitate suspension may be used.

Parenteral administration:

Large animals:	5·0 mg. per lb. (11·0 mg. per kg.) body weight once daily.
Small animals:	25·0 mg. to 75 mg. per lb. (55·0 mg. to 165 mg. per kg.) body weight once daily.

For intramuscular administration micronized chloramphenicol in aqueous suspension has been used. It must be remembered that absorption from the injection site is occasionally insufficient to give therapeutic levels. Subcutaneous injections must be avoided or local reactions may occur. The latest commercial injection is reported to be less irritant and more reliable in its action.

For intravenous injection it is usual to dissolve the chloramphenicol in propylene glycol.

In all severe cases, the higher dosage rates may be used until the acute symptoms have subsided, when the dosage may revert to the lower rates.

Official Preparations

The British Veterinary Codex recognizes only the powder and capsules containing the powder, usually of a 0·25 G. size.

The United States Pharmacopœia recognizes the powder and capsules, but adds an ophthalmic ointment, which is usually of a 1 per cent. strength.

The following are available commercially:

For oral administration:
- Capsules containing 0·25 G.
- Palmitate and cinnamate suspensions which liberate chloramphenicol in the intestines.

For parenteral administration:
- Micronized and buffered chloramphenicol powder for intramuscular injection. A permanent solution for intramuscular injection.

For topical use:

Dusting powder (5 per cent.).
Eye ointment (1 per cent.).
Topical cream (1 per cent.).
Eye drops—a dry buffered powder for solution in water.
Topical 10 per cent. solution in alcohol packed in bottles or as an ærosol.

For intramammary use:

Injections containing 0·5 G. chloramphenicol alone or 0·15 G. chloramphenicol with 0·3 G. dapsone as a synergist.

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CHAPTER 29

ANTIBIOTICS, NARROW AND MEDIUM SPECTRUM
(vi) NEOMYCIN, BACITRACIN, POLYMYXIN B

Neomycin

THIS antibiotic has a medium spectrum, affecting both Gram positive and Gram negative bacteria, strains of *M. tuberculosis*, Treponema and *Entamœba histolytica*. The compound is official in the British and United States Pharmacopœias as Neomycin Sulphate.

History

Neomycin was discovered by Waksman and Lechevalier in 1949 during their searches for an antibiotic which was effective against streptomycin resistant Gram negative and acid fast organisms. It was prepared from an actinomycete later identified as *Streptomyces fradiæ* found in a soil sample from the farmyard of the New Jersey State Agricultural College (Rutgers University) where *S. griseus*, and hence streptomycin, was discovered.

Manufacture

Neomycin is manufactured by the normal biosynthetic methods for submerged deep-vat fermentation using *Streptomyces fradiæ* cultures. Extraction and purification methods are similar to those adopted for streptomycin.

Chemistry

Neomycin is used as the sulphate, a white or slightly yellow crystalline powder which is almost odourless. The powder is hygroscopic and is soluble in water, almost insoluble in alcohol, and insoluble in other organic solvents. The official United States Pharmacopœia preparation of neomycin sulphate must contain at least 60 per cent. neomycin base, and 1·0 mg. pure sulphate is equivalent to not less than 600 units.

Neomycin was originally thought to be a mixture of four compounds named neomycins A, B, and C, and a further component *fradicin*. However, later investigations have thrown some doubt on the existence of all these components and the sulphate available commercially appears to be one substance only (U.S.D. 25th Edit. 1955 p. 884). Currently it is accepted that two neomycins exist—Neomycins B and C both conforming to the formula $C_{23}H_{46}N_6O_{12}$.

The partial structure of

$$C_{12}H_{25}N_4O_5—O—C_5H_7O(OH)_2—O—C_6H_7O(OH)_2(NH_2)_2$$

has been suggested but the complete structure of neomycin is unknown; it appears, with some reservations, to be related to streptomycin, and like streptomycin is a basic compound forming salts, of which the sulphate is the one commonly used.

Stability

Neomycin is one of the most stable of the antibiotics.

1. *Moisture.* In the dry state neomycin powder is stable for at least two years at room temperature. Solutions are also very stable and will retain their potency for at least a year at room temperature; they are also stable for several months at 37°C. Solutions darken on keeping and therefore, in spite of their thermostability they should be refrigerated to maintain appearance.
2. *pH.* Neomycin is stable over a wide range of pH ranging from pH 2 up to and beyond neutral and has even been said to be most active in alkaline solution (Antibiotics, 2nd Edit. 1952, Pharm. Press., p. 8). In this property it differs from all other antibiotics.
3. *Temperature.* Although relatively heat stable, neomycin will not withstand autoclaving or prolonged high temperatures. Solutions are thermostable in all climatic temperatures but will gradually darken in colour.
4. *Oxidizing Agents.* Neomycin is apparently unstable in the presence of these agents, for it has been reported that antioxidants will retard the colour change in solutions buffered to a range of pH 6–7.
5. *Enzymes.* So far no enzyme has been reported which has a specific action against neomycin.
6. *Miscellaneous.* All compounds containing sulphonic acids or similar compounds will precipitate and inactivate neomycin.

Pharmacology

Absorption and Administration Routes. Neomycin is absorbed to the extent of about 3 per cent. of an oral dose and systemic infections cannot be treated by orally administered neomycin. Parenteral injections may be given by all the normal routes but the intramuscular route is the one recommended. In man the parenteral use of neomycin is restricted to those cases where the infective organism is highly virulent, not susceptible *in vitro* to other antibiotics, but sensitive to neomycin, and only where there is no impairment of renal filtration: this is necessitated by the nephrotoxicity and neurotoxicity of the compound. There is no absorption from the skin so that topical application and oral dosing are the main routes of administration.

Blood Levels. Following intramuscular injection, maximum blood levels are achieved within an hour and appreciable amounts are present for from four to eight hours, so that the daily dose is usually split into four doses given at intervals of six hours.

Barriers. Neomycin penetrates the blood-brain, the pleural, and the peritoneal barriers following intramuscular dosing; it is only slightly absorbed from the intestines and not at all from the skin.

Excretion. Parenterally administered neomycin is fairly rapidly excreted by the kidneys. Orally administered neomycin is in the main excreted in the fæces unchanged.

Toxicity. Neomycin shows a similar and additive toxicity to that caused by streptomycin. It consists of loss of hearing due to irreversible damage to the auditory division of the 8th cranial nerve, and also damage to the kidney causing albuminuria, hæmaturia, and the formation of renal casts. There is practically no external irritant action even when applied to the eye, and skin sensitivity is practically unknown. A slight laxative action follows oral administration but is not usually detrimental. Neomycin therapy by all routes may be followed in man by an increase in the yeast and fungi population of the skin, mucous membranes, and alimentary tract: so far this has been of no significance in animals. Waksman and Lechevalier (1949) considered it as having 'limited or no toxicity to animals' when making their introductory announcement, but the compound has had little parenteral use in animals.

Action. Neomycin *in vitro* is highly bacteriostatic (Long *et al.*, 1950). The mode of action is unknown but penicillin, bacitracin, and polymyxin have been successfully combined with neomycin.

Antibacterial Spectrum. *In vitro* and *in vivo* activity in experimental animals indicates that neomycin is a broad-spectrum antibiotic with a wide activity against Gram positive and Gram negative organisms, and against a number of actinomycetes. *In vivo*, the spectrum is limited by toxicity considerations. Neomycin has been reported as the most active antibiotic against *Bact. coli* (*Esch. coli*), Aerobacter, Proteus and the paracolon organisms in man (Roantree *et al.*, 1956); it is also effective against *Staphylococcus albus* (*Micrococcus albus*), and *S. aureus* (*M. aureus*), but somewhat less active against streptococci. *Pseudomonas æruginosa* (*Ps. pyocyanea*) is even more resistant though neomycin is more active against this organism than are the other antibiotics, with the exception of polymyxin: Roantree *et al.* reported almost no effect on Pseudomonas infections of the urinary tract. Activity against *B. anthracis* is suggested, and both Treponema species and *Entamœba histolytica* are sensitive. Activity against *Mycobacterium tuberculosis* is more of academic

interest in the veterinary field, but the activity of neomycin against strains of organisms resistant to other bacteria, and particularly streptomycin, is of considerable Public Health importance.

Bacterial Resistance. Neomycin has so far shown little tendency to promote clinically the growth of resistant strains, though resistant strains have been produced *in vitro*. Naturally resistant strains exist, as shown by Roantree *et al.* (*loc. cit.*) when 49 out of 55 strains of hæmolytic streptococci, 140 out of 155 strains of Pseudomonas, only 14 out of 486 strains of *Bact. coli*, 3 out of 242 strains of *Staph. aureus* and 2 out of 41 ærobacter strains, were resistant to 10 μg. of neomycin *in vitro*. Of the 242 strains of *Staph. aureus* mentioned, 198 were resistant to penicillin, 125 to streptomycin, 127 to tetracycline and 14 to chloramphenicol.

Diseases and Neomycin Therapy. Bovine mastitis, coliform enteritis in all species, urinary infections due to coliforms, and skin, eye, and ear infections all respond favourably to neomycin treatment, especially where other antibiotics fail.

Bovine Mastitis

Neomycin has been used with good effect in staphylococcal, streptococcal, and coliform mastitis, and about half the cases of Pseudomonas mastitis (Drury, 1952; Hinze, 1952; Breautigam, 1953; and Tucker *et al.*, 1953) but for normal therapy of the coccal forms of mastitis, penicillin is preferred. Neomycin/penicillin combinations containing 200 mg. of the sulphate and 200,000 units of penicillin sodium were preferred by Vigue (1954) instead of a neomycin/bacitracin combination.

There has been little clinical use of neomycin *parenterally* in animals, mainly because of the reported toxicity to the auditory nerve and the kidney (Hawkins *et al.*, 1953 (cat.); Waisbren *et al.*, 1950; Carr *et al.*, 1950 (man.)). However, in man, dosage of 1·0 G. per day for up five days has not caused more than transient signs of toxicity, if at all (Waisbren *et al.*, *loc. cit.;* Nesbit *et al.*, 1952; Schüler, 1955 and Roantree *et al.*, *loc. cit.*), yet bacteriological response has been good following intramuscular injection. Results have been particularly good in treating urinary infections which were resistant to other antibiotics. These reports should encourage the parenteral use of neomycin where response to other antibiotics is not apparent or not anticipated. Large doses are not required for urinary infection treatment, for Goodman *et al.* (1955) have quoted urinary concentrations of 100–200 μg. per ml. after 0·5 G. intramuscularly every four hours as compared with 10 μg. per ml. which gave such good *in vitro* activity in the sensitivity tests of Roantree and his colleagues (*loc. cit.*).

Orally, neomycin has been used experimentally in dogs, usually with complete elimination of *Bact. coli* (*Esch. coli*) from the fæces within 48

hours, though resistant strains appeared if dosing was continued (0·4 G. per kg. daily in four equal doses) for 5–6 days (Schweinburg *et al.*, 1952). This group of workers reported at the same time a diminution, in most cases, of the normal enterococci, *Ps. æruginosa*, and *Pr. vulgaris* population, but no reduction in the numbers of clostridia.

Similarly, oral dosage of neomycin in calves and piglets gave good results in the treatment of scours (Bicek, 1954), and McCarty (1953) used it in a fowl paratyphoid outbreak in goslings due to *Salmonella derby* with effects encouraging enough for him to suggest further investigation, especially as he gave only two doses of 50 mg. each, with an interval of eleven days between doses.

In man, oral dosing is used in the following manner to achieve pre-operative disinfection of the colon: the patient is fed on a low residue diet and a purgative given; this is followed by 1·0 G. neomycin sulphate every hour for four doses, and then by 1·0 G. every four hours for one to three days before surgery, but not longer than three days. The laxative effect of the neomycin produces slightly increased intestinal activity (N.N.R. 1955, p. 153 summarizing numerous reports in American literature). This provides a minimum administration of 9·0 G. and a maximum of 21·0 G. neomycin sulphate.

Topical applications usually contain 5 mg. neomycin sulphate per ml. or per gramme, in either aqueous solution or ointment form. The solutions are useful as wet dressings for wounds and eyes, whilst the ointment is useful for a wide variety of superficial conditions, including otitis, corneal ulcers, conjunctivitis and keratitis, furunculosis, abscesses, and dermatitis. It has been used mainly in small animals but similar conditions in farm animals also respond. Combined bacitracin and neomycin preparations are available giving almost complete coverage over the range of Gram positive and Gram negative bacteria. Occasionally fungicidal compounds are included in the applications.

Dosage. Parenteral dosage is problematical, but for small animals, in which the antibiotic is most likely to be used, the human dose of 1·0 G. daily in two to four equal doses given intramuscularly can be taken as a provisional maximum. Concentrations of more than 0·1 G. per ml. are painful on injection, though up to 25 per cent. solutions have been recommended.

Oral administration:

Horses and Cattle:	4·0–7·5 G.
Foals and Calves:	2·0–3·0 G.
Lambs and Young Pigs:	0·75–1·0 G.
Dog:	0·2–0·5 G.

These are all daily doses and should be divided into two to four equal doses given at regular intervals. Doses are not standardized and this list is only for general guidance.

Official Preparations

The United States Pharmacopœia contains the official powder, an ointment with not less than 3·5 mg. base (equivalent to approximately 5·0 mg. neomycin sulphate per gramme) and tablets which usually contain 500 mg. neomycin sulphate. British Official preparations are confined to the powdered sulphate but ointments and tablets are also available commercially.

Bacitracin

This antibiotic has an antibacterial spectrum which follows that of penicillin very closely; many penicillin resistant strains are susceptible to its action. The compound is official in both the British and United States Pharmacopœias and is one of the few antibiotics of clinical value derived from bacteria.

History

The discovery of bacitracin was announced in 1945 by Johnson and his colleagues, who noticed the bacteriostatic activity of a Gram positive sporulating organism derived from tissue removed during treatment of a compound tibial fracture. The organism was of the Bacillus group and the patient a Margaret Tracy: hence the name of the antibiotic 'bacitracin'.

Manufacture

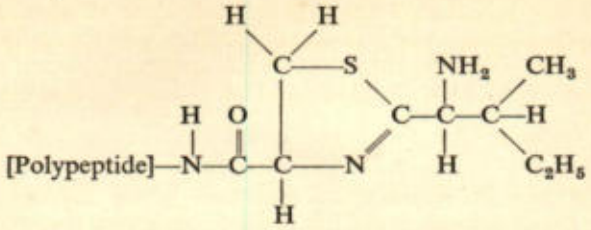
Originally prepared from surface cultures of *Bacillus subtilis* (some authorities say the organism is a strain of *B. licheniformis*) the manufacture now follows the general pattern and the deep vat culture method is used. The yield is dependent on the ratio of carbon to nitrogen in the nutrient medium and is greatest at a ratio of 15 : 1, soya bean meal, starch, calcium lactate and calcium carbonate being used as sources for essential elements (U.S.D., 25th Edit., 1955, p. 131). Purification proceeds through various stages including extraction by butyl alcohol, distillation under reduced pressure to remove the alcohol, clearing with charcoal, acidification and precipitation with salicylic acid.

Chemistry

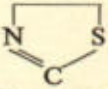
Bacitracin is a white to pale buff powder with sometimes a slight odour and a very bitter taste: the insoluble salts such as zinc bacitracin are almost without taste. The powder is hygroscopic and therefore soluble in water; it is partially soluble in ethyl and methyl alcohol and glacial acetic acid, leaving an insoluble residue. It is insoluble in acetone, chloroform, and ether. The purest form, which is used parenterally, must contain a minimum of 50 units per mg. antibacterial activity.

There are four substances present in the crude liquors obtained by fermentation. Three of these, bacitracins A, B and C, are active but the fourth, bacitracin F, is almost, if not entirely, inactive as an antibacterial agent.

Structurally, these substances are described as polypeptides which can be represented by:



Among the amino acids forming the peptide are phenylalanine, leuceine, glutamic acid, lysine, histidine, cysteine etc.

It will be noticed that the thiazolidine ring  present in penicillin is also present in bacitracin, and as penicillin may be considered as a condensed dipeptide these two antibiotics have been classed, together with polymyxin and the cephalosphorins (close relatives of penicillin), as the peptide antibiotics.

Stability

Bacitracin is slightly more stable than penicillin but is still less stable than most of the newer antibiotics.

1. *Moisture.* The dry powder is stable at room temperature when dry and will maintain its potency for 15 months at 37°C. Solutions deteriorate rapidly at room temperature but retain 90 per cent. potency when kept refrigerated for 2–3 months.
2. *pH.* The optimum pH of solutions is between pH 5 and 7.
3. *Temperature.* As already inferred the dry powder is stable at normal working temperatures but should the temperature be raised above 30°C. deterioration occurs and is rapid at 56°C. All solutions once made should be used immediately or refrigerated.
4. *Oxidizing agents.* All oxidizing agents destroy bacitracin.
5. *Miscellaneous.* Heavy metals and their salts will precipitate and inactivate bacitracin, though it is suggested that in some cases precipitation is not accompanied by inactivation; zinc is one of these. Some organic acids will inactivate the antibiotic; tannic, benzoic, and salicylic acid are three such acids. High concentrations of sodium chloride are also incompatible with bacitracin solutions owing to precipitation.

Pharmacology

Absorption and Administration Routes. Bacitracin is similar to streptomycin in that almost no absorption takes place following oral dosing or inhalation, and consequently systemic infections can only be treated by

parenteral injection. Parenteral injections may be given by any of the normal routes but the intramuscular route is the commonest for veterinary purposes. Following intramuscular administration, absorption is slightly slower than with penicillin; however, excretion is by glomerular filtration and is therefore slower than penicillin so that blood levels are higher and persist longer than with penicillin. Some toxicity occurs, partly due to impurities in the antibiotic produced by the initial manufacturing methods, but also due to the polypeptide nature of the antibiotic and until recently the main use in man has been for topical application. This is also true in animals.

Blood Levels. Maximum blood levels may take up to two hours to be achieved and adequate levels may be maintained for six to eight hours depending on dosage and administration route.

Barriers. Following intramuscular injection, bacitracin will penetrate into most tissues of the body, but therapeutic amounts do not accumulate in either the pericardial or cerebrospinal fluid (Zintel *et al.*, 1949). Any infection which develops in a body cavity, though bacitracin passes freely into pleural and ascitic fluid, should be treated by injections directly into the cavity. Little absorption occurs from the intestines or lungs, or from topical applications.

Excretion. Almost all of any absorbed bacitracin is excreted by the kidneys at the rate of glomerular filtration (Eagle *et al.*, 1947). Most of any oral dose is destroyed in the intestines (Scudi *et al.*, 1947).

Toxicity. Bacitracin, in the early days of production, was strongly nephrotoxic but since purification has been improved these effects have been reduced sufficiently to allow normal parenteral dosing, providing there is no renal impairment already present. It is advisable to check for albuminuria from time to time when parenteral treatment is being used. Bacitracin is virtually non-toxic when administered orally or topically.

Action. The main antibacterial activity of this antibiotic is due to the bacitracin A component. Bacitracin is a bactericidal antibiotic, the speed of bactericidal action being directly proportional to its concentration, and therefore to its dose. Its activity is unaffected by blood or tissue breakdown products. The mode of action is not known but, though bacitracin is synergistic with penicillin (Eagle *et al.*, 1948, Bachman, 1949) and therefore might be thought unlikely to work in a similar manner, it would appear that bacitracin also interferes with cell wall formation.

Antibacterial Spectrum. Bacitracin is a narrow-spectrum antibiotic and is active against a range of organisms similar to that affected by penicillin. In some cases clinical response is not as good as with penicillin, but frequently bacitracin is active against penicillin resistant organisms. The drug is thus effective against most Gram positive cocci, ærobic or anærobic, Gram positive rods and some spirochætes. It has also been found of value

against intestinal amœbiasis in man. Most, but not all, Gram negative bacteria are unaffected by bacitracin at normal dosage levels.

Bacterial Resistance. The sensitivity of an organism to bacitracin is not related to its sensitivity to other antibiotics such as penicillin and the broad-spectrum antibiotics (English, 1956), so that it can be used where these fail, and *vice versa*. So far, no bacterial resistance to bacitracin of any clinical significance has been reported although it is known that bacterial resistance to bacitracin does exist in human pathogens (Meleney *et al.*, 1949) for, of a series of 237 cultures examined, 122 were susceptible to both penicillin and bacitracin, 104 were resistant to penicillin but sensitive to bacitracin, and only 11 were sensitive to penicillin but resistant to bacitracin.

Diseases and Bacitracin Therapy. So far, bacitracin has not been widely used for veterinary purposes in Great Britain but is becoming increasingly popular for local application.

Bovine Mastitis. Bacitracin has been used in bovine mastitis (Benson, 1947, 1948; Hershman, 1950), but seems to have no advantage over penicillin, and the synergistic action demonstrated *in vitro* has not materialized *in vivo* (Jones, 1954).

Specific Systematic and Organic Diseases.

Pasteurellosis

Transit fever of cattle and sheep has been treated with bacitracin (Thomas *et al.*, 1951; Martin, 1951 and 1952; Prier *et al.*, 1953 (sheep)), Martin reported on bacitracin used in conjunction with penicillin: rapid clinical responses followed subcutaneous injections of 5000 units bacitracin and 1·0 mega unit procaine penicillin intramuscularly in calves under 1 year old, and double the amount of bacitracin with 1·2 mega units penicillin in animals over 1 year; a second injection twelve to twenty-four hours later was required in some cases. In sheep, 20,000 units intramuscularly on two successive days have given good results.

Erysipelothrix Infection

Infections in turkeys have responded to intramuscular doses of 5000 units repeated in 24 hours (Klussendorf, 1953, 1955).

Non-Specific Systemic Diseases. Bacitracin has been used occasionally in dogs for systemic infections at the rate of 500 units per lb. (1100 units per kg.) body weight without any signs of toxicity (Rose, 1950).

Intestinal Conditions.

Vibriosis

Dysentery in pigs due to Vibrio infections has shown good clinical response to 100,000 units bacitracin given orally every day for six days to animals

of up to 100 lb. (5 score or approx. 45·0 kg.) bodyweight (Boley *et al.*, 1951). It was pointed out by Klussendorf (1953 and 1955) that 50,000 units for four days, though it would give clinical response, would not give a bacteriological clearance of the gut; he also showed in these limited trials that bacitracin with either sodium arsenilate, neomycin, or penicillin was effective.

The antibiotic is also used in dogs, cats, and poultry in the treatment of diarrhœas. It has been used as a feed supplement at the rate of 1·0–10·0 G. per ton of food in chickens and turkey poults, with good effect on growth (Braude *et al.*, 1953). Klussendorf (1952) also reports effective growth response and better food conversion in pigs when given bacitracin supplemented food.

Topical Applications. Bacitracin was initially restricted to topical application because of the nephrotoxic action of the impurities. Since purification, the initial work on topical application has maintained a prejudiced and preferential usage externally and it is widely used for all types of external infections usually in conjunction with neomycin sulphate. Bacitracin has been of value in the treatment of infectious keratoconjunctivitis of cattle when applied in ointment form (Freeland, 1951). It is very effective for skin surgery, for infected wounds, fistulæ, abscesses, and furunculosis. It has also been used with good results in *otitis externa* of dogs and cats, for ocular and nasal lesions, and for teat infections and surgery in cattle.

Dosage. No standard dosages have been agreed upon, but the following will serve as a guide.

Intramuscular injection:

Horse and Cow (over 200 lb.):	10,000 to 20,000 units daily.
Sheep:	100 units per lb. (220 units per kg.) body weight daily.
Dog:	50 units per lb. (110 units per kg.) body weight daily.

These doses are preferably given divided into 12-hourly injections, but have frequently been given as a single daily dose.

Oral Administration:

Pigs:	Up to 20,000 units daily.
Dogs:	Up to 5000 units daily.

Topical Application:

For normal skin and ear infections, ointments and solutions containing 250 to 1000 units per gramme or per ml. are used. The official United States Pharmacopœia ointment contains 500 units per gramme.

Maximum doses used without *observed* toxicity are as follows (U.S.D. 25th Edit. p. 1948).

Horse:	50,000 units twice daily for 7 days (intramuscular injection).
Cow:	16,000 units three times at 12-hourly intervals (subcutaneous injection).
Sheep	60,000 units (intramuscular injection).
Pig:	100,000 units daily (oral dosage).
Dog:	450 units per lb. (1000 units per kg.) body weight daily for 5 days (intramuscular injection), 30,000 units (oral dosage).
Turkeys:	5000 units repeated in 24 hours (intramuscular injection).

Official Preparations. Apart from the powder, the only other official preparation is the ointment containing 500 units per gramme in an anhydrous paraffin base. Both are official in the United States Pharmacopœia but only the sulphate as a powder appears in the British Pharmacopœia.

Polymyxin B

This is the least toxic of five antibiotics known as the polymyxins and designated alphabetically A to E. It is a narrow-spectrum antibiotic with activity against Gram negative organisms. Polymyxin B Sulphate is official in the British Pharmacopœia 1958, in the British Pharmaceutical Codex 1954, Supplement 1957, as well as in the United States Pharmacopœia. The antibiotic contains not less than 6000 units in each mg.

In 1947 three groups of workers, two American and one British simultaneously announced the discovery of a new type of antibiotic, later known as the polymyxin group (Stansly *et al.*; Benedict *et al.*; Ainsworth *et al.*). The compounds discovered by the two American groups proved to be identical and by agreement the substance was called Polymyxin D whilst Polymyxin A was the name given to the compound, originally named Aerosporin, discovered by the British workers. Three more antibiotics were subsequently discovered, among them Polymyxin B (Aerosporin is now used as a trade name for Polymyxin B).

Manufacture

Polymyxins are produced by the usual deep vat culture method using *Bacillus polymyxa* (*ærosporus*). Many different strains of the organisms are used and fermentation conditions must be adapted to the requirements of individual strains. Several medium supplements such as yeast extract are used.

Chemistry

Polymyxin B sulphate is a white or creamy white powder with little or no odour. It is very soluble in water and normal saline but less so in methyl and ethyl alcohol and is insoluble in ether, chloroform, acetone, and hydrocarbons.

The structure of the polymyxins is not completely known but they are

considered to be similar to bacitracin in that they are polypeptides, and complex polypeptide structures have been provisionally assigned to them (Newton and Abraham, 1958). They are basic in character and form acid salts.

Stability

Polymyxin B sulphate is a relatively stable compound.

1. *Moisture.* In the dry state this antibiotic will remain stable for long periods. Solutions are stable for at least six months when refrigerated and can be heated without loss providing the pH is optimum.
2. *pH.* Polymyxin is stable in near neutral solutions (pH 5–7), but strong acids, and alkalis destroy the potency very rapidly.
3. *Temperature.* The antibiotic, though classed as thermostable, will not withstand autoclaving and solutions must be sterilized by filtration.
4. *Oxidizing agents.* Though no information on this point is given in official monographs it may be assumed that such compounds will have a deleterious effect (cf. polypeptide bacitracin).
5. *Enzymes.* No anti-polymyxin enzyme has so far been reported.
6. *Miscellaneous.* All bivalent metallic ions block the action of polymyxin by interfering with its absorption by the bacteria, so that magnesium, cobaltous, ferrous and manganous ions, for example, should not be used when formulating compounds containing polymyxin (Newton, 1953). This blocking effect can be partly reversed by citrate ions.

Pharmacology

Absorption and Administration Routes. Polymyxin B sulphate is another antibiotic which is normally not absorbed from the intestines, but Brownlee *et al.* (1952) reported its absorption from the intestines in the new-born. This possibility should be considered when treating very young animals. Parenteral injections must therefore be given to obtain systemic activity. Absorption from either subcutaneous or intramuscular sites is at approximately the same rate as penicillin. The toxicity of the compound, as well as its expense, make polymyxin unsuitable for routine veterinary parenteral use, but if it is used, a course of treatment should not continue for more than a few days. Topical application and oral administration are more commonly used routes.

Blood Levels. As absorption is similar to penicillin, blood levels are achieved fairly rapidly following parenteral administration and are maintained for four to six hours. The antibiotic circulates mainly in the plasma and is not absorbed by the cells. Four-hourly dosage results in cumulation and the development of high blood levels, as high as 26 units per ml. being observed by Brownlee *et al.* (*loc. cit.*) in man. The daily dose of polymyxin in man is given in four equal doses at six-hourly intervals.

Barriers. Polymyxin B does not penetrate the blood-brain barrier and meningitis must therefore be treated by intrathecal injection (30,000–50,000

units once or twice daily in a concentration of 30,000 units per ml. normal saline is usual in human medicine). It is not absorbed from the intestines or skin.

Excretion. Very little polymyxin is excreted unchanged either by the kidney, bile or fæces: only 0·3 per cent. of a 10,000 unit intramuscular dose was recovered in an active form from a dogs urine over a 24 hour period. This makes it necessary to give relatively large doses parenterally to obtain active levels in the urine. Almost the whole of any oral dose is destroyed in the alimentary canal and only small amounts are recovered from the fæces in an active form.

Toxicity. The toxic effects of the polymyxins are of three types.

1. *Neurotoxic* effects including loss of the sense of balance and of skin sensation in the head and extremities with muscular weakness have been reported in man.
2. *Nephrotoxic* effects with albuminuria, renal casts, and in severe cases hæmaturia and pyuria are also seen and the non-protein nitrogen content (urea, etc.) of the blood increases. As little as 2·5 mg. per kg. given intravenously as a single dose will cause acute renal damage in the dog.
3. *Local* pain and swelling is often experienced at the site of injection, necessitating the use of procaine simultaneously with the antibiotic injection.

All symptoms are reversible and regress when dosing is stopped, providing the doses have not been excessive. Currently manufactured polymyxin B sulphate is far less toxic than that originally produced. When applied topically, concentrations of less than 1 per cent. are non-irritant. So far neither acquired bacterial resistance nor skin sensitivity have been seen clinically.

Actions. Polymyxin B sulphate is a bactericidal antibiotic, the mode of action being as yet unknown. It is synergistic with oxytetracycline (Neter *et al.*, 1952) only ½–1/16 of the normal dose of each being required when used in combination. *In vitro* synergism has also been shown with chloramphenicol and, to a lesser degree, with neomycin against 72 strains of Salmonella (Manteu *et al.*, 1956). Topical action is often improved by combining polymyxin with neomycin or bacitracin. The combination of oxytetracycline with polymyxin B has been widely used in the treatment of mastitis.

Antibacterial Spectrum. Polymyxin is a narrow-spectrum antibiotic with an activity entirely limited to the Gram negative bacteria. *Bact. coli* (*Esch. coli*), *Aerobacter ærogenes* (*B. ærogenes*) and related species, Hæmophilus and Klebsiella species, and *Ps. æruginosa* (*Ps. pyocyanea*) are all susceptible *in vitro* to concentrations of 0·05 to 2 μg. per ml. (0·3 to 12 units), although Roantree *et al.* (1956) used 5 μg. as their standard for

polymyxin when comparing the relative activity of seven different antibiotics against 1698 strains of clinically important bacteria. Activity against Proteus species was comparable with that against *Bact. coli*, but inferior to that of neomycin. Wright *et al.* (1954) have expressed an opinion that polymyxin is the most active antibiotic against Pseudomonas species, which is supported by the work of Roantree *et al.* (*loc. cit.*), although several workers, including Huebner and his colleagues (1956), have disputed this activity against Pseudomonas. It is probable that some depressant factor in the culture medium has been involved (Price *et al.*, 1956) and Sherwood *et al.* (1954) suggested that strains of Pseudomonas reported as being resistant could not have been tested correctly.

Diseases and Polymyxin Therapy. This antibiotic has not been used extensively on its own in Great Britain, but in conjunction with oxytetracycline considerable amounts have been used both for intramammary injection and for topical application. In both applications the use of polymyxin has been particularly directed against species of Pseudomonas, mainly *Ps. æruginosa* (*Ps. pyocyanea*).

Bovine Mastitis

Polymyxin B sulphate is effective in many cases of mastitis due to *Ps. æruginosa* (*pyocyanea*), particularly when combined with oxytetracycline, but the combination is not always successful in such cases (Lambardt, 1956). The two antibiotics have also been used effectively in a few cases of mastitis due to Klebsiella species (Barnes, 1954).

Semen Additive

Polymyxin has been used in bulls semen which contained Pseudomonas organisms; 50 μg. per ml. diluent was sufficient to inhibit the growth of the organisms. The addition of polymyxin along with penicillin and streptomycin was sufficient to eliminate all contaminating bacteria (Baier *et al.*, 1955). The same workers also reported that preputial irrigation with polymyxin eliminated Pseudomonas organisms from 13 bulls, though 7 were reinfected later.

Septicæmia

Five litters of puppies with a septicæmia attributed to *Ps. ærogenes* (*pyocyanea*) contracted by suckling were successfully treated by polymyxin B (Mosier, *et al.*, 1956).

Topical applications have been especially useful in *otitis externa* in dogs, intramammary formulations containing oxytetracycline and Polymyxin B being a popular form of application. English (1956) reports the recovery of one out of three cases of otitis due to Pseudomonas treated at the Queensland Veterinary School with 0·1 per cent. aqueous solutions of polymyxin B.

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Dosage

No standard dosages have been agreed upon. The human daily doses are 15,000 to 25,000 units per kg. body weight divided into four equal six-hourly doses. For children, the daily dose should not exceed 20,000 units per kg. Intrathecally the doses are 50,000 units and 40,000 units respectively, given once or twice daily. Doses of 30,000 units per kg. have caused a temporary nephritis.

Note that intramuscular injection of Polymyxin E has caused severe reactions in horses (McCollum *et al.*, 1951) and that 1 per cent. procaine is frequently used as a diluent for intramuscular injections. Procaine should not be used for intrathecal injection.

Topical applications in ointment or aqueous solution form are usually of a 0·1 per cent. strength.

Official Preparations

Only the powder of Polymyxin B Sulphate is official in the British publications but the United States Pharmacopœia contains an official tablet of a 500,000 unit potency.

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CHAPTER 30

ANTIBIOTICS

(vii) MISCELLANEOUS

ALMOST daily the discovery or marketing of new antibiotics is announced. Many of these promise to have veterinary applications but so far few of them are available for such use in Great Britain and many are so expensive as to be grossly uneconomic. Amongst the more important of these are tetracycline, erythromycin, carbomycin, cycloserine, nystatin, novobiocin, puromycin, griseofulvin, and viomycin, but many others such as subtilin, framycetin, spiramycin, oleandomycin, and vancomycin have received attention. Undoubtedly as production of these compounds increases prices will decrease, so that a few details of the more promising examples of different types may be useful.

Tetracycline

This is a broad-spectrum antibiotic with similar but not identical activity to that of oxytetracycline and chlortetracycline, which are its derivatives. It is official in the British and United States Pharmacopœias and the British Pharmaceutical Codex 1954 Addendum 1957. Tetracycline Hydrochloride must contain not less than 900 units per mg.

History

This antibiotic was discovered independently and in two different ways by three groups of research workers in 1953. Two of the groups arrived at it by the study of degradation products and derivatives of oxy- and chlortetracycline, whilst the third group produced the compound biosynthetically. It is known commercially either as Achromycin or Tetracyn, and is used as the hydrochloride (*Note:* Achromycin should not be confused with puromycin, an antibiotic produced biosynthetically by *S. albo-niger* and originally named Achromycin).

Manufacture

Tetracycline is produced commercially by catalytic reduction of the oxy- or chlor-tetracycline derivative. The hydrochloride is obtained by acidifying a solution of the base in *n*-butylalcohol.

Chemistry

Both the amphoteric base and the hydrochloride are yellow, odourless, crystalline powders. The base is slightly soluble (1 in 2500) and the

hydrochloride fairly soluble (1 in 10) in water. Both base and hydrochloride are almost insoluble in organic solvents but dissolve readily in dilute acids or alkalis. The hydrochloride is slightly hygroscopic and solutions become turbid due to hydrolysis and precipitation of the base.

The graphic structure has already been given (see Oxytetracycline).

Stability and Pharmacology

With a solubility slightly less than oxytetracycline (*q.v.*), tetracycline is more stable in solution; it is superior to chlortetracycline in both these aspects.

Tetracycline may be given by all the normal routes but absorption from the gastro-intestinal tract is better than from an intramuscular injection. Blood levels are slightly higher and are maintained longer than those following equal doses of the other two members of the group. Distribution is similar though higher levels are achieved in the cerebrospinal fluid when the meninges are abnormal; urine and bile excretion is high. The antibiotic passes the placental barrier and achieves milk levels of ¼ to 2/3 that of the blood in humans (Posner *et al.*, 1955). Blood and tissue fluids do not inactivate tetracycline.

Resistance to tetracycline occurs in the same way as with the other tetracyclines but, though cross resistance does occur, tetracycline will occasionally give a good result where the other two have failed. However, where resistance has occurred to one of the tetracyclines, an entirely unrelated antibiotic should be used in preference to another of the tetracycline group. According to experiments *in vitro* by Manten (1956), tetracycline is synergistic with streptomycin but usually antagonistic to penicillin when tested against staphylococci. There was no interaction with chloramphenicol or erythromycin.

Actions and Uses. The effects of tetracycline are similar to those of oxytetracycline and chlortetracycline, but variations do occur and tetracycline may prove on the whole to be slightly more active than either of the other two. Toxic side actions are similar but occur less frequently. The number of reports on the clinical use of tetracycline are increasing but much clinical investigation still remains. *Pasteurellosis:* transit fever in cattle, sheep, and pigs responded to two intramuscular injections at the rate of 2·0 mg. per lb. (4·4 mg. per kg.) bodyweight given with a 24 hour interval. Eleven out of twelve cows, twenty-one of twenty-two pigs, and eleven of fifteen sheep recovered (Johnson, 1955).

Leptospirosis: Ringen *et al.* (1956) found that single daily intramuscular injections of tetracycline at the rate of 2·5 and 5·0 mg. per lb. (5·5 to 11·0 mg. per kg.) successfully eliminated *Leptospira pomona* from the urine of five experimentally infected cattle when given for five days. Lower concentrations were not successful. Howarth (1956) used 3·0 mg. per lb. (6·6 mg. per kg.) body weight intramuscularly in pigs to treat *L. pomona*

carriers in a herd of pigs. The injections were continued for five days and were highly successful.

Vibriosis in sheep was treated with single 1·0 G., 0·5 G. and 0·25 G. doses intramuscularly but, as with oxytetracycline and dihydrostreptomycin, it did not influence abortion, even though blood levels were maintained for a period three times longer than with oxytetracycline and the vibrios were susceptible *in vitro* (Ryff *et al.*, 1956).

Anaplasmosis carriers were very successfully treated with tetracycline at the daily rate of 5·0 mg. per lb. (11·0 mg. per kg.) body weight by both intravenous and intramuscular injection: intramuscular treatment daily for ten days was recommended (Pearson *et al.*, 1957).

Virus diseases have also responded favourably to the virustatic action of tetracycline.

Virus pneumonia of pigs will not affect animals given tetracycline orally as a prophylactic measure at the rate of approximately 73·0 mg. per lb. (160·0 mg. per kg.) daily even if experimentally challenged, and approximately 23·0 mg. per lb. (50·0 mg. per kg.) body weight will prevent natural infection (Lannek and Börnfors, 1956).

Feline influenza virus did not attack chick embryos even when administration of tetracycline was delayed until 12–24 hours before the embryo would normally be expected to die following experimental infection. However, once the virus was removed from the antibiotic's influence it again multiplied freely, indicating a virustatic action (Katz, 1956). This emphasizes the need for supportive treatment in clinical cases to assist the animals own system to destroy the virus.

Goat pneumonia virus also responds to tetracycline (Ishii *et al.*, 1955) and also contagious pleuropneumonia of goats (Biswal *et al.*, 1957).

Dosage

The daily intramuscular dose of tetracycline recommended commercially consists of

Horse, Cow, Sheep and Pig:	1·0–2·0 mg. per lb. (2·2–4·4 mg. per kg.)
Dog and Cat:	2·0–5·0 mg. per lb. (4·4–11·0 mg. per kg.)

Doses should be diluted to a strength of 50·0 mg. per ml. and doses of more than 0·5 G. total should be divided and injected into several different sites. All doses should be given by deep intramuscular injection.

Official Preparations

The United States Pharmacopœia includes tetracycline base, the hydrochloride, capsules, tablets and an oral suspension. The British Pharmacopœia and the 1957 Addendum of the B.P.C. 1954 recognize the hydrochloride only, but the B.P. also recognizes an intravenous and an intramuscular injection, tablets and capsules.

These forms are available commercially; an intravenous injection buffered with ascorbic acid, an intramuscular injection, a 3 per cent.

topical ointment, an eye ointment and eye drops (as a powder for solution when required), and several flavoured oral preparations are all suitable for veterinary use though not specifically designed for veterinary purposes.

Carbomycin

This antibiotic belongs to a large group of antibiotics known as *the macrolides*. They are so called to indicate that each member contains a large lactone ring; this ring is linked glycosidally with one or more complex sugars. As a group they have a range of activity similar to penicillin but have the advantage of being active against organisms resistant to penicillin or the tetracyclines. Erythromycin, the spiromycins, and oleandomycin are other examples of the group.

Carbomycin was announced in 1952 and is known commercially as Magnamycin. It is active against Gram positive cocci, rickettsiæ, some protozoa and some viruses. It is manufactured biosynthetically using an actinomycete mould, *S. halstedii*. Its structure is complex, consisting of a large seventeen membered ring to which are attached two sugars, *mycaminose* and *mycarose*, and the empirical formula is $C_{42}H_{67}O_{16}N$. The antibiotic is a monobasic white crystalline substance which readily forms acid salts. The hydrochloride is normally used and this is soluble to the extent of 10–13 per cent. in water. The dry powder is stable, but aqueous solutions deteriorate over a period, losing 25 per cent. potency after 3 weeks at 4°C. *Absorption* from the intestines is variable, but it is approximately equal to that obtained from an intramuscular injection. *Blood levels* are not high but tissue levels are better than blood levels would suggest. The *blood-brain barrier* and *placental barriers* are resistant to carbomycin and peritoneal diffusion is not easily achieved. About 10 per cent. of a single dose is *excreted* in the urine but levels are not high, bile concentrations being greater than either serum or urine levels.

Bacterial resistance develops rapidly in a step-like manner and shows complete cross resistance with erythromycin. Carbomycin has been successfully used in conjunction with neomycin and oxytetracycline.

Present information indicates almost *no toxicity*.

Carbomycin has not been used very widely in veterinary medicine, probably because the resistant organisms for which this antibiotic is mainly indicated do not occur commonly as yet. Antyles (1954) used the compound for enteritis and metritis in dogs which had not responded to other chemotherapeutic treatment, and for upper respiratory infections in dogs and cats, possibly associated with viruses. He was impressed by the clinical results but the work was not supported by bacteriological evidence. Nevertheless, it was apparent that though the viruses were not affected, any secondary invaders resistant to routine antibiotics may well respond to this antibiotic. This is supported by a report from Hawley and Downing quoted in the U.S.D. p. 1565. Its use as an oral feed supplement at the rate of 2·0 G. per ton is suggested in a report by

Reynolds *et al.* also quoted here. This last use is to be deprecated because of the rapidity with which resistance develops.

Note: Confusion has arisen between Carbomycin and Erythomycin which, though similar in many respects, are *not the same antibiotic* under two different names.

Dosage. Antyles (*loc. cit.*) used for the dog and cat daily doses of 15·0–30·0 mg. per lb. (33·0–66·0 mg. per kg.) body weight in divided oral doses. The antibiotic is available commercially in tablets of 0·1 G. and 0·25 G. under the name of Magnamycin.

Erythromycin

This antibiotic, with an activity against most Gram positive bacteria, some Gram negative bacteria, many rickettsiæ and some viruses, as well as activity against some protozoa, is very similar to carbomycin. It is official in the United States Pharmacopœia and in the British Pharmacopœia and the 1957 Addendum to the British Pharmaceutical Codex. It must contain not less than 850 units per mg. and is known commercially as Ilotycin.

Erythromycin was first announced in 1952 when it was obtained biosynthetically from the growth of cultures of *Streptomyces erythreus* isolated from soil samples taken in the Philippines. *Manufacture* is by normal deep culture fermentation and extraction according to established principles. The antibiotic is a white or yellowish white crystalline powder which is odourless and has a bitter taste. Its *solubility* is 1 in 1000 in water but it is freely soluble in alcohol and ether. Various *salts* and esters are available, the solubilities of which differ so that some are suitable for intravenous or intramuscular injection whilst others may only be used orally.

The *constitution* of erythromycin is similar to that of the other microlide antibiotics. Its lactone ring contains 14 atoms and the two sugars attached to the ring are *desosamine* and *cladinose*: the empirical formula is $C_{37}H_{67}O_{13}N$.

The *stability* of erythromycin compares favourably with other antibiotics. As a dry powder it is quite stable at room temperature and refrigerated or frozen solutions do not lose their activity even on prolonged storage (at least 8 weeks), although at room temperature or higher quite rapid deterioration occurs.

Erythromycin is *absorbed* rapidly when administered orally and, as with intravenous or intramuscular dosage, diffusion occurs into most tissues and fluids. The *blood-brain barrier* is not readily passed when the meninges are normal. Diffusion occurs across the placenta and into the pleural and peritoneal cavities. The base is partially destroyed by the gastric acidity and oral forms must either be acid resistant, as with the stearate, or tablets must have an acid resistant coating. *Excretion* is mainly via the kidney, and excretion concentrations are higher than for

chlortetracycline at all times, and higher than those of oxytetracycline in the first few hours following administration only. Very high concentrations can be achieved in the urine. Some excretion via the bile occurs and concentrations far higher than those of plasma are achieved. The toxicity is low and similar to carbomycin in that the nausea and gastro-intestinal disturbances in carnivores are rare. The *action* of erythromycin is similar to that of carbomycin, and it has been recommended in human medicine that its use be restricted to the control of Gram positive organisms which resist penicillin (mainly staphylococci). *In vitro* tests indicate that 'stepwise' development of resistance occurs in a manner similar to penicillin, though *in vivo* resistance develops rapidly. Cross resistance occurs with carbomycin but not with other antibiotics.

Erythromycin has not been widely used in veterinary medicine and few reports are available. It would appear to be effective against the secondary invaders concurrent with virus diseases and pyogenic infections of small animals. *Leptospira icterohæmorrhagiæ* infections of laboratory animals have responded favourably. Streptococcal and staphylococcal diseases of large animals may also respond more favourably than to antibiotics with a broader spectrum.

Dosages are speculative.

Oral administration. (Erythromycin base).

Dog: Approx. 5·0 mg. per lb. (10·0 mg. per kg.) body weight three or four times daily.
Cat: 200 mg. daily in three to four equal doses.

Parenteral administration (Lactobionate or glucoheptonate).
Intravenous injection:

Horse and Cow: 0·5 to 1·0 G. every 12 hours
Sheep and Pig: 0·1 to 0·3 G. every 12 hours.

For *intramuscular* injection, twice these doses have been used in the farm animals and 2·5 mg. per lb. (5·0 mg. per kg.) body weight in dogs.

Official preparations include the base as a powder and 100·0 mg. tablets. *Commercially* the official forms are available, also an oral suspension of the ethyl carbonate ester, vials containing 0·25 G. of the base as glucoheptonate for intravenous injection, vials containing 0·3 G. and 0·1 G. of the base as lactobionate for intravenous or intramuscular injection, and an oral suspension and tablets of erythromycin stearate.

Novobiocin

Novobiocin is a medium-spectrum antibiotic with marked bacteriostatic and bactericidal action against Gram positive organisms. In this it is therefore similar in action to carbomycin and erythromycin. It is known commercially under the names of Albamycin (not to be confused with a

Russian discovered antibiotic generically named albamycin), Biotexin, Cathomycin, Cathocin and Cardelmycin (crystallinic acid). It was also known as streptonivicin.

The antibiotic, announced in November 1955, is manufactured biosynthetically from at least two actinomycetes, *Streptomyces niveus* and *S. spheroides*. It is a dibasic acid but is marketed as a light yellow amorphous monosodium salt or as a purer half-neutralized calcium salt. Though it is more soluble in alkaline solution it is more stable when in acid solutions.

Novobiocin reacts on administration in a similar manner to the tetracyclines. It is thus rapidly absorbed and therapeutic blood levels can be achieved following oral, intravenous, intramuscular and intraperitoneal administration. Serum levels are maintained for at least eight hours following a single oral dose but no appreciable penetration of the blood-brain barrier occurs. *In vitro* studies have shown high degrees of activity against Gram positive cocci, including most strains of staphylococci (micrococci). Sensitive Gram negative organisms include species of Proteus, Pasteurella, Salmonella and Klebsiella genera. There is a tendency to develop resistance during therapy as with erythromycin, and investigations are in progress to find combinations of such antibiotics which will overcome this problem.

Toxicity in man is relatively mild with the exception of a very small percentage of skin reactions and pruritis.

Clinically in man and animals, various streptococcal and staphylcoccal conditions have responded favourably: anthrax, mastitis and cellulitis have also shown good responses.

Oral doses of 1·0–2·0 G. per day have been given in man which are approximately equivalent to 0·5 to 1·0 G. in small animals. Recently an intramammary preparation containing 0·25 G. novobiocin has been marketed in Great Britain.

Puromycin

Puromycin was discovered in 1952 and is a product of the fermentation of *S. albo-niger* and initially called achromycin; this name is now discontinued as a generic name. The antibiotic is a purine derivative of known structure.

The importance of puromycin is its demonstrated action in mice against *Trypanosoma equiperdum* and *T. cruzi*, the causes of dourine in equines and trypanosomiasis of man in Brazil, respectively. It is also active against Entamœba and, perhaps of most interest, against certain glandular tumours in mice—mammary adenocarcinomata. Its antibacterial activity is not exceptional. Puromycin activity is thought to be due to interference with the synthesis of nucleic acid or nucleoproteins at a stage in the metabolism which varies in different tissues and systems.

Toxicity is not high and the main side action is emesis, irrespective of the route of administration.

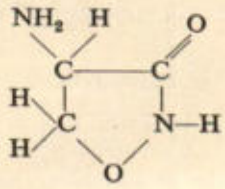
Viomycin

Viomycin was discovered independently in 1950 by laboratories of two different commercial organizations. It is elaborated in submerged culture fermentation by an actinomycete now named *S. puniceus*. It is a basic polypeptide of unknown structure. The sulphate and hydrochloride, which are readily soluble in water are used clinically. Solutions are reasonably stable in acid solution but deteriorate rapidly in alkaline solutions; at pH 2 aqueous solutions lose no activity in 24 hours at 25°C. and will withstand boiling at 100°C. for fifteen minutes.

The most important indication for viomycin is its activity against tuberculosis caused by streptomycin sensitive or resistant organisms. It is therefore of use in streptomycin sensitive patients and for cases caused by resistant strains; these may number as high as one in every three or four cases of human tuberculosis. Toxicity is moderate and concerns electrolyte metabolism, kidney function and hæmopoiesis. Its veterinary application in the treatment of acid fast infections remains to be seen.

Cycloserine

Cycloserine was discovered in 1954 by two different laboratories using two different organisms. It is known commercially as Oxamycin and Seromycin. The two actinomycetes concerned are *S. orchidaceus* and *S. garyphalus*; they elaborate the antibiotic in submerged culture fermentation. The antibiotic is soluble in water to the extent of 1 : 10; acid and neutral solutions are unstable but alkaline solutions are stable. The structure is simple and is represented by:



Absorption following oral or parenteral administration is fairly rapid and maximum blood levels are achieved in 3–4 hours—cumulation may occur during the first three days of treatment. The antibiotic diffuses throughout the body tissues and appears to diffuse readily into the cerebrospinal fluid—levels almost equal to those in the blood can be achieved.

Excretion is mainly by the kidneys and high urine levels are achieved so that urinary infections can be effectively treated. Over 60 per cent. of any single dose, following oral or intramuscular administration, can be recovered from the urine unchanged. Very little is excreted in the fæces

and approximately 35 per cent. must be destroyed in the intestines or metabolized in the body.

Cycloserine is only moderately active *in vitro*, but *in vivo* tests show that its broad-spectrum activity is greater than the *in vitro* tests would indicate. Its main value, however, is its action against acid fast organisms but insufficient work has so far been carried out to make a true assessment possible. *Toxicity* appears to be low, particularly when the daily dose is divided; toxic symptoms are of a nervous type, mainly taking the form of convulsions. Synergism occurs with iso-nicotinic hydrazide (Isoniazid). Its value would appear to be similar to that of viomycin in the treatment of tuberculous cases which do not respond to normal therapy or are allergic to streptomycin. Veterinary use has not been reported and it is possible that the low fæcal level may detract from its value for Johne's disease.

Nystatin

Nystatin is significant for its antifungal properties. Known originally as fungicidin and available commercially as Mycostatin, this antifungal compound discovered in 1949 is elaborated by an actinomycete *S. noursei*. It is unique amongst antibiotics in that it can be extracted from the mycelium as well as from the fermentation liquor. The antibiotic is only slightly soluble in water, but soluble in organic solutions containing 10–20 per cent. water. Solutions are relatively unstable, being destroyed by heat, light, oxidation, and extremes of pH. At room temperature about 50 per cent. potency is lost in 5 days. The dry powder is stable for about six months when refrigerated in sealed ampoules or vials.

Toxicity is rare and mild, taking the form of gastro-intestinal disturbances. Dogs will tolerate 900 mg. per kg. body weight for prolonged periods without showing any ill effects.

The main indication for using nystatin is for its action against yeasts and similar fungi. It is used in conjunction with the tetracyclines to offset the excessive growth of yeasts during broad-spectrum therapy. It may assume considerable importance for the treatment of fungal skin diseases.

Dosage in man has been about 500·0 mg. orally two to four times daily. The yeasts reappear when dosage ceases.

Nystatin is available in ointment, powder, and soluble tablet form.

Other antifungal antibiotics are known, including candicidin produced by *S. griseus* (the producer of streptomycin), but until very recently none had reached the degree of importance that attaches to nystatin.

An antibiotic named *griseofulvin* has been shown to be effective when given orally in the treatment of *Microsporum canis* and *Trichophyton mentagrophytes* in guinea pigs (Gentles, 1958), and *T. mentagrophytes* in cattle (Lauder *et al.*, 1958).

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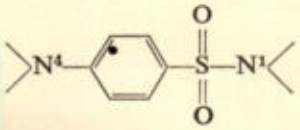
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CHAPTER 31

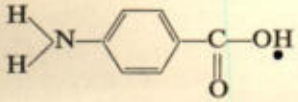
THE SULPHONAMIDES

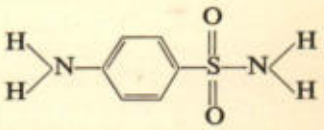
INTRODUCTION

THE sulphonamides are a group of complex synthetic organic chemical compounds with chemotherapeutic activity, They have a common chemical nucleus—with one exception of no veterinary importance—which is essential for antibacterial activity. This nucleus, graphically written as in (i),

(i) 

is very closely related to para-aminobenzoic acid, an essential member of the vitamin B complex which can be written as in (ii).

(ii) 

(iii) 

This similarity can be emphasized by reference to the simplest member of the sulphonamide group, sulphanilamide or para-aminobenzene sulphonamide (iii). Emphasis is required, for it is this similarity which is considered to lead to substitution and interference in cell metabolism by the sulphonamides.

The group can be divided into two main sections according to the site of therapeutic action. These divisions may be termed (1) The systemic sulphonamides, which are absorbed reasonably well from the intestines, and (2) the so-called 'gut active' sulphonamides which are, in the main, poorly absorbed from the intestines and therefore exert their effect only on the intestinal flora and possibly those organisms situated in the superficial cells of the mucosa.

The more important members of these divisions are set out in Table 1.

History

Sulphanilamide was first synthesized in 1908 by Gelmo, but it was not until 1935, when Domagk, of I. G. Farben Industrie, discovered the ability

of certain azo-dyes related to sulphanilamide to protect mice against challenges with streptococci, that attention became concentrated on these products of the dye industry. Prontosil and Neoprontosil, the latter a water

Table 1

Systemic sulphonamides	'Gut active' sulphonamides
Sulphanilamide	†Sulphaguanidine
*Sulphacetamide	Phthalylsulphathiazole
Sulphapyridine	Succinyl sulphathiazole
Sulphadimidine (Sulphamethazine)	Phthalylsulphacetamide
Sulphathiazole	
Sulphamerazine	
Sulphadiazine	
Sulphafurazole (Sulfisoxazole)	
‡Sulphaquinoxaline	

* Sulphacetamide is similar to sulphanilamide in activity but in Great Britain is rarely used for its systemic effects.
† Sulphaguanidine is absorbed to the extent of 50 per cent. or more of any single dose and systemic activity can also be anticipated.
‡ Used only in poultry.

soluble red dye which stained everything it contacted, were the first of these azo-compounds to be used therapeutically and with good effect. It was stated during the same year in Paris by Trefouël *et al.* (1935) that the activity of the prontosils and other azo-dyes was due to their release of sulphanilamide in the body. This work in Paris was followed in 1936 by work in England (Buttle *et al.*, 1936) which showed that sulphanilamide was less toxic than Prontosil and yet equal in activity.

Since 1936 a great amount of investigation has produced many sulphonamides but only a few have been of therapeutic value, of which a number were British discoveries. Amongst these British discoveries sulphapyridine (M. & B. 693), sulphathiazole (M. & B. 760), and sulphadimidine (Sulphamezathine) are outstanding. In recent years the sulphonamides have been displaced therapeutically by the antibiotics, the development of which was initially deferred by the advent of the sulphonamides. Nevertheless, interest in the sulphonamides continues, expecially as synergism and a delay in the development of antibiotic resistance has been shown to occur with some sulphonamide-antibiotic combinations; the concurrent use of sulphadiazine and chlortetracycline or chloramphenicol in the treatment of Hæmophilus meningitis in man is an example. Sulphonamide research is now concentrated more on finding means of reducing the toxicity of the group or on finding new sulphonamides with reduced toxicity; sulphafurazole (sulfisoxazole) with its low incidence of crystalluria is an example.

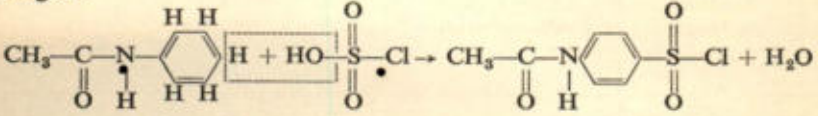
Another angle of approach is typified by the production of sulphamethoxypyridazine, for which Nichols *et al.* (1956) have reported the existence of significant blood levels in man over four days after a single 4·0 G. oral dose.

Manufacture and Chemistry

The sulphonamides are all manufactured synthetically. Those in common use and without any prefix to the 'sulpha-' part of the name, such as sulphanilamide and sulphadiazine, may be synthesized using the same principles and many of the same chemicals. This is because these compounds differ only in the groupings which are substituted for a hydrogen atom of the $—SO_2·NH_2$ group of the basic compound, sulphanilamide.

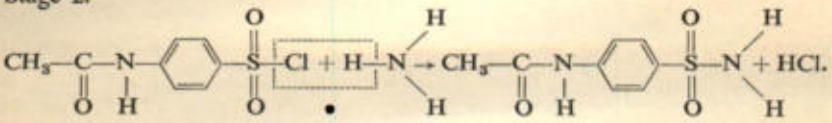
Synthesis may be represented by the following scheme:

Stage 1.



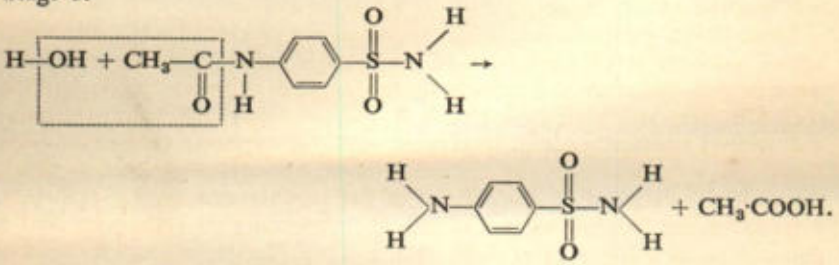
Acetanilide + chlorsulphonic acid → N.acetylsulphanilyl chloride

Stage 2.



N.acetylsulphanilyl chloride + ammonia → N.acetylsulphanilamide

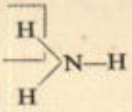
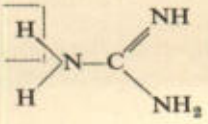
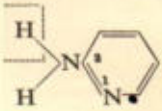
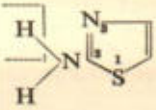
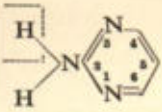
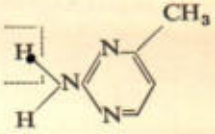
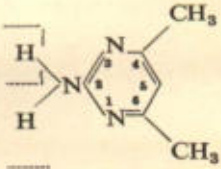
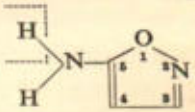
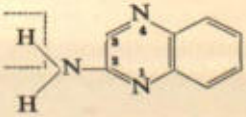
Stage 3.



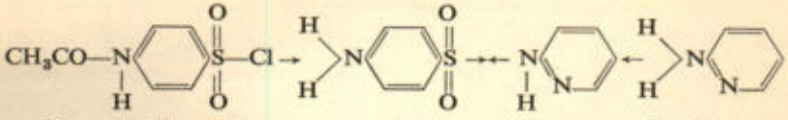
N.acetylsulphanilamide $\xrightarrow{\text{hydrolysis}}$ sulphanilamide + acetic acid

The other non-prefixed sulphonamides, with a few exceptions, may be prepared by using various cyclic amines instead of ammonia in stage 2. These amines are set out in Table 2.

Table 2

Sulphonamide	Amine	
Sulphanilamide	Ammonia	
Sulphaguanidine	Guanidine	
Sulphapyridine	2 Aminopyridine	
Sulphathiazole	2 Aminothiazole	
Sulphadiazine	2 Aminopyrimidine	
Sulphamerazine	2 Amino,4methyl-pyrimidine	
Sulphadimidine	2 Amino,4,6dimethyl-pyrimidine	
Sulphafurazole	5 Amino,3,4dimethyl, iso-oxazole	
Sulphaquinoxaline	2 Aminoquinoxaline	

The graphic formulæ of these sulphonamides can be deduced by attaching the amine minus one hydrogen atom (dotted) to the nucleus derived from N.acetylsulphanilyl chloride in stages 2 and 3, e.g.

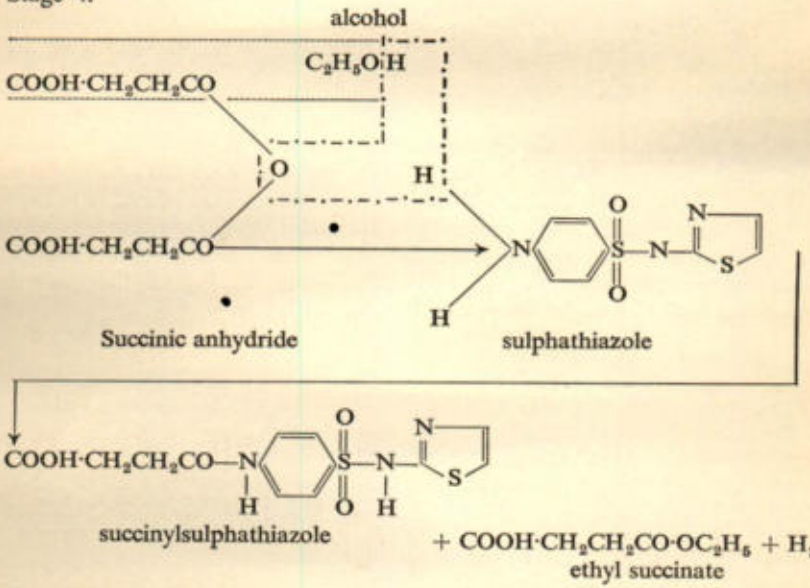


N.acetylsulphanilyl chloride — sulpha—pyridine — 2 amino-pyridine

With sulphonamides possessing a prefix, such as succinylsulphathiazole, further reactions are necessary, involving the amino-grouping attached in the para-position at carbon 4 of the benzene ring.

This reaction, in the case of succinylsulphathiazole, can be achieved by the use of succinic anhydride and anhydrous alcohol. The process may be represented as follows:

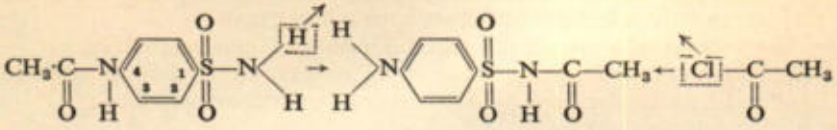
Stage 4.



Phthalylsulphathiazole and the two corresponding salts of sulphacetamide can also be prepared by this use of anhydrides and alcohol.

There are exceptions to these principles, and other methods of manufacture are used, but all the sulphonamides now in veterinary use in Great Britain conform and are included here, with the exception of Sulphacetamide. Sulphacetamide is prepared from N.acetylsulphanilamide by

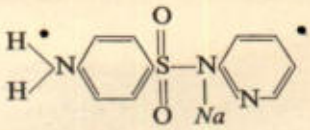
acetylation of the sulphonamide group using acetylchloride: alkaline hydrolysis later provides a p.amino-group at C_4 in the benzene ring.



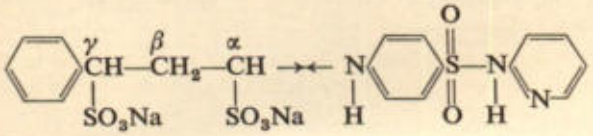
N.acetylsulphanilamide ⟶ sulphacetamide ⟵ acetyl chloride.

Sodium Salts. The sulphonamides are insoluble as a group and therefore the soluble *monosodium* salts may be used where it is necessary to administer them by injection; these salts, following injection, split off the sodium ions releasing the parent sulphonamide. Their structure consists of a sodium ion substituted for the remaining hydrogen ion attached to N_1, (the nitrogen of the $—SO_2NH_2$ group of the basic sulphanilamide): e.g.

Sulphapyridine sodium



Complex *disodium salts* have also been developed with the commercial names of Soluseptasine, Solupyridine and Soluthiazole, of which the first is included in the B.P.C. as Sulphasolucin. These compounds have a pH of about 8 and may be injected by most of the parenteral routes, whereas the monosodium salts are in general too alkaline (pH 9–11) to be given by any route other than the intravenous one. Their structure includes a disodium disulphonated organic group attached at N_4 of the parent compound with the displacement of a hydrogen atom—



Disodium-disulphonate-phenyl-propyl-⟶⟵-amino-benzene-sulphonamido-pyridine, normally written: disodium 2-(p.(γphenyl-propylamino)-benzene-sulphonamido) pyridine α:γdisulphonate.

Chemical and Physical Properties. The sulphonamides as a group are white or off white crystalline powders which darken on exposure to light and should therefore be stored in tins or coloured glass containers. Sulphaquinoxaline differs in being yellow in colour, but the structure of others can be modified to produce a colour without affecting their therapeutic properties. This property, due to the azo dye relationship of

the sulphonamides, has been used commercially to provide coloured sulphonamides to unvarying standards without the need for extra time and handling required for colouring by more normal methods. As a group they are mainly odourless but most have a bitter taste.

The sodium salts are similar and differ only in their solubilities.

All these compounds are stable in all respects other than reaction to light and may be sterilized by heat either as powders or solutions.

Solubility. The therapeutic effectiveness of the sulphonamides is dependent to a great extent on their solubility in water, for their concentration in the tissues is governed first by their rates of absorption from injection sites or intestines, and secondly by their concentration in the water present in the various body tissues. Absorption rates are roughly proportional to water solubilities as set out in Table 3.

Table 3

Sulphonamide	mg. in 100 ml.	
	In water at 37°	In blood at 37°
Sulphacetamide	1587	1970
Sulphanilamide	1460	1970
Sulphafurazole	530 (25°C.)	—
Sulphaguanidine	100 (25°C.)	—
Sulphathiazole	96	330
Sulphadimidine	75	—
Sulphapyridine	52	60–75
Sulphamerazine	31·8	—
Sulphadiazine	12·7	161
Succinylsulphathiazole	21·0 (20°C.)	—

Solubilities in acid urine are similar to those for water, but in alkaline urine the solubilities may be twice as great, and in the case of sulphadiazine may be 100 times greater.

The sodium salts are all soluble in water, the monosodium salts achieving solubilities greater than 1 in 2 at body temperature.

Pharmacology

The members of the sulphonamide group follow a pharmacological pattern common to all members except those which are not absorbed from the intestines, particularly succinylsulphathiazole, phthalylsulphathiazole and the corresponding sulphacetamide compounds. Differences are only of degree.

Absorption and Administration Routes. The *parent sulphonamides* are administered by oral and topical routes only. Following oral administration, absorption rates are roughly proportional to solubilities with perhaps the exception of sulphapyridine, which is slowly and irregularly absorbed in most species, and sulphadimidine which is second only to sulphanilamide and sulphacetamide in its rate of absorption. Maximum blood levels for carnivores, following single oral doses, are usually achieved in a minimum of 1 hour for the rapidly absorbed and a maximum of 8 hours, with an average of about four hours for those absorbed more slowly. Absorption rates vary between the species but are related in the main to the bulk of material within the intestines. Thus dogs and cats absorb the sulphonamides rapidly and almost completely, whereas cattle take much longer and the pig and horse are placed intermediately. Birds absorb sulphonamides better than other domestic species.

The *monosodium* salts may be given by intravenous injection but, with the exception of sulphadimidine sodium, it is not advisable to give them by any other parenteral route. Following intravenous injection, or deep intramuscular injection in the case of the sulphadimidine salt, maximum blood levels are rapidly achieved and these salts may therefore be used to institute therapeutic blood levels rapidly, maintenance of these levels being achieved by subsequent oral dosage. These salts may also be used to medicate drinking water but should be suitably buffered to prevent deposition.

The *disodium salts* may be used instead of the monosodium salts, but in addition may be given subcutaneously or intramuscularly. Approximately 5·0 ml. contain the equivalent of 1·0 G. of the parent sulphonamide although sulphasolucin contains less than the other two.

With these solutions of sodium salts the intraperitoneal route is sometimes used.

Blood Levels. As with the antibiotics, blood and tissue levels are of great importance. Blood levels, however, cannot be used for comparing the activity of different sulphonamides, nor is it possible to define an effective blood level which will apply to all sulphonamides, for, as with chloramphenicol (*q.v.*), proportions of most sulphonamides combine loosely with blood proteins. This limits the availability of the compounds to diffuse into the tissues and exert an antibacterial effect. Acetylation, which occurs in the liver and turns the sulphonamide into an inactive form, further reduces the significance of blood levels. Both these factors vary from compound to compound and from species to species. However, levels of 8–15·0 mg. per 100 ml. blood in man, and 5 mg. per cent. in animals (Maclay *et al.*, 1947) are taken as being therapeutically effective, though levels of some sulphonamides are still effective when below these standards.

Once adequate blood levels have been established, oral dosing every eight hours in simple stomached animals and every 12 hours in adult

ruminants is sufficient to maintain them. Large doses are usually given to establish therapeutic blood and tissue levels initially, but subsequent doses are smaller. Increasing the dose does not increase the blood levels proportionately.

Barriers. The sulphonamides as a group diffuse very widely into the tissues, penetrating into all fluids.

Blood-brain barrier. The penetration of the blood-brain barrier is largely governed by the proportion of sulphonamide which is circulating in the blood combined with protein or in an acetylated form. This can be well illustrated by the pyrimidine derivatives: sulphadimidine when compared with sulphadiazine and sulphamerazine is acetylated more easily and in greater quantity, it is also bound to protein to a greater degree; thus, although sulphadimidine diffuses into the cerebrospinal fluid in appreciable quantities, the levels of active sulphadiazine ($\frac{2}{3}$ of blood level) and sulphamerazine ($\frac{1}{2}$ of blood level) are superior and they are preferred for the treatment of meningeal and brain infections. Of the other sulphonamides, sulphanilamide penetrates better than sulphadiazine, sulphafurazole slightly less; sulphathiazole penetrates poorly when compared with all others, including sulphapyridine.

Other Barriers. With the exception of the blood-brain barrier, all other natural barriers are passed and effective concentrations appear in all tissues, body cavities, and secretions, including urine, bile and milk; the placenta is also crossed.

Pathological barriers exist in abscess capsules and purulent foci, where vascularity is either minimal or absent.

Excretion. The sulphonamides are excreted mainly via the urine. They are excreted either in an unchanged form, or as a conjugated excretory product which has considerably reduced antibacterial activity. The conjugation takes place in the liver where N_4 acetyl derivatives are formed; these compounds are those formed in stage 2, and from which the sulphonamides were originally obtained in stage 3 of manufacture (see p. 555). The proportion of changed to unchanged sulphonamide varies with the different sulphonamides and also with the different species. In the dog and poultry the amount of circulating and excreted acetyl derivatives is extremely low: it is suggested that processes of acetylation and de-acetylation occur at an equal rate so that no appreciable blood level of acetyl derivatives can be accumulated. In other species, de-acetylation is the slower process and blood levels of the acetylated sulphonamides build up. The degree of acetylation is important, for with all but the pyrimidine derivatives (sulphadiazine, sulphamerazine and sulphadimidine) the acetylated sulphonamides are far less soluble than their parent compounds. Also of importance is the fact that all acetyl derivatives are more soluble in alkaline urine than in neutral or acid

urine: it is a common practice in human medicine to administer bicarbonates, citrates, and acetates as alkalizers. A third factor of equal excretory importance is the degree of 'renal clearance,' which is the amount of a sulphonamide excreted by the glomerulus and not resorbed by the tubules. These three factors, in conjunction with the excretion rate, determine whether or not urine solubilities are exceeded, and consequently whether a particular sulphonamide is safe to use. For example: sulphathiazole is rapidly excreted, up to 90 per cent. passing into the urine in 24 hours, has a renal clearance of 87 per cent. and an acetylation rate of 20 per cent.; the acetyl derivative has a solubility in urine of about 7·0 mg. per cent. (per 100 ml.) at pH 5·5 (up to 40·0 mg. per cent. at pH 7·5): sulphadiazine is excreted more slowly, probably because of a higher protein adsorption, only 50 per cent. passing into the urine in 24 hours, has a renal clearance of 31 per cent. and an acetylation rate of 25 per cent., the acetyl derivative being soluble to the extent of 20·0 mg. per cent. in urine at pH 5·5 (512·0 mg. per cent. at pH 7·5). It will be seen that, of these two sulphonamides, sulphathiazole is far less safe to use, for at a given time more sulphonamide, with about the same acetylation rate and an acetyl derivative solubility far below that of sulphadiazine, is present in the kidney. The urine saturation level is therefore more likely to be exceeded and crystallization to occur. This renal crystallization is referred to as 'crystalluria'.

The figures quoted above refer to human sulphonamide excretion; the situation in veterinary medicine is not so serious for acetylation is not so great in animals and in herbivores the urine is normally alkaline (pH 8+). For cats and dogs, urinary alkalization is advisable.

Some sulphonamide is excreted in the bile and appreciable amounts may be found in the milk. Sulphanilamide provides a higher milk level than most sulphonamides, and though it has been said that oral sulphonamide treatment of mastitis has not been satisfactory (Jones, 1954), this sulphonamide was the first chemotherapeutic of any real value against streptococcal mastitis: until the advent of penicillin, sulphanilamide was very widely and successfully used for this purpose in Great Britain.

Fæcal excretion is relatively high, as much as 10 per cent. of a single dose of sulphanilamide, and more of other sulphonamides, remains unabsorbed in the intestines; if dosing is excessive or protracted, there is a tendency to cause disturbances in the intestinal flora, and there is also an irritant effect exerted by the compound itself. Continued oral use in cattle causes enteritis with scouring.

Toxicity. The acute toxicity of the sulphonamides reported so frequently in man is of far less significance in animals, possibly because symptoms are mainly subjective—nausea, temporary blindness, giddiness etc., few of which may be noted by an owner. Skin rashes, photosensitization, hæmolytic anæmia, and agranulocytosis have all been reported and are due to sensitivity reactions following previous courses of treatment.

Chronic toxicity is of more importance and assumes two forms, one associated with depression of the intestinal flora and interference with vitamin B metabolism, and the other associated with crystalluria.

Continued use of sulphonamides in ruminants results in diarrhœa, dehydration, and debility, with a loss of appetite and milk yield. In normal animals recovery follows cessation of dosage; this recovery is slower in sick animals. These toxic effects are due mainly to the direct irritation of the intestines and to the digestive disturbances caused by the suppression of ruminal flora activity and vitamin B synthesis.

In other species, depression, loss of appetite, nausea, and vomiting in those species capable of this reaction, are the usual signs of sulphonamide toxicity.

Crystalluria has been reported in animals but is of less frequent occurrence than in man because acetylation, which produces less soluble, inactive compounds for excretory purposes, is not so great as in man. Nevertheless, crystalluria, with deposition of sulphonamide crystals in the tubules, pelvices, and ureters, does occur and results in urinary obstruction and ulceration of the mucosa in contact with the crystals. It produces a decrease in the quantity of urine, whilst any urine passed contains crystalline and tissue casts, albumin, and blood.

The causes of crystalluria are numerous, but the condition normally results because dosage has been excessive, either in quantity, frequency or duration; or because the intake of water and its excretion have been restricted or the pH of the urine has become acid. In most cases it is a combination of two or more of these factors.

Treatment consists in all species of stopping dosage, increasing fluid intake, and alkalizing the urine: the last of these is assisted by the fact that sulphonamides in urinary filtrates restrict bicarbonate resorption by the tubules. Where anuria (cessation of urination) occurs increased fluid is contra-indicated. Ureteric irrigation is used in human cases of this type.

All types of toxicity, but particularly crystalluria, are encouraged by conditions which result in dehydration with tissue fluid concentration and a decrease in urine production (oliguria); sulphonamide therapy is therefore contra-indicated in such cases.

Avoidance of crystalluria is achieved by paying strict attention to dosage rates and frequency of administration, and also by stopping administration about twenty-four hours after the temperature has become normal. Free access to unlimited water supplies is essential. No course of treatment should continue for longer than seven days. The choice of sulphonamide is of the greatest importance, for those such as sulphapyridine with very low solubility should not be used where more soluble and probably more effective sulphonamides are available.

Where there is a danger of crystalluria and sulphonamides must be used, *triple sulphonamides* should be given. These are combinations of sulphonamides, frequently of the three pyrimidines which possess considerable excretory advantages over equal weights of single sulphonamides.

[With combinations of sulphonamides, therapeutic activity is equivalent to the sum of the activity of the individual members, but during excretion the members each act as if they were in solution alone. In this way therapeutic potency is retained without running the risk of exceeding the urinary solubility of any member of the combination.]

Poultry. Toxicity in poultry is indicated by a decrease in egg yield and a thinning of the shell. These symptoms take about two weeks to disappear.

Topically, sulphonamides have been shown to retard healing of uncontaminated wounds so that this group of chemotherapeutics should not be used in routine surgery.

Action. The sulphonamides in very low concentrations stimulate cell growth, but in low therapeutic concentrations they are bacteriostatic and in high therapeutic concentration may be bactericidal. They are normally used as bacteriostats and consequently the patient's own resistance and body defences must be encouraged concurrently with sulphonamide therapy.

The sulphonamides act against bacteria by substituting and replacing essential vitamins upon which these susceptible bacteria are actually dependent but which are less essential to their animal hosts. The most important of these compounds with regard to the sulphonamides is para-aminobenzoic acid. Interference also occurs in the synthesis of folic acid (pteroylglutamic acid) from p.aminobenzoic acid, and the heterocyclic pyridine and thiazole derivatives disrupt nicotinamide metabolism and the working of coenzymes I and II. Synthesis of various amino-acids including methionine, a precursor of choline, may also be interrupted. Interference in the metabolism of the vitamin B complex within the bacteria is therefore fairly comprehensive.

As activity is one of competitive substitution, the tissue concentration of a sulphonamide must be kept high enough to prevent access of the p. aminobenzoic acid to the bacteria. Consequently, with a standard dose, the fewer the bacteria present the more sulphonamide will be available to approach each individual organism and therefore be absorbed by the bacterium in preference to the p.aminobenzoic acid because of its higher concentration. This may be expressed more scientifically '—the activity of a sulphonamide varies inversely to the concentration of the bacteria'. As the sulphonamides interfere with cell metabolism the maximum effect must be exerted when the bacteria are multiplying rapidly; in any infection the bacteria will therefore be most susceptible during the logarithmic phase of the disease, soon after infection. It follows that, for maximum effect, the sulphonamides must be given early in the course of the infection and in maximal doses, and also that the greater and more severe the infection the higher the dosage must be, commensurate with toxicity considerations.

The difference in activity of the various sulphonamides is now thought

to be more of degree rather than of selective effect (Jones, 1954), but nevertheless there is some selectivity which is typified by the activity of sulphathiazole against staphylococci (micrococci). The difference in degree of action has been ascribed to the degree of dissociation of each individual sulphonamide (Bell *et al.*, 1942) which in turn will be related to the pH of the medium.

Antagonists. The competitive action of the sulphonamides was proved by supplying bacteria with the metabolic products which the organisms are unable to synthesize in the presence of sulphonamides: this eliminated the antibacterial action of the sulphonamides. It is therefore obvious that any of these metabolites will antagonize sulphonamides:

(a) p.aminobenzoic acids and related compounds, particularly the local anæsthetics with a p. aminobenzoic acid nucleus such as procaine, butacaine and benzocaine, but also compounds associated with these such as procaine penicillin.

(b) Other members of the vitamin B complex such as nicotinamide, folic acid (pteroylglutamic acid), choline etc., and precursors of these, including various amino-acids, of which glutamic acid and methionine are related respectively to folic acid and choline.

A second group of antagonists are the proteins which combine loosely with the sulphonamides and at least temporarily eliminate their antibacterial activity. Gelatin, albumin, peptone, and serum protein all antagonize the sulphonamides; the activity of sulphonamides circulating in blood and tissue fluids is therefore constantly antagonized by the medium in which it is circulating. Associated with this latter group are the products of cell and tissue death, especially pus, which acts also as a non-vascular mechanical barrier.

A number of other compounds including coenzymes, glucose, and mercuric chloride are all reported to have antagonistic effects against sulphonamides.

Protagonists. It has been shown that sulphonamides are more active at the higher body temperatures which occur in fevers. Goodale *et al.* (1942) quoted by the United States Dispensatory 25th Edit. 1955, p. 1877, showed that urea increased the actions of the sulphonamides by increasing solubility and decreasing their combination with protein.

'Gut Active' Sulphonamides

The members of this group of sulphonamides consisting of sulphaguanidine, phthalylsulphathiazole, phthalylsulphacetamide and succinylsulphathiazole, are generally of low solubility and are poorly absorbed; sulphaguanidine is an exception in that about 50 per cent. of any single dose may be absorbed and will therefore not be available for intestinal activity. It has been found, however, that a degree of absorption is useful because of the local effect in the intestinal mucosa during and after

absorption. This is important because the bacterial content of the mucosa is frequently very high and purely intra-intestinal activity would be ineffective against these organisms.

The action of the N_4 substituted products is mainly due to their release of the parent sulphonamide after the large intestine, where absorption is minimal, has been reached. Sulphathiazole and sulphacetamide are therefore the active parts of the molecules.

Any part of these sulphonamides which is absorbed reacts in much the same way as do the systemic sulphonamides. Sulphaguanidine, following absorption, has a pharmacological pattern similar to that of sulphanilamide.

The derivatives of sulphathiazole are slightly absorbed—up to about 3 per cent. of a single dose, which is insufficient to have either therapeutic or toxic effects. This has, in fact, been considered disadvantageous in that insufficient penetration into the mucosal cells has occurred and bacteria present in these cells have escaped. Phthalylsulphacetamide, on the other hand, is slightly more soluble and is absorbed to a greater extent; penetration of all the tissues of the intestinal wall occurs (Lehr, 1949) but no systemic level is achieved nor is toxicity common, owing to the rapid excretion of the compound.

A soluble systemic sulphonamide is often combined with one of these 'insoluble' sulphonamides so that bacterial invasion of the blood and tissues can be countered at the same time as the intestinal infection is attacked.

In other respects the 'insoluble' sulphonamides act in the same way as the systemic members.

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CHAPTER 32

SULPHONAMIDE THERAPY

ALTHOUGH the superior action of antibiotics has reduced the importance of sulphonamides in veterinary medicine, the abuse of antibiotic activity is rapidly creating strains and species of bacteria which are resistant to the action of most broad-spectrum antibiotics. Unless a new generation of broad-spectrum antibiotics is discovered, veterinary surgeons may eventually look once again to the sulphonamide group for their main defence against disease, just as the human physicians are making increased use of sulphonamides to check the development of antibiotic resistant strains and also to prevent the overgrowth of resistant bacteria or fungi which sometimes follows elimination of the antibiotic-susceptible organisms. Some sulphonamides, of which sulphadimidine is the main one, still retain their popularity because of convenience in dosing and greater economy.

Antibacterial Range

The sulphonamides are, as a group, active mainly against Gram positive organisms but there is also some activity against certain Gram negative organisms, a few rickettsiæ, and some protozoa. The least active are sulphanilamide and sulphaguanidine, whilst, of the established and official sulphonamides, sulphathiazole is acknowledged as the most active, with the pyrimidine compounds only slightly less so. This, however, is not the order when usefulness is considered, for the low solubility of sulphathiazole deposes it in favour of the sulphapyrimidine group, sulphafurazole and some of the newer more complex sulphonamides. Determination of the relative activity of sulphonamides *in vitro* is difficult because of many conflicting reports, few of which can be compared because of a lack of uniformity of method. The following details are generally accepted (Florestano *et al.*, 1952; Maclay *et al.*, 1947), with sulphanilamide and sulphaguanidine as the least active and sulphathiazole as the most active of the systemic sulphonamides.

1. Sulphanilamide, Sulphaguanidine, Sulphacetamide — Active against streptococci and *Bact. coli*, the last being slightly more active than the other two.
2. Sulphapyridine, Sulphadimidine — Active in higher degree against streptococci and *Bact. coli*, but with additional activity against staphylococci, salmonellæ and pasteurellæ. Sulphadimidine is also active against some rickettsiæ and protozoa.

3.	Sulphamerazine Sulphafurazole	These are approximately equal in activity and slightly more effective than group 2, but sulphamerazine has particular activity against *Bact. coli* and pasteurellæ whilst sulphafurazole is almost equal in activity with sulphathiazole against staphylococci.
4.	Sulphadiazine	This is almost equal in activity with sulphathiazole but is less active against streptococci and staphylococci and more active against *Bact. coli.*
5.	Sulphathiazole	This is the most active sulphonamide *in vitro*, possessing the greatest activity against streptococci, staphylococci and pasteurellæ.

The more active sulphonamides also have some action against Pseudomonas, Proteus and clostridial species. This activity is particularly shown by the pyrimidine derivatives.

In vivo preferences alter this order considerably. In man, sulphathiazole is used only for anti-staphylococcal action because its low solubility makes it dangerous. Sulphadiazine is therefore preferred as the most active sulphonamide for routine use. In animals, however, sulphadiazine is not absorbed evenly and reliably in all species, and consequently the less active but more reliable sulphamerazine becomes first preference. Sulphafurazole is more soluble and is better for urinary tract infections. Neither of these persists as long as sulphadimidine and both require more frequent dosage: it is for this reason that sulphadimidine has become the standard sulphonamide for routine veterinary use even though its antibacterial activity is lower than that of the others. The insolubility and toxicity of sulphapyridine and the low antibacterial activity of sulphacetamide and sulphanilamide make their use for routine purposes inadvisable.

This may be summarized as follows:

Routine use: sulphamerazine or sulphadimidine.
Staphylococcal and pasteurellæ infections: sulphathiazole or sulphafurazole.
Bact. coli, Proteus and Pseudomonas infections: sulphadiazine, sulphamerazine.
Urinary infections: sulphafurazole.

The '*gut active*' *sulphonamides* are not clearly differentiated, but sulphaguanidine is of minor importance compared with the sulphathiazole and sulphacetamide substitution products. Poth (1953), referring to human therapy, rescinded previous reports (Poth *et al.*, 1944; Poth, 1945, amongst others) in stating that succinylsulphathiazole is the most effective of the 'insoluble' sulphonamides for pre-operative elimination of intestinal bacteria except where diarrhœa is present, when phthalylsulphathiazole is preferred. Succinylsulphathiazole is slightly more toxic and produces semi-liquid fæces. In practice, where diarrhœa is nearly always present

when enteritis is treated with sulphonamides, phthalylsulphathiazole should give better results. Neither of these compounds allows a compensatory increase of other non-susceptible organisms, which frequently occurs when the tetracyclines are used (Poth, 1953, *loc. cit.*), but a more rapid response can be achieved by combining phthalylsulphathiazole with neomycin.

Phthalylsulphacetamide is said to be very effective in intestinal infections (Christian, 1952; Rogoff, 1950; Harris, 1951), but insufficient veterinary information is available to compare it with the sulphathiazole derivatives, though the results of human therapy are encouraging.

Sulphaguanidine is much less active than the other three compounds, possibly because of the large proportion which is absorbed.

The antibacterial range of these enteric sulphonamides extends mainly to coli-ærogenes and Salmonella species, but also to clostridial organisms as well as coccidia.

Sulphaquinoxaline. This sulphonamide is relatively toxic to mammals and has a narrow margin of safety. Its use is therefore restricted almost entirely to the treatment of poultry. The pharmacology of sulphaquinoxaline in poultry has been studied and described by Schlenker and Simmons (1950). The drug is absorbed quite rapidly when the crop is empty, but somewhat variably otherwise. Once absorbed, excretion is slow and detectable blood levels have been found up to 4½ days after a single dose. Excretion is via the kidneys and fæces. This slow excretion rate causes cumulation, and discontinuous treatment recommended by Davies *et al.* (1954) should be used to avoid the development of toxic blood levels. *Toxicity* symptoms are a decline in egg yield in laying birds, inappetance, dullness, anæmia and death. Post-mortem lesions include subcutaneous hæmorrhages and local necrosis. The causes are thought to be due to a lack of vitamin K and a drug allergy (Sanger *et al.*, 1956).

Although active against the organisms normally susceptible to sulphonamide action, and although reasonable results have been claimed for its action against Pasteurella infections in cattle and pigs (Eveleth *et al.*, 1949), the most striking action is against coccidia in poultry in which it is about four times more active than sulphadimidine (Grumbles *et al.*, 1948; Wilson, 1951; Marthedal *et al.*, 1951); it is also more palatable.

Bacterial Resistance. The development of bacterial resistance to the sulphonamides was the first indication of a phenomenon which has since been found to apply to most chemotherapeutics.

The development of resistance to one sulphonamide usually means that the organism will be resistant to all members of the sulphonamide group. Where this develops, chemotherapeutics not related to the sulphonamides must be used, for resistance to the sulphonamides does not confer resistance to other chemotherapeutics.

Resistance develops quite rapidly and, normally, treatments should not be continued for longer than seven or eight days.

Therapeutic Principles

There are several features of the sulphonamides which predetermine the general routine of sulphonamide therapy:

1. The effect of a sulphonamide decreases as the number of organisms increases, therefore the indicated sulphonamide should be *given as early in the course of the disease as possible*. For the same reason, *the more severe the infection the larger should be the dose*.

2. Maximum blood levels are achieved in 1–2 hours with the most soluble sulphonamides. Where the infection is acute and severe, this time lag between dosing and effect may be fatal, so *in these critical cases treatment should be initiated by parenteral injection* of a monosodium or disodium salt.

3. Also, because of the low solubility, relatively slow absorption rate, and the relation of maximum blood level to dosage rate, it is usual to *give a large dose initially* at a standard rate according to body weight in order to establish adequate blood levels; these levels, once established, can be *maintained by regularly repeated doses of a smaller size*.

4. The excretion products of the sulphonamides are not very soluble in acid urine and crystallization may occur. *Unlimited water must therefore be available to an animal during sulphonamide therapy* and *urinary alkalizers may be given* concurrently with the sulphonamides.

5. *Any signs of a decrease in urine production, difficulty or pain on urination, or cloudiness and blood in the urine, should be the signal to stop all sulphonamide dosing*, to increase the fluid intake, even to the extent of forcibly administering fluid orally or parenterally, and to institute the administration of urinary alkalizers.

6. Blood levels after the first two or three days may increase if relatively high level dosing continues. To *decrease the possibility of systemic toxicity, dose sizes should be cut by a half after this initial period*. This also lowers the excretion rate and lessens the danger of crystalluria.

7. Because bacterial resistance develops rapidly, and also because vitamin synthesis by the normal intestinal flora is depressed (this is of special importance in herbivores), *no course of treatment should last longer than seven or eight days*. If no response is shown within the first two or three days sulphonamide therapy should cease, for no action can then be expected.

8. Sulphonamides are bacteriostatic and *dosing should continue for about 48 hours after the disappearance of clinical symptoms*. If this is not observed, a resurgence of the infection may occur, resulting in a relapse. Doses may be further reduced in size or frequency during this period.

The Sulphonamides and Disease Therapy. In most of the diseases mentioned antibiotics have relegated the sulphonamides to a second choice, but in a few, such as 'foul-in-the-foot' or 'foot rot' in cattle and coccidiosis, the sulphonamides are preferred (in the latter case nitrofurazone appears to be a better product for some purposes (Blount, 1955).

Mastitis

The sulphonamides are not completely effective in bovine mastitis. Clinical improvement is sometimes quite dramatic in acute *Strep. agalactiæ* infections when sulphanilamide is given orally, but bacteriological cure is not assured (Stableforth *et al.*, 1942). In conjunction with penicillin intramammary injections, however, oral sulphanilamide can be quite useful in acute cases. The usual dosage during the pre-antibiotic period was 3 oz. as an initial dose followed by 1 oz. given three times daily. Intramammary infusions of 120–300 ml. (4–10 fl. oz.) of a 10 per cent. Sulphasolucin B.P.C. solution have been used and also suspensions of sulphanilamide in liquid paraffin; Kakavas *et al.* (1942) and Edwards *et al.* (1947) recommended four daily doses of 40·0 ml. per quarter of such a suspension containing 0·3 G. per ml. sulphadimidine sodium has been effectively used as an udder infusion in 50·0 ml. doses of a 10 or 25 per cent. solution per quarter, usually combined with 50,000 or 100,000 units of penicillin, and given after 3 or 4 consecutive milkings (Christian, 1948; Gibbons, 1948; Fuller, 1949). Penicillin with sulphadimidine cerates are also available commercially and compare favourably with penicillin and streptomycin combinations.

Sulphamerazine has also given good results when used both locally and systemically.

In *staphylococcal mastitis*, the sulphonamides either singly or in combination are not very effective. Insufficient information is available to determine their effect when combined with antibiotics.

Mastitis due to *C. pyogenes* does not respond to sulphonamide therapy; the systemic sulphonamides may modify the febrile systemic symptoms. Reports such as that of Thompson (1940) on sulphapyridine are suspect in that summer mastitis, originally thought to be purely of *C. pyogenes* ætiology, is now known to be occasionally caused by streptococci and other organisms.

Specific Systemic and Organic Diseases. Wherever possible antibiotics are now used because of toxicity considerations, but nevertheless large quantities of the sulphonamides are used annually in Gt. Britain.

Strangles

As with the antibiotics, variable results are obtained but sulphonamides administered in the early febrile stages will reduce the temperature (sulphanilamide: Minett *et al.*, 1945; sulphamerazine: Bryan, 1946; sulphadimidine: Rodgers, 1947). Once abscesses begin to form sulphonamides serve only to slow down abscess maturation; they are then contraindicated. With stomatitis and pharyngitis, local applications in electuary form are effective and should be smeared liberally on the horses teeth three or four times daily. A suitable electuary might contain 30 per cent. by weight of sulphanilamide in glycerin, stiffened if necessary with starch. This is somewhat expensive but quite effective.

Joint-Ill

A large proportion of joint-ill cases in foals, calves, pigs and lambs are due to sulphonamide sensitive streptococci and many such cases will respond to sulphanilamide. It is more usual to use the more active sulphonamides, for a wider scope is afforded including activity against the staphylococci, coli-ærogenes, and Pasteurella organisms which may also be involved. Sulphamerazine, sulphapyridine, sulphathiazole, and sulphadimidine, have all been used with good effect.

Pasteurellosis

Hæmorrhagic septicæmia of cattle, horses, sheep, and pigs all respond to sulphonamides of the heterocyclic type but sulphanilamide is relatively ineffective (Francis, 1947). As little as 1 oz. (30·0 G.) of sulphamerazine on two occasions, with an interval of 12 to 24 hours, has given a good cure rate (Harris, 1951). Sulphathiazole is also efficient and sulphadimidine has been used.

Fowl Cholera. This condition caused by *Pasteurella multocida* has been responsible for considerable poultry losses. These losses have been controlled by the sulphonamides and more recently, by the antibiotics. Of the sulphonamides, sulphamerazine (Alberts, 1950), sulphadimidine (Kiser *et al.*, 1947 and 1948; Hilbert *et al.*, 1948; Pomeroy, 1950), sulphapyridine (Shanks, 1941) and sulphaquinoxaline (Delaplane *et al.*, 1948; Peterson, 1948; Pomeroy, *loc. cit.*) have been used with a considerable decrease in mortality and a maintenance of weight, but no immunity is gained during treatment and relapses occur when treatment is stopped. Of these, sulphadimidine and sulphaquinoxaline are the most popular and may be used in food or water.

Contagious Coryza

This disease, due to an organism *Hæmophilus gallinarum* responds to sulphadimidine in drinking water at the rate of 0·2 per cent. or in mash at the rate of 0·4 per cent. Sulphathiazole either as the sodium salt, but more commonly as the complex neutral disodium salt, at the rate of 0·1 per cent. in the drinking water for three to five days, is successful in the majority of cases.

Broad-spectrum antibiotics have superseded sulphonamides to a large extent.

Fusiformis Infections

Both foul-in-the-foot (foot rot) in adult cattle and calf diphtheria respond extremely well to sulphonamides but sulphapyridine, suggested as an injection for the former disease by Forman (1946) and orally for the latter by Farquharson (1942), and sulphadimidine, are the most important.

In *foul-in-the-foot* an intravenous injection of sodium sulphapyridine on one or two occasions with an interval of four or five days has been confirmed by extensive trials (Davies *et al.*, 1947) as being very effective.

The dose is estimated at the rate of 6·0 G. per 100 lb. dissolved in sufficient water to make a 12 per cent. solution, but it is more usual to give 60·0 G. in 500·0 ml. as a single dose irrespective of weight. Extravascular leakage is dangerous and has caused very severe sloughing. Sulphadimidine sodium is greatly preferred for this purpose because perivascular leakage rarely causes more than a slight transient reaction. It is used as a 33⅓ per cent. solution administered at the rate of not less than 15·0 ml. per 100 lb. body weight. Sulphamerazine sodium is equally effective.

Calf diphtheria has to all intents and purposes been eradicated in Great Britain following the use of sulphapyridine and later sulphadimidine. Both are very effective when given as an oral tablet. In many cases intramuscular sulphadimidine sodium is used to initiate treatment, and single intravenous doses of not less than 10·0 ml. of the 33⅓ per cent. solution per cwt. (50·0 kg.) cure most cases (Bateman, 1949).

Actinobacillosis

Wooden tongue will respond in a majority of cases to the use of either sulphamerazine (Walker *et al.*, 1949) or sulphadimidine. Hannequin (1952) gave 100·0 ml. of a 33⅓ per cent. solution of sulphadimidine sodium either intravenously or subcutaneously, following which, in about 100 cases, repeat doses were rarely needed.

Coliform-Salmonella Infections

White scour in calves and enteritis in pigs, dogs, and poultry, have all been treated successfully with the sulphonamides. Sulphaguanidine was first used and was reasonably effective, but later the less toxic and more effective phthalylsulphathiazole, phthalylsulphacetamide, and succinylsulphathiazole displaced it.

In calves, Thorp *et al.* (1944) found both the succinyl- and phthalyl-derivatives of sulphathiazole effective but preferred the phthalyl-derivative; this was confirmed by Sandstedt (1946). Christian (1952) obtained 25 recoveries out of 27 cases of calf scours with phthalylsulphacetamide using twice daily dosing for 2–3 days. Thorp *et al.* (1946), reporting on the use of sulphadimidine, found three single daily doses very effective in enteritis of pigs and calves. Dogs and cats respond to similar treatment.

Salmonella infections of poultry have been effectively controlled by sulphamerazine, sulphadimidine, and sulphaquinoxaline, but though birds will survive (Bottorff *et al.*, 1946; Boney, 1951; Pomeroy, 1950), many remain carriers (Bottorff, 1947) and mortalities remain low only during treatment (Simms, 1946). Wilson (1948) stated that sulphonamides were contra-indicated in breeding stock as it has been found that treated birds reacted to the crystal violet spot test and that the culling of carrier birds was consequently impossible. Furazolidone is becoming the accepted treatment for Salmonella infections in poultry, for it has been shown to be capable of clearing B.W.D. reactors (Gordon *et al.*, 1955).

Coccidiosis

This is a protozoan parasitic disease in which the protozoa may enter and destroy cells in the liver (rabbit) and intestines (cattle, sheep and goats, pigs, dogs, cats, rabbits and fowls); one species attacks the cæcum in the fowl. There are two genera, *Isospora* which affect the small intestine of dogs, cats and man, and *Eimeria*, species of which cause lesions in all the sites and species mentioned above.

The parasite has a life history which involves two types of multiplication, an asexual method or schizogony stage which is in itself cyclical, and a sexual type or sporogony stage. During the schizogonous stage multiplication can occur with fantastic speed and whole stretches of mucosa, in the cells of which the *schizonts* or asexual dividing structures grow, may slough as the mucosal cells are burst open by the swelling schizonts which in turn themselves burst, releasing merozoites to attack other cells. This leaves a raw bleeding surface which provides an easy route of access to the body for pathogens already in the intestines. The sporogonous stage is of less importance to the host, for fewer cells are damaged. During this phase a female cell or *macrogamete* is fertilized by a *microgamete* and forms a capsulated zygote, which is then passed out in the fæces (or urine, in renal coccidiosis of geese and swans) and is known as an *oocyst*. The oocyst is therefore the means of transmission of infection to other individuals, and the damage caused during their formation in the first host is relatively small when compared with damage caused by the sporozoites they release and the schizonts formed from them in the new host.

The majority of therapeutics suppress the production of the second generation schizonts in the dangerous asexual stage of reproduction (Davies *et al.*, 1952; Ripsom *et al.*, 1945, but some influence is exerted on gametocyte formation (Ripsom *et al.*, *loc. cit.*; Horton-Smith, 1957).

The main signs of coccidiosis in all species are diarrhœas, which may be intermittent in the mild chronic cases; the fæces may vary in colour from yellow to bright red with blood clots and shreds of tissue, depending on the severity and acuteness of the attack. The appetite is usually maintained, but as digestion processes are dislocated by the damage caused in the mucosa, animals become debilitated, and emaciated in the more severe cases; anæmia and death follow. All the signs associated with this type of condition in the various species will occur; for example, raised tail, caked hindquarters, dropped in flanks, staring coats with loss of colour, and a drooping, miserable appearance in badly affected calves; or caked vent feathers, huddled and ruffle-feathered stance with drooping wings in poultry.

Treatment in Mammals. This was attempted with sulphaguanidine, and conflicting reports were published for the treatment of calves (Boughton, 1943; Arthur, 1944), but mepacrine was far more effective and economic. Good effects were reported in lambs (Foster *et al.*, 1941) rabbits (Joshua,

1943), and poultry (Allen *et al.*, 1943), but not dogs (Whitney *et al.*, 1941). However, as more sulphonamides were discovered it was realized that sulphaguanidine was relatively inactive.

In America, Fox and Roberts found phthalylsulphathiazole with either sulphamerazine or sulphadimidine very satisfactory in a ratio of 1½ gr. : ¾ gr. per lb. (173·0 mg. : 105·6 mg. per kg.) body weight given daily for 2–3 days. This was supplemented with a dried yeast/mineral mixture for up to four weeks in the more debilitated individuals. Udall (1954) considered this the best available treatment for coccidiosis in young farm stock. Sulphadimidine alone has also proved effective following similar courses of treatment in *calves* (Thorp *et al.*, 1946); and *lambs* (Salisbury *et al.*, 1953). Coccidiosis in *goats* should be treated by initial doses of sulphadimidine at the rate of approximately 1½ gr. per lb. (0·2 G. per kg.) body weight followed by half this dose every 12 hours (B.V.A. Public. No. 18).

In *dogs*, coccidiosis is more resistant to the sulphonamides though high dosages of sulphadimidine (2 gr. per lb. or 286·0 mg. per kg.) have been used successfully (Jones, 1954) in conjunction with antibiotic treatment and attention to diet and hygiene.

Rabbits affected with intestinal coccidiosis respond well to sulphathiazole and its derivatives, to sulphamerazine and to sulphadimidine, but the hepatic forms require systemic sulphonamides; sulphadimidine, sulphamerazine, and sulphaquinoxaline are used in drinking water or food at approximately the same dosage rates as for poultry.

Treatment in Poultry. Sulphadimidine and sulphaquinoxaline are the only sulphonamides considered to be therapeutically and economically sound in the treatment of coccidiosis in chickens and turkey poults (Blount, 1955). Sulphaquinoxaline is slightly more palatable and is preferred for turkeys because of this. However, nitrophenide and nitrofurazone are also extremely effective and may replace the sulphonamides due to their lower toxicity, non-interference with pullorum agglutination tests, and greater palatability. There are two forms of coccidiosis in chickens, that due to *Eimeria tenella* which causes cæcal coccidiosis and that due to *E. necatrix* causing duodenal or 'intestinal' coccidiosis. The latter is more resistant to treatment.

In *cæcal* coccidiosis the drugs may be given in the food or drinking water using one of two methods. Medication may be continuous for five days or intermittently on the '3 : 2 : 3' basis. The intermittent method, first suggested by Davies and Kendall (1954) and now accepted as the best method for administering sulphonamides to poultry, consists of two medication periods, each of three days duration, divided by a two day period when normal food and drinking water are provided. This intermittent method of dosing serves two purposes; the first is relatively incidental in that cumulation and toxicity due to the sulphonamide is avoided; the second is of extreme importance. It is fairly certain that when deaths or fæcal changes are first noticed in a flock there will be a large

proportion of its members unaffected by the coccidia; on a continuous method of administration it is probable that the coccidia would not become established in these birds and no immunity could develop. Thus when treatment is stopped these birds will again be susceptible to infection and further outbreaks will occur.

The aim of all methods of treatment is to allow first stage schizogony to progress normally; this stimulates the production of antibodies by the host and the disease is then terminated at the level of second stage schizogony by the use of drugs. However, the second stage selectivity of sulphonamides is lost if dosage is too high or if high concentrations occur through cumulation, and first stage schizogony is also suppressed. With this suppression the stimulation of antibody formation ceases and with the cessation of treatment the bird, still susceptible, is once more at the mercy of any further infection. *This danger of suppressing the development of immunity cannot be stressed too strongly.*

Sulphadimidine is administered most commonly in the drinking water at the rate of 2 fl. oz. (60·0 ml.) of a 16⅔ per cent. solution of the sodium salt in one gallon (4·5 l.) of water. This provides a concentration of 0·2 per cent.

Sulphaquinoxaline may be given in drinking water (Wilson, 1951) at the rate of 2 fl. oz. (60·0 ml.) of a 10·23 per cent. solution of the sodium salt in 3 gallons (13·5 l.) which provides a concentration of 0·0424 per cent.; or in mash (Horton-Smith, 1951) at the rate of 4 oz. (113·6 G.) of a premix in each hundredweight (51·0 kg.) of mash, which gives a concentration of approximately 0·05 per cent. sulphaquinoxaline. Wilson (1951) prefers a concentration of 0·06 per cent. for both chickens and turkey poults. Sulphaquinoxaline is also used prophylactically in the food of chickens and turkeys (Horton-Smith, 1954; Wilson, 1955) at the rate of 1 oz. (28·4 G.) premix to each hundredweight of food for the first eight weeks of life (chickens); the concentration provided is 0·0125 per cent. However, Horton-Smith (1957) reports variable results when this concentration is used and it is probable that the American method of feeding at a concentration of 0·05 per cent. for the first two days in every five days over a period of a month will prove superior.

Duodenal coccidiosis is treated in a similar manner using sulphaquinoxaline following the report by Grumbles *et al.* (1947). Preventive medication is suggested as being the best method of controlling the disease (U.S.D. 25th Edit. 1955, p. 1026) but a warning is given that medication should cease four days before killing to allow time for sulphonamide elimination.

In all cases of curative therapy, treatment should be initiated immediately signs of disease are shown if the best results are to be obtained.

Sulphonamide resistance by some strains of coccidia are now being reported (Cuckler *et al.*, 1955; Horton-Smith, 1957) and such resistance has been attributed to the widespread use of sub-inhibitory levels in medicated food stuffs (Kendall, 1957).

Sulphonamide potentiation and synergism have also been reported (Joyner and Kendall, 1956). It has been found that proguanil (Paludrine) and several related compounds, possibly by their interference in nucleic acid formation by antagonism to folic acid, will potentiate the action of sulphadimidine against coccidia when present in as small a concentration as five parts per million of feed. Very little further information is at present available.

Non-Specific Systemic Infections.

Pneumonia

Perhaps the most spectacular effect of the sulphonamides on their introduction was the great reduction they effected in the numbers of fatal pneumonia cases in both man and animals. In the *horse*, the majority of pneumonias are due to streptococci which respond extremely well to sulphanilamide, there being no necessity to resort to the more active sulphonamides. In *cattle* and *pigs*, sulphapyridine and sulphadimidine have been widely and successfully used. In *small animals*, sulphadimidine and sulphathiazole have been very effective both for primary infections and infections secondary to viruses, though in the latter case antibiotics are far superior.

Metritis

In *cattle*, metritis has been treated successfully with compressed tablets of sulphadimidine or mixed sulphonamides, but here also broad-spectrum antibiotic tablets have proved more efficient in bacterial metritis. The same refers to the *mare*. Parenteral administration of sulphonamides has been found useful in cattle but more especially in *sows*. In the latter species, sulphapyridine and sulphadimidine are equally effective.

Urinary Tract Infections

The urinary tract infections in animals are frequently caused by coliforms and it has been found that in cystitis or metritis the more soluble sulphafurazole and sulphamerazine are of most value. Antibiotics of the tetracycline group are more commonly used owing to their greater activity and lower toxicity, but it occasionally happens that resistance to these antibiotics develops and the sulphonamides are then resorted to.

Topical Application. The use of sulphonamides for wound dressings and during abdominal surgery, as well as intraperitoneal and intrathoracic injections, are no longer recommended in the United States. This is due to tests carried out during World War II which indicated that non-infected wounds healed more slowly when dressed with sulphonamides. Meleney (1945) reported irritation of tissue and foreign body reactions in abdominal wounds dressed with sulphonamides.

Nevertheless, sulphanilamide continues to be widely used as a wound dressing, for which it is more suitable than most of the sulphonamides

owing to its greater tissue solubility. Both sulphadimidine and sulphathiazole are nevertheless used extensively for dusting infected abdominal wounds and enterotomy incisions. They are commonly combined with the acridine dyes and antibiotics.

Besides their successful use as wound dressings, the sulphonamides are effective as eye ointments and topical ointments, for which sulphathiazole with its high activity and wide scope is probably the best of the group. The high solubility and neutral reaction of sodium sulphacetamide has made this compound particularly suitable for eye lotions. A 10 per cent. w/v solution is used for superficial effects and a 35 per cent. w/v solution for penetration: both are buffered with about 2 per cent. w/v of boric acid and should be applied about three times daily. The sulphonamides have been used effectively in infectious keratitis (New Forest disease) in cattle at one extreme and in distemper conjunctivitis in dogs at the other.

It should be remembered that pus actively antagonizes sulphonamides and abscesses should be drained and wounds or inflamed membranes cleared of pus before applying the sulphonamide. It is also important to avoid, if possible, the use of all local anæsthetics of the procaine series, including procaine itself, and benzocaine: where large quantities of sulphonamides of the more active type—sulphathiazole—are used the p. aminobenzoic acid released by the anæsthetic is of minor importance.

Dosage

These may be given in tabulated form:

Systemic Sulphonamides:

Sulphonamide	Initial dose according to bodyweight*		Maintenance dose*
	Grammes per kilogramme	Grains per lb	
Sulphadiazine	0·2 Grammes	1½ grains	Half initial dose twice daily.
Sulphamerazine	,,	,,	Half initial dose once daily.
Sulphadimidine	,,	,,	Half initial dose once daily.
	,,	,,	Dog ½ initial dose twice daily.
Sulphathiazole	,,	,,	Ruminants ½ initial dose three times daily.
Sulphafurazole	,,	,,	Others ⅓ initial four times daily

* For all species unless stated.

Systemic Sulphonamides (continued):

Sulphonamide	Initial dose according to bodyweight*		Maintenance dose*
	Grammes per kilogramme	Grains per lb	
Sulphanilamide	0·2 Grammes Small species 0·15 Grammes	1½ grains 1 grain	⅓ initial dose 3 times daily or ½ initial dose twice daily.
Sulphacetamide	0·15–0·2 Grammes	1–1½ grains	Initial dose repeated daily.
Sulphapyridine	0·15 Grammes	1 grain	Half initial dose twice daily.

* For all species unless stated.

With very young animals it is advisable to administer sulphonamides at 2/3rds the above rates, divide the daily doses into smaller quantities, and give them more frequently. Monosodium salts are given at the same rate as their parent compound; dosages of solutions should be multiplied by their dilution, e.g. sodium sulphadimidine 33⅓ per cent. solution will be administered at the rate of 0·6 ml. per kg. which is three times the dose rate of the dry, pure salt.

'*Gut Active*' *Sulphonamides.*

Sulphaguanidine — 0·1–0·3 G. per kg. daily in divided doses (¾–2¼ gr. per lb.)

Phthalylsulphathiazole, Succinylsulphathiazole — 0·1–0·15 G. per kg. in two doses daily. (¾–1 gr. per lb.)

Phthalylsulphacetamide — Calves: 0·35–0·57 G. per kg. (2½–4½ gr. per lb.)
Dogs: 0·15–0·3 G. per kg. (1–2 gr. per lb.)

Sulphaquinoxaline. (*Poultry Only*)

Curative: In food 0·05 per cent.
In water 0·04 per cent.
Prophylactic: In food 0·0125 per cent.

Official Preparations. The following *sulphonamides* occur in the B.Vet.C. in the powder form and as a tablet of unstated strength.

Sulphadiazine	Sulphathiazole	Sulphaguanidine
Sulphamerazine	Sulphapyridine*	Phthalylsulphathiazole*
Sulphadimidine*	Sulphanilamide	Succinylsulphathiazole

Tablets are normally of 0·5 G. size but those compounds marked * are also available in 5·0 G. sizes.

Sulphacetamide and sulphaquinoxaline are official in powder form, but a 6 per cent. eye ointment of sulphacetamide is also official. Sulphafurazole is recognized by the British Pharmaceutical Codex.

The following *sodium sulphonamide salts* are official in the B.Vet.C. as powders only:

Sulphadiazine Sulphapyridine Sulphamerazine

Sodium sulphadimidine and sodium sulphathiazole are official as both a powder and an injection of unstated strength. Sodium sulphacetamide, which has an almost neutral pH in solution, is official as the powder but 10 per cent. and 30 per cent. eye drop solutions (Weak and Strong respectively), and a 6 per cent. eye ointment are also official.

The only *disodium sulphonamide salt*, which is official is Sulphasolucin, derived from sulphanilamide and recognized by the British Pharmaceutical Codex.

Sulphathiazole, sulphaguanidine, sulphanilamide and sulphaquinoxaline are not recognized in the United States Pharmacopœia but appear in the National Formulary. There are also variations in the recognition of various sodium salts and pharmaceutical compounds.

In the United States sulphadimidine is known as sulfamethazine (not to be confused with the British commercial name of Sulphamezathine) and sulphafurazole is known as sulfisoxazole.

Commercially the sulphonamides are available in most pharmaceutical forms. Thus, solutions of sulphadimidine, sulphathiazole, and sulphaquinoxaline are available for addition to drinking water for the treatment of poultry, rabbits etc. Compressed tablets for intrauterine insertion are made, eye ointments, topical ointments, sterile dusting powders, injections of neutral disodium salts, and creams are all available. These may or may not be combined with antibiotics, dyes and other antibacterial substances or potentiators such as urea.

Perhaps the most important commercially available compounds are the triple sulphonamides, the dosage and usage of which depend largely on the individual sulphonamides contained. Combinations may be sulphadiazine, sulphamerazine, and sulphadimidine; sulphadiazine, sulphathiazole and sulphamerazine are contained in Trisulphonamide Tablets of the British National Formulary; sulphadiazine, sulphamerazine, and sulphapyridine, was one of the earliest of the commercial combinations. The proportions are usually equal, but the B.N.F. combination for example, contains less sulphamerazine than the amounts of the other two, which are equal: the variations take into account slower excretion rates and other factors.

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CHAPTER 33

MISCELLANEOUS CHEMOTHERAPEUTICS

UNDER this heading will appear such compounds as the sulphones (relatives of the sulphonamides), the diamidines, the nitrothiazole derivatives, better known in the United States as the Enheptins, nitrophenide, and an additional reference to the nitrofurans; reference will also be made to the trypanosomidal and similar antiprotozoan drugs.

The Sulphones

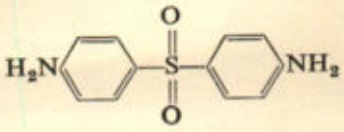
The sulphone chemical grouping has been known for many years, the ethyl sulphones (including sulphonal, a hypnotic) having been introduced as long ago as 1888 by Baumann and Kast, but it was with the discovery by Buttle *et al.* (1947) that 4:4diamino-diphenylsulphone was very effective in protecting mice from streptococcal infections that modern research methods were applied to the sulphones as a group.

In the veterinary field, McEwen *et al.* (1941) found that the compound investigated by Buttle and his colleagues, now officially known as Dapsone in the British Veterinary Codex, was well tolerated by cattle. This stimulated further work by Francis and his colleagues who have shown in numerous publications the value of dapsone in the treatment of bovine mastitis and coccidiosis. Concurrent with this work various sulphone derivatives have been developed which have been used in the treatment of human diseases due to acid fast organisms: their use in tuberculosis has lapsed in favour of antibiotic therapy but they are used extensively in the treatment of leprosy.

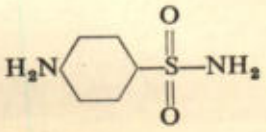
Dapsone, B.Vet.C.

This compound may be considered as the 'parent sulphone' and bears the same relationship to the sulphone group that sulphanilamide does to the sulphonamide group. Chemically it consists of two amino-benzene groups joined by a sulphone (—SO_2—) bridge:

Dapsone



Sulphanilamide



The close relationship with the sulphonamides is immediately apparent. The compound exists as a white odourless crystalline powder which is almost insoluble in cold water, soluble in alcohol, acetone and in dilute hydrochloric acid solutions.

Pharmacology. The *absorption* rates following oral administration are similar to those of sulphanilamide, sulphamerazine, and sulphadimidine, whilst blood levels are maintained for long periods: a single oral dose at the rate of 0·2 G. per kg. body weight provided blood levels of over 1·0 mg. per cent. in a calf for five days (Francis, 1947). *Milk levels* following oral dosing are disappointing, being only a third of the blood levels, whilst those of sulphanilamide are slightly higher (Francis, *loc. cit.*). Nevertheless, dapsone is about three to four times more active than sulphanilamide and the levels following intramammary injection persist for several days.

Excretion via the kidney is slower for dapsone than any of the other sulphones. The *toxicity* of dapsone restricts its use to bovines, in which species it is no more toxic than sulphapyridine or sulphathiazole (Francis, *loc. cit.*): McEwen *et al.* (*loc. cit.*), concluded that it was better tolerated than sulphanilamide. Dapsone is very toxic in sheep.

Action. The *action* of the sulphones is considered to be similar in method to that of the sulphonamides. It is bacteriostatic and coccidiostatic. The drug is mainly active against Gram positive organisms, particularly streptococci, against which it is about three times more potent than sulphanilamide, whilst when compared with the hyterocyclic sulphonamides it appears to be one to two times less active. However, dapsone is much less active than these same heterocyclic compounds against the Gram negative organisms.

Uses. There are only two diseases in which dapsone is used: they are streptococcal mastitis and coccidiosis of cattle. For the latter use the high dosage makes it a very expensive treatment; the oral *dosage* consists initially of 0·1 G. per kg. ($\frac{3}{4}$ gr. per lb.) body weight, followed by half this dose daily for up to five days.

In *mastitis*, dapsone may be used alone or in conjunction with penicillin as an oily suspension. The *dosage* is 8·0–10·0 G. in the form of a 33$\frac{1}{3}$ per cent. mineral oil suspension injected into infected quarters on two or three occasions at 48 hour intervals. When combined with 50,000 or 100,000 units of penicillin one dose is often sufficient. It is essential to leave dapsone preparations in the udder for as long as possible without milking (24–36 hours has been recommended) if the best results are to be obtained, mainly because of the low milk solubility and the prolonged action. Dapsone has for this reason been recommended in 12·0 G. doses for dry cows in which the dapsone compound is injected and left until

calving. Milk clots and slight irritation have been reported (Simon *et al.*, 1950) following the introduction of dapsone into the udder, but these effects are of a temporary nature. The intramammary injection has also been used effectively in rickettsial keratoconjunctivitis (pink-eye) of cattle and sheep.

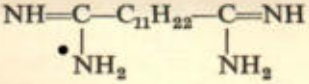
The *official* preparations consist of Dapsone, B.Vet.C., Intramammary Injection of Dapsone, B.Vet.C. which is a 33⅓ per cent. suspension in a mixed paraffin base, and a similar preparation containing in addition 50,000 units of penicillin.

Commercially there are available dapsone powder, an intramammary injection containing 4·0 or 10·0 G. of dapsone with 100,000 units of penicillin, and also one containing 0·15 G. chloromycetin and 0·3 G. dapsone per tube. These antibiotic-dapsone preparations make use of the synergistic action which is shown by such combinations.

The Diamidines

These are a group of chemotherapeutic compounds found to have a trypanocidal activity related directly to the guanyl (that is, the amidine) organic group, $NH{:}C(NH_2)$—. The presence of two of these groups separated by a paraffin hydrocarbon chain was found to give a high trypanocidal effect which increases as the length of the paraffin chain is increased and reaches a maximum at undecane diamidine (i).

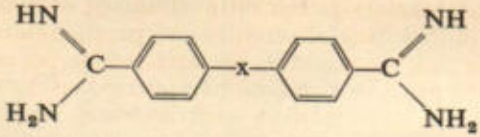
(i)



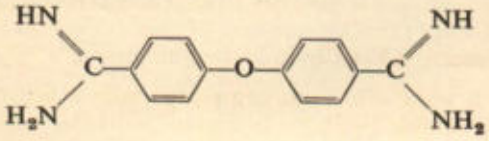
Investigations were extended from these alkyl diamidines to the aromatic or benzene ring diamidines, and it was found that if two benzamidine groups $NH{:}C(NH_2)$—C$_6$H$_4$—were joined, either by (a) an oxygen atom, (b) a dioxyalkyl chain —O—C_nH_{2n}—O—, or by (c) an ethylene linkage —C(H)=C(H)—, a series of trypanocides of even greater activity was produced. It was also found that these compounds possessed activity against other protozoa such as the babesias, and in addition antibacterial activity similar in character to that of the sulphonamides, but of a lesser degree (Wien *et al.*, 1948); the action is thought to be one of interference with oxidation processes within the bacteria.

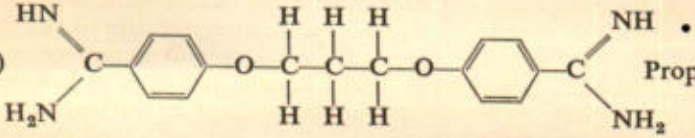
When administered internally the diamidines cause an arterial dilatation and a lowering of blood pressure; there is also an increase in tone and movement of intestinal muscles. Kidney and liver damage are the main toxic effects: these effects result in vomiting, diarrhœa, jaundice etc.

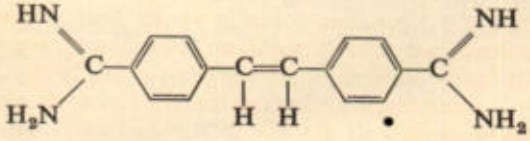
The main examples of aromatic diamidines conforming to the group formula (ii), where 'X' may be any one of the three linkages a, b, or c,

(ii) 

mentioned above, are Phenamidine where x = a, Propamidine where x = b, 'n' being 3, and Stilbamidine where x = c. The formulæ for these three are therefore as in iii, iv, and v, respectively.

(iii)  Phenamidine.

(iv)  Propamidine.

(v)  Stilbamidine.

A further compound similar to Propamidine in formula but where 'n' is 5 has also been widely used as a trypansomidal drug: the propane of propamidine becomes pentane, giving the name pentamidine.

The diamidines have been used either as free bases or as one of three salts, the dihydrochloride, the dimethylsulphonate or the isethionate (dihydroxyethane sulphonate). In the veterinary field the isethionates are used most frequently. Substitution products have also been used, the dibromopropamidine isethionate probably being the best known of these.

Propamidine Isethionate, B.Vet.C.

This white, hygroscopic, odourless, bitter tasting powder is soluble in water, reasonably so in alcohol and glycerin, but insoluble in other organic solvents. The halogen derivative *Dibromopropamidine Isethionate*, B.Vet.C. is similar in its characters but its solubility in water is greater, and in alcohol less, than that of its parent compound.

These compounds were, but are no longer used for Babesia infections in dogs, their indications being for topical and intramammary use only. They are applied as wound dressings in the form of water miscible creams

[illegible]propamidine has been used along with sulphathiazole for intramammary injection in the treatment of mastitis. The halogen salt is several times more active than the parent compound.

Both these compounds are somewhat irritant to normal tissue.

Phenamidine Isethionate, B.Vet.C.

This compound is a white odourless compound with a bitter taste. It is soluble in water but almost insoluble in organic solvents.

Although the compound has been used in the treatment of demodectic mange in dogs, this practice is largely discontinued because of the toxic effects and the variability of response. Its use is therefore confined to the treatment of Babesia infections in cattle, horses, and dogs. It is administered subcutaneously to horses and cattle in doses of 0·03 ml. of a 40 per cent. solution per kg. body weight (1·5 ml. per cwt.), and to dogs at the rate of 0·3 ml. of a 5 per cent. solution per kg. body weight (0·136 ml. per lb.). Single doses are usually sufficient, but doses may be repeated after 5–6 days in canine Babesia infections (Rao *et al.*, 1948). *Stilbamidine* has been used in human trypanosomiasis but the less toxic *pentamidine* is now preferred even though its activity in some cases is less. Neither is now used for veterinary purposes to any appreciable extent, though in *Anaplasma marginale* and *Theileria dispar* infections in cattle (Camou *et al.*, 1953) pentamidine, at the rate of 4·0 mg. per kg. given intramuscularly, was combined with an equal amount of euflavine given intravenously: good results were claimed. Jones (1954) also draws attention to the strong action against *T. brucei* and *T. evansi*, neither of which responds to the phenanthridium compounds, though they are reasonably sensitive to quinapyramine. A diamidine with the commercial name of Berenil in which X = —NH.N:N— has been reported to have anti-trypanosomidal action (Bauer, 1955a, and b; Milne *et al.*, 1955) but so far this has not been convincingly demonstrated. Davey (1957) suggests it might prove of value where resistance to ethidium and quinapyramine develops.

Other Trypanosomidal Drugs. The phenanthridium amine compounds, Quinapyramine (Antrycide), and suramin can be conveniently mentioned here.

The amino-phenanthridium compounds. The main preparations in use are the two compounds, dimidium bromide and ethidium bromide.

Dimidium Bromide, B.Vet.C.

Chemically, dimidium bromide consists of 2 : 7 diamino, 10 methyl, 9 phenyl, phenanthridium bromide. It is a dark red crystalline bitter tasting, odourless substance which is soluble in water to the extent of 1 in 250; it is soluble in alcohol at a ratio of 1 : 70. Because of this low solubility in cold water the compound is used as a freshly prepared supersaturated solution at a concentration of 1–2 per cent. This may be given by the subcutaneous, intramuscular, or intravenous route: large reactions occur following subcutaneous injection, but reaction is relatively slight following intramuscular injection: the latter route appears to be preferred by most workers. The compound causes a slight fever during the first few days after dosage and delayed photosensitization occasionally occurs, though recovery usually follows improved grazing (Evans, 1948). This situation in Sudan does not apply to Nigeria where large scale toxicity has occurred (Carmichael, 1950). This latter report is difficult to reconcile with reports of a few cases of photosensitization in the Gold Coast, where better grazing was also followed by the absence of any outbreaks. Liver damage, to which the photosensitization is attributed, is marked during the first nine weeks subsequent to doses of 1·25 mg. per kg. body weight (N. Rhodesia, Report 1952.)

The chemotherapeutic action of the phenanthridium compounds including dimidium bromide is believed to be due to interference with cell division. The drug is markedly active against *T. congolense*, but less active against *T. vivax*, and inactive against *T. brucei* and *T. evansi*. The first three cause *nagana* or *tsetse fly disease* in almost all species of domestic animals in tropical Africa, whilst the last named causes *surra* in most species, but occurs in the non-tsetse areas—N. Africa, India, Australia, America and the Philippines. The diseases are transmitted by biting and blood sucking flies.

Dimidium bromide is mainly a curative drug but protection has been conferred for an average of 138 days (Robson *et al.*, 1954). The British Veterinary Codex mentions 28 days as the protective period.

Drug resistance develops but the organisms may still be sensitive to ethidium bromide or quinapyramine (Robson *et al.*, *loc. cit.*; Report: Kenya, 1953). The reverse does not hold good, for an organism resistant to quinapyramine may also be resistant to dimidium bromide (Robson *et al.*, *loc. cit.*).

Dosage of dimidium bromide varies from 1·0 to 1·5 mg. per kg. body weight (51·0 to 76·5 mg. per cwt.) in *horses* and *cattle*. In *dogs* the lower rate of 1·0 mg. per kg. is usual.

Ethidium bromide differs in composition from dimidium bromide only in the substitution of an ethyl group for a methyl group, and is therefore 2:7 diamino-10 ethyl, 9 phenyl, phenanthridium bromide. The compound is far more active than dimidium bromide against *T. congolense* and *T. vivax*, and toxicity is less; photosensitization does not occur (Annual

Report, Kenya 1953; Unsworth, 1954; Thienpont *et al.*, 1955), but severe local reactions result from subcutaneous injection and the intramuscular route is preferred, for the reactions and lameness which follow its use are only slight (Leach *et al.*, 1955).

Dosage consists of a 1 per cent. aqueous solution given at the rate of 0·25 to 1·0 mg. per kg. bodyweight (12·75 mg. to 51·0 mg. per cwt.). Higher rates do not cause appreciable toxicity but more than 2·5 mg. per kg. (127·5 mg. per cwt.) should not be given because of local reactions at injection sites (Leach *et al.*, *loc. cit.*). These doses clear the parasite from the blood in 24 hours and a febrile reaction may also occur 24 hours subsequent to dosing: protection may last for more than 4 months (Wilson *et al.*, 1953; Unsworth, 1954a, and b; Thienpont *et al.*, 1955).

Following a report by Woolfe in 1956 that the changing of the methyl group of phenanthridial compounds to ethyl, propyl, or allyl groups, resulted in increased trypanosidal action, various derivatives of phenanthridium have been tried in the field with encouraging results. One in particular referred to as R.D. 2801 and subsequently given the commercial name of Prothridium gave protection for 6 months at a dosage rate of 2·0 mg. per kg. (102·0 mg. per cwt.) in both Tanganyika and Nigeria, with no toxicity other than local reaction from subcutaneous injections (Watkins and Woolfe, 1956; Robson *et al.*, 1957.).

Quinapyramine Chloride, B.Vet.C. and Sulphate, B.Vet.C.

These salts of quinapyramine, known commercially as Antrycide, are white to pale yellow crystalline powders which are odourless but have a bitter taste. The chloride is soluble to the extent of 2 per cent. in boiling water but is only slightly soluble in cold water. On the other hand the sulphate is water soluble (1 : 2). Both are almost insoluble in organic solvents. Because of their different solubilities these two compounds have complementary effects against trypanosomes when combined in a single injection. The soluble compound has short but rapidly acting therapeutic effect, whereas the long acting slowly absorbed chloride is prophylactic. The sulphate provides initial protection and eliminates subclinical infections, whilst the chloride continues the protection after the effect of the sulphate has disappeared.

Quinapyramine is active against *T. congolense*, *T. evansi*, and *T. vivax* in cattle, horse species, camels and dogs. *T. equiperdum* is also susceptible (Georgescu *et al.*, 1955). *T. brucei* is less affected; action against *T. simiæ* is reported (Nash, 1956). The action is attributed to the inhibition of growth and cell division (Ormerod, 1951).

Toxicity is not so important as with the phenanthridium compounds except in young stock, where overdosage may cause trembling, sweating, and salivation, followed, in severe cases, by an increase in respiration and

heart-rate, collapse, and death. In normal dosage, symptoms, when they occur, are only of a mild and transitory nature.

Dosage need not be assessed meticulously except in young stock, and animals weighing less than 3 cwt. (150·0 kg.).

Quinapyramine Sulphate:

Animals weighing: up to 150·0 kg. (3 cwt.) individually assessed at the rate of 5 mg. per kg. body weight (2·27 mg. per lb.).

150·0–200·0 kg. (3–4 cwt.) body weight: 1·0 G.
200·0–350·0 kg. (4–7 cwt.) body weight: 1·5 G.
Over 350·0 kg. (7 cwt.) body weight: 2·0 G.

These doses are given subcutaneously as a 10 per cent. solution, though in horses, where sloughing may be severe, it is advisable to inject intramuscularly a 5 per cent. solution (Hiermann, 1955), or to divide the dose into two or three injections given at different sites.

Sulphate/chloride prophylactic mixture:

This is available in powder form consisting of three parts sulphate and four parts chloride. The official solution contains 10 per cent. of the sulphate and 13·3 per cent. of the chloride, and the following doses are suggested:

Animals weighing:

Up to 150·0 kg. (3 cwt.)—0·05 ml. per kg. body weight. (0·0227 ml. per lb.)
150–200·0 kg. (3–4 cwt.)—10·0 ml.
200·0–350·0 kg. (4–7 cwt.)—15·0 ml.
Over 350·0 kg. (over 7 cwt.)—20 ml.

It will be seen that the dosage is estimated according to the sulphate content. The chloride is ignored, for absorption from the subcutaneous depot is so slow as to be insignificant from a toxicity view point. Indurations and reactions may persist for several months following subcutaneous injection.

Protection against dourine transmission has been conferred by injecting stallions with the prophylactic mixture on one or two occasions in the breeding season, an interval of 90 days between injections being satisfactory. Transmission during service can also be prevented by injecting mares at least 18 days before the day of service (Georgescu *et al.*, *loc. cit.*).

Protection against *T. congolense* infection in cattle has been conferred for an average of 230 days (almost twice that of dimidium bromide) according to Robson *et al.* (1954), but prophylactic doses are normally repeated every two months: this can prevent deaths from *T. congolense*

or *T. vivax* for at least 18 months (Annual Report N. Rhod. 1952). Suramin will considerably increase the protective power of quinapyramine (Nash, 1956; Williamson *et al.*, 1956) as well as that of ethidium.

An interesting report (Soltys, 1955) indicated that a solid immunity was achieved during 28 months of protective treatment with quinapyramine. He was unable to break this immunity either artificially or by natural infection. This experiment is being repeated but the results are not yet available. Should this discovery by Soltys prove repeatable the position of trypanosomiasis as one of the major veterinary problems will change radically.

Resistant strains develop in animals which become infected as the tissue levels fall but parasites may not be detected in the blood, though they should be apparent in gland smears. Chronically infected cases of this type deteriorate in condition and treatment with other agents such as suramin often fails. However, it has been shown that quinapyramine resistance is not permanent (Nash, 1954), and that resistance to 5·0 mg. per kg. doses may be lost after about 110 days (a *T. congolense* strain resistant to 8·0 mg. per kg. and then passaged through rats was used in the experiments reported). This indicates that quinapyramine resistance may be of less importance than previously thought.

Compounds related to quinapyramine, including one commercially known as Tozocide, are being developed. Experimentally they are less toxic and more active than the parent compound (Austin *et al.*, 1957), but field reports are not yet available. It is probably that these also will benefit by combination with suramin.

Suramin, B.Vet.C.

This is a complex aromatic organic compound with an empirical formula of $C_{51}H_{34}O_{23}N_6S_6Na_6$. This sodium salt is a white or pinkish white hygroscopic powder with a solubility of 1 in less than 1 of water, though it is almost insoluble in organic solvents.

It has marked curative, but less useful prophylactic properties against *T. evansi* (the cause of surra) in horses, camels, cattle, and dogs, against *T. brucei* (nagana) in horses, dogs, and sometimes cattle, and against *T. equinum* which causes Mal de Caderas in equidæ. It has also been used against *T. equiperdum*, the cause of dourine in horses.

The future of suramin would seem to be as a synergistic potentiator of the phenanthridium and quinaldine derivatives, for when suramin is combined with such compounds the period of protection is approximately twice that of the compound alone. The reason for this is unknown, but may be associated with the protein binding capacity of the suramin.

Toxicity is a real danger, for the therapeutic index is very narrow: horses and donkeys are very susceptible but camels are quite resistant. Symptoms are those associated with liver, kidney, spleen and adrenal gland damage.

Therapeutic dosage:

Horse: 7·0–10·0 mg. per kg. body weight (0·35–0·5 G. per cwt.)
Camel: 8·0–12·0 mg. per kg. body weight (0·4–0·6 G. per cwt.)
Cattle: 12·0 mg. per kg. body weight (0·6 G. per cwt.)

The dose in horses may be repeated up to 3 times at weekly intervals.

Prophylactic doses for the three species vary from 1·0–2·0 G. repeated at 10-day intervals.

These doses are given as a 10 per cent. solution.

A recent report (Holz *et al.*, 1956) indicates that administration, which, although the intravenous route is officially recommended, is usually by intramuscular or subcutaneous injection, may be assisted by the inclusion of 50 units of hyaluronidase in each dose. This prevents the development of local swellings and necrosis without affecting the anti-trypanocidal action of the suramin.

Other drugs which have been used for their trypanosomidal action are: *Antimony and Potassium Tartrate*, B.Vet.C. (Tartar Emetic) in intravenous doses of 3·0–5·0 mg. per kg. for horses and cattle (0·15 –0·225G. per cwt.), and 1·0–3·0 mg. per kg. for dogs and cats (0·45–1·36 mg. per lb.); *Stibophen*, U.S.P., a sodium salt of a complex antimonial organic compound; and earlier still, several dyes such as *Trypan Red* and *Trypan Blue*. These compounds are neither so safe nor so effective as the more modern drugs.

Antibiotics may be used in future if the good experimental reports which are now appearing (Packchanian, 1957) are substantiated in the field.

Davey (1957) recommends the following drugs for the treatment of trypanosomiasis in the different species.

Curative Therapy. T. congolense and *T. vivax.*

Cattle: Ethidium bromide or quinapyramine methyl sulphate.
Horse: *T. congolense:* quinapyramine methyl sulphate 3·0 mg./kg.
T. vivax: quinapyramine methyl sulphate 5·0 mg./kg.
Dog: *T. congolense:* quinapyramine methyl sulphate 3·0 mg./kg.

T. simiæ.

Pig: Quinapyramine methyl sulphate. (Up to 5·0 mg./kg., repeated)

T. evansi, T. equinum and *T. equiperdum:*

Horse: Quinapyramine methyl sulphate—up to 5·0 mg./kg.

T. evansi.

Cattle: Quinapyramine methyl sulphate—3·0 mg./kg. (India).
Camel: Either suramin or quinapyramine methyl sulphate.

Prophylaxis. The prophylactic quinapyramine salt mixture is the only drug recommended. It should be effective against *T. congolense, T. vivax, T. evansi, T. equiperdum* and possibly *T. equinum.*

Antipiroplasm Drugs. The use of phenamidine has been mentioned (p. 587). Other compounds which are active against babesia infections are Quinuronium Sulphate, B.Vet.C., Euflavine, B.Vet.C. and Trypan Blue, B.Vet.C. Redwater and anaplasmosis premunitive inoculations are also used in controlling these tick-borne infections.

Quinuronium Sulphate, B.Vet.C.

This complex urea compound has been widely used under the commercial names of Acaprin, Acapron, Babesan, Diveronel, Pirevan and Piroparv. It is a white to yellow crystalline powder with a bitter taste which is usually marketed as a stable 5 per cent. aqueous yellow solution.

The drug is used in *Babesia caballi* infections (biliary fever) in horses, *B. bovis* and *B. bigemina* infections in cattle, (bovine redwater and tropical redwater or Texas fever, respectively), *B. ovis* and *B. motasi* in sheep, *B. suis* of pigs, and *B. canis* (biliary fever or malignant jaundice) of dogs.

If used in the early febrile stages of the disease clinical cures (not necessarily eradication of infection), can be achieved in 24–48 hours, though a second injection may be needed on the day following or the second day. The course of treatment should not be repeated for a period of at least two weeks, but preferably 3 months: this is due to the occasional development of sensitization, which may result in severe shock and death when treatment is repeated.

Complete elimination of the Babesia from the body renders the animal susceptible to reinfection and therefore, in areas where the disease is endemic, it is usual to inoculate animals with blood containing virulent strains of the parasite, controlling any fever with chemotherapeutics, including quinuronium sulphate. On recovery, these animals retain a number of organisms in their system which maintain the resistance of the animal to reinfection. This phenomenon is known as *premunition.*

Toxic reactions to quinuronium sulphate are similar to those for quinapyramine, with muscle tremors, salivation, urination, and defæcation: these symptoms may persist for 6–10 hours. Severe shock may also occur, with a rapid fall in blood pressure, and may result in sudden death.

Dosage for *horses* is at the rate of 0·3–0·5 mg. per kg. (30·0–50·0 mg. per cwt.), for cattle, sheep, and pigs, at the rate of 0·5 mg. per kg. (50·0 mg. per cwt.), and for dogs 0·25 mg. per kg. body weight (0·117 mg. per lb.).

The official solution is of a 5 per cent. concentration; this should be given *subcutaneously only*, in all species except the sheep and dog. For sheep and dogs the solution should be diluted to give a 0·5 per cent. concentration (i.e. ten times dilution) for administration by subcutaneous injection.

Trypan Blue, B.Vet.C.

This is one of the azo dyes and is therefore related distantly to the sulphonamides. It is a bluish grey, water soluble powder which in solution gives a blue-violet colour.

It was one of the earlier agents used against the babesias, but is ineffective against *B. equi*, *B. bovis* or *B. gibsoni*. The drug is relatively non-toxic but stains tissues and secretions, including milk, a blue-green colour which may persist for several weeks.

Dosage by intravenous injection only:

Horse and Cow	1·0–4·0 G. (15–60 gr.)
Sheep:	0·5–1·0 G. (7½–15 gr.)
Dog:	20·0–150·0 mg. (⅓–2½ gr.)

Solutions should be freshly prepared and given at body temperature in concentrations of from 1–2 per cent. Shock may result if injections are given too rapidly. Subcutaneous injections cause sloughing.

Other compounds used include arsenicals such as neoarsphenamine, and antimony preparations have also been used.

Phenamidine has largely replaced all these compounds.

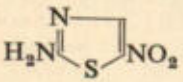
The 'Nitro' Drugs

This group of compounds has developed rapidly in recent years. Veterinary applications are mainly in the poultry field, though the nitrofurans have antibacterial applications in other species. The most important are the nitrothiazole compounds (better known in the United States as 'enheptins'), the two nitrofurans, nitrofurazone and furazolidone, and nitrophenide.

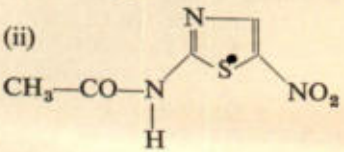
Aminonitrothiazole, B.Vet.C.

The chemical formula is 2-amino-5 nitrothiazole (i)

(i)



(ii)



and the compound is a greenish, or orange-yellow, bitter tasting, odourless powder only slightly soluble in water.

The compound is used both therapeutically and prophylactically against blackhead (histomoniasis) in turkeys. This is a disease in which the liver is badly damaged by the attack of a protozoan parasite *Histomonas meleagridis:* infestations are contracted by ingestion of the eggs or adult worm of *Heterakis gallinæ*, which itself parasitizes fowls and acts as an intermediate host for the protozoan. Until the advent of aminonitrothiazole there was no drug capable of controlling the infection once contracted, though sodium acetarsol is a useful prophylactic when given before infection occurs and administered continuously. McGregor (1949) introduced aminonitrothiazole and demonstrated its superiority over all other compounds. It is now used extensively wherever turkeys are

reared. The compound must be used continuously to give maximum protection. It acts on both parasite and worm intermediate host (Swales, 1950).

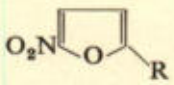
Treatment is achieved by feeding mash medicated at the rate of 0·1 per cent. for 14 days when *prophylaxis* should commence by reducing the level to 0·05 per cent. or by giving water medicated at the rate of 0·03 per cent. with a soluble salt. Medication should continue for at least 20 weeks. Individual treatment may be achieved by giving 100·0 mg. capsules to birds *after feeding*. Unlimited water supply should be available at all times to offset the toxic effects which are especially dangerous in young stock and are mainly associated with the kidneys (Blount, 1955).

The acetylated compound with the chemical composition of 2-acetyl-amino-5 nitrothiazole represented as in (ii) is also available and is just as effective as well as being cheaper to produce. Brander *et al.* (1950) reported no ill effect on fertility in males or females, or on hatchability of eggs, when fed for several months, and the compound may therefore be used in breeding stock at the levels quoted for the parent compound. The nitro-thiazole derivatives are also useful in other species of poultry.

In the United States aminonitrothiazole is known as Enheptin T, and the acetyl compound as Enheptin A.

The Nitrofurans

The compounds of this group, which have a general formula represented as in (iii), have been mentioned in Chapter 21 for their antibacterial effect. Their main use in the veterinary field is in the treatment of coccidiosis

(iii) 

and Salmonella infections of poultry, and furazolidone has also been shown to be very effective in experimental histomoniasis of turkeys (Horton-Smith *et al.* 1956).

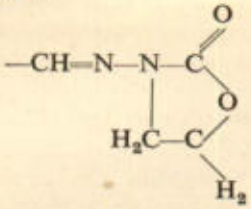
Nitrofurazone, B.Vet.C.

This compound has a chemical composition in which the side chain 'R' consists of CH═N—NH—CO—NH_2. It is only slightly soluble in water.

In the *treatment* of cæcal coccidiosis it is given for 7–10 days in the food at a concentration 0·02 per cent. (1 lb. of a 2·5 per cent. premix in 1 cwt. of feed—1·0 kg. in 125·0 kg.). For *prophylaxis* it may be given at the rate of 0·01 per cent. for 10 days subsequent to moving onto suspected ground or it may be given continuously during the first 3 months of life, when the danger is maximal, at the rate of 0·005 per cent. If the continuous method is used, vitamin B supplements are advisable either in the form of yeast, dried grass or lucerne, or milk products.

A soluble form is available for administration in drinking water at the rate of 0·01 per cent. for curative purposes and 0·005 per cent. for intermittent prophylaxis.

Furazolidone in which 'R' is



has found a far wider application. It is effective against coccidiosis in the same concentrations as nitrofurazone but in addition it is very effective against Salmonella infections in pigs, calves, and poultry. Furazolidone has been used effectively in experimental blackhead infections in poultry, and Blount (*loc. cit.*) suggests it as the drug of choice for hexamitiasis of poultry.

Dosage of furazolidone in poultry for purposes other than the treatment of coccidiosis is 0·04 per cent. of the feed for 10 days as a curative treatment and 0·005–0·01 per cent. continuously for prophylactic purposes. Horton-Smith *et al.* (1956, *loc. cit.*) showed that 0·015 per cent gave protection from experimental infection with *H. meleagridis* in turkeys. This concentration, however, will produce serious side effects in the testes of cockerels (Cooper *et al.*, 1956), and furazolidone is therefore contra-indicated in breeding stock until more is known about the effects of the compound in poultry.

In salmonellosis of calves, 0·5 G. twice daily for seven days has been recommended. Tablets may be used (50·0 mg. size) for all species where individual dosing is required. In birds, no individual weighing less than 1 lb. (0·45 kg.) should be treated: birds of 1–4 lbs. (0·45–1·72 kg.) take ½ a tablet, 4–10 lbs. (1·72–4·5 kg.) take 1 tablet, and over this weight two tablets may be needed. Up to 2 fl. oz. (60·0 ml.) of water should be administered to each bird after the tablets. This treatment should be given on three successive days and then medicated mash therapy instituted.

Toxicity of the nitrofurans should not be seen when the recommended doses are used, but if water supplies are restricted, or excessive doses given, birds may show symptoms. Blount (1955 *loc. cit.*) described the typical picture of nitrofurazone poisoning: motionless, silent birds, ruffled and bedraggled, with no interest in food or water; post-mortem lesions were cardiac degeneration and patchy enteritis. Jordan (1955) added the symptoms of extreme nervous excitement, from observations in day old chicks following a long journey in cold weather.

Nitrophenide or m, m′ dinitrodiphenyldisulphide has been used to control cæcal and duodenal coccidiosis in poultry in the United States.

It interferes with the production of oocysts and also with the sporulation of any oocysts passed, but otherwise appears to be little better than other compounds. (Horton-Smith, 1957).

Dosage for curative purposes is at the rate of up to 0·05 per cent. in the feed, whilst for prophylactic purposes 0·0125–0·025 per cent. concentrations have been used continuously. At these doses toxic symptoms are not frequent but the safety margin is narrow. Symptoms are of a nervous type with convulsions.

Nitrophenide is extremely toxic to dogs (Elsasser, 1951).

Substituted Carbanilide Complexes. One of these, known commercially as Nicarbazin, is being assessed and so far has been found to be reasonably well tolerated. Prophylactic feeding of 0·01–0·02 per cent. concentrations have protected chickens from both cæcal and duodenal coccidiosis (Cuckler *et al.*, 1956), and it has been claimed not to interfere with the development of immunity. However, depression of hatchability, loss of shell pigmentation, and changes in egg quality, make the drug contra-indicated in laying hens (Horton-Smith, 1957, *loc. cit.*).

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PART FOUR

SPECIFIC THERAPEUTICS AND BIOLOGICALS

CHAPTER 34

THE VITAMINS

A VITAMIN is an organic compound which, in very small quantities, is essential to normal tissue metabolism. In the absence of vitamins a syndrome often develops that is specific to each vitamin. Definitions which have included references to 'essential nutritional factors' or 'accessory nutritional factors' are incorrect in that some vitamins need not be included in the diet of some species, for they are either synthesized by the intestinal flora (vitamin B complex in ruminants) or in some body tissue as yet unknown (vitamin C in most domestic animals—guinea pig, monkeys and man do not synthesize vitamin C and must therefore obtain all their requirements from outside sources).

Vitamin deficiencies were at one time very common but the dangers of such deficiencies and the specific symptoms are now so widely recognized that acute deficiencies are rare. Chronic deficiencies do not cause such characteristic symptoms and may exist unrecognized: intensively reared animals, especially those reared on synthetic or near synthetic diets, are more likely to suffer from such deficiencies. This possibility is also well recognized and reputable manufacturers of animal feedstuffs are extremely careful when formulating and compounding rations, to ensure that wherever possible adequate and stable vitamins are included.

Because some species are normally independent of certain vitamins in their diet, it must not be assumed that such species cannot suffer from deficiencies or insufficiencies of those vitamins. For example, vitamin B_{12} is a cobalt compound; should a ruminant be kept on a cobalt free diet, vitamin B_{12} is not synthesized by the ruminal flora and a vitamin B_{12} deficiency arises.

The presence of a vitamin in a foodstuff is also no guarantee that a deficiency of that vitamin will not occur, for other factors may be present in the diet which prevent assimilation. It is well known that continuous therapy with liquid paraffin will prevent the absorption of carotene by dissolving the compound and forming a solution which is not absorbed by the intestinal mucosa: vitamin A deficiencies may result. It is also an established fact that excess cod-liver oil in the diet will quickly produce a vitamin E deficiency with the onset of muscular dystrophy. Intestinal infections interfere with vitamin A absorption and utilization; the disturbance of fat hydrolysis and absorption automatically influences the absorption of all fat soluble vitamins: the absence of bile salts or pancreatic enzymes prevents the absorption of both fats and fat soluble vitamins.

It had, until recently, been thought that excess of a vitamin was of little significance but it has been shown by several groups of workers that a gross excess of vitamin D, known to decrease the incidence of milk fever if fed in large quantities for about 5 days before calving, will cause widespread calcification of tissues if given in the same doses for a further three or four days.

The *assay* of the vitamins has been mainly biological and these methods must still be used for estimation of the natural vitamin content of foodstuffs. Nevertheless, most vitamins can now be produced synthetically and chemical methods of estimation are increasingly used.

The *nomenclature* of vitamins is undergoing metamorphosis as more of their chemistry becomes known. Initially the name *vit-amine* was adopted for an essential nutritional and growth factor, but it was later found that all such compounds were not proteins or amino-acids, and the name was reduced to *vitamin*. As different forms of vitamins were recognized they were designated by numbers, as, for example, vitamins D_1, D_2 etc.: later it was found that vitamin D_1 was not one but two different compounds so that no vitamin D_1 is now recognized. This nomenclature has led to confusion and the vitamins are now more frequently referred to by their chemical names: calciferol or vitamin D_2; pyridoxine or vitamin B_6; cyanocobalamin or vitamin B_{12}; α, β, and γ, tocopherols or vitamin E.

Classification of the vitamins is an arbitrary one which divides the vitamins into two groups according to their solubility in water, or fats and oils. As absorption is better when substances are water soluble or water miscible, compounds exerting the actions of fat soluble vitamins but having water solubility as a characteristic have been devised: these are referred to as water-soluble analogues, e.g. Menadione Sodium Bisulphite, U.S.P. which is a water-soluble salt of menaphthone. Water miscible dispersions of vitamin A are available.

1. Water soluble vitamins.

The Vitamin B complex:	Aneurine—vitamin B_1.
	Riboflavine—vitamin B_2 or G., lactoflavin.
	Pyridoxine—vitamin B_6.
	Nicotinic Acid or pellagra preventing (P.P.) factor, niacin.
	Cyanocobalamin—vitamin B_{12}.
	Biotin—vitamin H, coenzyme R, bios II.
	Para-aminobenzoic acid—PABA, vitamin H.
	Inositol—Bios I.
	Folic Acid—*L. casei* factor.
	Pantothenic Acid—filtrate factor.
	Choline.
Vitamin C.:	Ascorbic Acid.
(Vitamin P.):	

2. Fat Soluble Vitamins.

Vitamin A.:	Precursor: α, β, γ, carotenes and kryptoxanthine.
	Vitamin A_1.
	Vitamin A_2.
Vitamin D.:	Calciferol: vitamin D_2
	7, dehydrocholesterol: vitamin D_3.
Vitamin E.:	α, β and γ tocopherols.
Vitamin K.:	menaphthone: vitamin K_3.

Two other vitamins have been postulated but so far the evidence advanced has been inconclusive. These are vitamin P which has been considered an associate of vitamin C concerned with vascular permeability, and vitamin U reputed to be associated with vitamin K and responsible for the prevention of gizzard ulceration in chickens.

The *stability* of vitamins varies considerably but certain principles can be applied to all. The majority of vitamins are sensitive to light and should be stored in light proof containers. Some, but not all, are susceptible to oxidation, and it is wise to store them in airtight containers: calciferol for example is kept under nitrogen in sealed ampoules. The majority of water soluble vitamins are less stable in solution, whilst the fat soluble vitamins are generally more stable in solution. Most vitamins are heat stable, the main exceptions being vitamins A, D and E; calcium pantothenate is also heat labile but vitamin C, once thought to be heat labile has been shown to be heat stable in the absence of oxygen.

Water Soluble Vitamins

The water soluble vitamins comprise the vitamin B complex, vitamin C and the disputed vitamin P. They may all be obtained from either plant or animal sources; in addition vitamin C is manufactured in the tissues of domestic animals, possibly in the gastro-intestinal mucosa. The vitamin B complex is available to ruminants following synthesis by ruminal bacteria: in other species the vitamin B complex is synthesized by cæcal bacteria, especially in the horse, but very little is available to the animal short of coprophagia, which is not an uncommon source of vitamin B in the animal kingdom.

The Vitamin B Complex

This complex includes a number of familiar names but there is also a number of vitamins the functions and importance of which are imperfectly understood:

Aneurine or vitamin B_1.
Riboflavine or vitamin B_2.
Pyridoxine or vitamin B_6.
Nicotinic acid.
Cyanocobalamin or vitamin B_{12}.

Subsidiary, but nevertheless quite important members of the group, are: biotin or vitamin H; para-aminobenzoic acid or vitamin H^1; pantothenic acid; choline; inositol and folic acid.

Aneurine Hydrochloride, B.Vet.C.

This vitamin is also known as Thiamine (U.S.P.), and vitamin B_1. Aneurine hydrochloride is a white crystalline powder with a slight but characteristic odour. It is very soluble in water (1 : 1), and in glycerin, but not in ethyl alcohol, ether, acetone, or similar organic solvents.

Sources. The majority of aneurine used therapeutically is a synthetic product, but it is present in most plants, the most concentrated sources being yeast and wheat germ: ruminant requirements are met by bacterial synthesis in the rumen. Milk, meat, eggs, and fish, are the main sources for carnivores.

Stability. Aneurine is one of the least stable of the B complex members, but in the dry state it will withstand 100°C. for as long as 24 hours without appreciable deterioration. At pH 5 or less solutions may be sterilized by steaming or autoclaving, but above this pH the vitamin is very susceptible to high temperatures. The powder absorbs moisture on exposure and is affected by light: it should therefore be stored in air- and light-tight containers. Solutions also deteriorate when exposed to air.

Assay. The assay is chemical, relying either on the fluorescence produced on conversion to thiochrome by oxidation, on gravimetric estimation following precipitation of the silicotungstate, or on estimation of the chlorine content. Biological assays are also available.

Action. Aneurine is readily *absorbed* from the intestines; very little is *stored*, the liver and heart muscle being the main depots. Excess is *excreted* in the urine.

When absorbed, aneurine is converted, probably in the liver, into aneurine pyrophosphate (co-carboxylase). As such, it acts as a coenzyme for several decarboxylating enzyme systems, the most important of which is probably *decarboxylase*. This enzyme is necessary for the decarboxylation of pyruvic acid, well known as an intermediate stage in carbohydrate build up or breakdown.

Deficiency results in a loss of energy, a build up of pyruvic and lactic acids in the tissues, and a decreased intestinal absorption of glucose.

Clinical symptoms are associated with brain lesions, which may be partly responsible for the cardiac and intestinal abnormalities that also

occur. The main symptoms are muscular inco-ordination, especially of the hind legs, paralysis with the head turned over the back (opisthotonus), convulsions, possibly vomition where possible, and diarrhœa. The symptoms and lesions have been reported in the fox (Evans *et al.*, 1942), the cat (Jubb *et al.*, 1956, Berry *et al.*, 1945), pigs (Allcroft, 1945; Follis *et al.*, 1943; Wintrobe *et al.*, 1944), non-ruminating calves (Johnson *et al.*, 1948), horses (Carroll *et al.*, 1949), and lambs (Draper and Johnson, 1951). The workers reporting on the chronic deficiency in pigs, and Berry and his co-workers experimenting on cats, indicated that the polyneuritic syndrome in man did not apply to these animals; nor was any effect on the peripheral nerves observed. The work so far recorded on other species has not commented on this aspect.

The ætiology of these deficiencies has been commented on by Innes and Saunders (1957) when reviewing aneurine deficiencies, but though diets that include species of raw fish which contain thiaminase (an anti-aneurine enzyme), diets containing horsetail (Equisetum species), and various synthetic experimental diets were mentioned, the effect of bracken which, like Equisetum, also contains thiaminase, is not mentioned. Bracken poisoning in horses is probably the main form in which practitioners are likely to meet pure acute aneurine deficiencies (see Evans, and Rees-Evans, 1949; Rees-Evans, Evans, and Roberts, 1951; Carpenter *et al.*, 1950). The condition in cattle is not one of pure thiamine deficiency (Evans, Rees-Evans, and Hughes, 1954).

Deficiencies in aneurine can be induced in a very short time in carnivores, birds, non-ruminating calves, lambs and goats, and also horses. Dogs will show symptoms in about four weeks, and pigeons in about two weeks, when kept on an aneurine free diet. Adult ruminants and horses will not show deficiency symptoms on normal diets but bracken poisoning will induce acute deficiencies in horses. Intensively reared fur bearing animals and poultry are particularly open to aneurine deficiencies, usually associated with deficiencies of others of the vitamin B group, although poultry obtain adequate amounts if on a whole grain diet. Dogs on a meat free diet may also suffer from such deficiencies. Necrotic enteritis in pigs involves similar deficiencies.

Uses. Aneurine is specific for the treatment of bracken poisoning in horses but cattle and sheep do not respond. Up to 80 per cent recoveries have been achieved in cattle by the slow intravenous injection or intramuscular injection of about 1·0 G *δl.* butyl alcohol in an emulsified form (Evans *et al.*, 1958). Oxytetracycline 0·5 G intravenously and procaine penicillin 3 mega units intramuscularly were also administered; doses of about 100·0 mg. should be given daily for four days. The thiaminase induced deficiencies in other species respond favourably. Aneurine injections have also been used empirically, in common with many other vitamins, for the treatment of nutritional hysteria in dogs, nutritional gastro-enteritis particularly of pigs, in nervous diseases, and in general debility of all

species. Known *nutritional requirements* are (Nat. (Amer.) Res. Council. Comm. Animal Nutrit. No. 1, 11, VII, VII (1944–1954)):

Dog:	8·0 micrograms per lb. body weight daily.
Fox and Mink:	0·5 mg. per lb. dry food.
Chicken:	0·8 mg. per lb. of feed.
Pig:	2·5 mg. per 100 lb. body weight (50·0 kg.). (0·5 mg. per score live weight) daily.

Dosage. By mouth or by subcutaneous or intramuscular injection:

Horse:	100·0 mg.
Calf:	10·0 mg.
Pig:	2·5–15·0 mg.
Dog:	1·0–10·0 mg.
Cat:	1·0–5·0 mg.

Most frequently yeast, brewers' grains, or vitamin extracts such as Marmite, are used for the treatment of vitamin B deficiencies irrespective of any particular requirements, for a specific deficiency is uncommon.

Riboflavine, B.Vet.C.

Synonyms for this member of the B complex are *lactoflavin* and *vitamin G*, and, more frequently used, *vitamin* B_2. It is an orange-yellow crystalline powder with a slightly bitter taste and slight odour. It is more soluble in normal saline and 10 per cent. urea solutions than in water, and is almost insoluble in organic solvents.

Sources. As with other B. vitamins, riboflavine is present in yeast and may be extracted commercially, but by far the most important source is synthetic manufacture. Riboflavine is present in milk and milk products, meat, eggs, fish roes, malt and, to a lesser degree, in fruit and vegetables.

Stability. When crystalline and dry, riboflavine is light- and air-stable—it is a strong oxidizing agent—but solutions deteriorate on exposure to light, especially alkaline solutions. Correctly compounded solutions will withstand autoclaving.

Assay. This is now chemical, relying on the fluorescence or on the nitrogen content of the compound. As with aneurine, biological tests may also be used.

Action. Riboflavine is rapidly *absorbed* from the intestines or injection site and is rapidly distributed throughout the body.

Excretion via the urine commences within about ½ hour of administration. Little *storage* occurs in the body and most of what is stored may be found in the liver, though small quantities exist in practically all organs and tissues.

Following absorption riboflavine is phosphorylated, forming two coenzymes, riboflavine phosphate (riboflavine mononucleotide) which consists of one molecule each of riboflavine and phosphoric acid, and riboflavine adenine dinucleotide which is one molecule each of riboflavine and adenine but two molecules of phosphoric acid. Both are esters. The simple phosphate coenzyme is associated with, amongst other flavoprotein enzymes, cytochrome-C reductase and *l*-amino-acid oxidase. The more complex compound is coenzyme to *d*-amino-oxidase, xanthine oxidase, aldehyde oxidase and others. All these flavoproteins promote alternate oxidation and reduction reactions, often in conjunction with other enzymes such as those containing nicotinic acid. Riboflavine thus has a direct effect on the metabolism of carbohydrates, amino-acids and aldehydes.

Deficiency which is normally confined to simple stomached animals and pre-ruminating ruminants, results in a slowing of growth; abnormal hæmopoiesis with anæmia; decreased fertility; ocular disorders with pain, irritation and ocular discharges, in severe cases vascularization of the cornea and in most cases photophobia; generalized dermatitis with ulceration and deep skin fissures. Cuthbertson (1957), quoting the National Academy of Sciences Research Council publications on animal nutrition and other authorities, summarizes the clinical effects as follows:

Chickens:	curl toe paralysis of young chicks and reduced egg yield in adults.
Turkeys:	dermatitis at angles of beak, scaly foot pads and inflamed vents.
Pigs:	vomiting, skin ulcers, abnormal gait and still births.
Calves:	scours, salivation, dermatitis.

In horses, it has been suggested that periodic ophthalmia may be prevented but not cured by riboflavine. In dogs, partial blindness, especially at night, and dermatitis are reported. Of these conditions the 'curl toe paralysis' of chicks is the only riboflavine deficiency in which symptoms are pathognomonic (permitting a definite diagnosis). The symptoms of the disease are described in the N.V.M.A. (B.V.A.) publication No. 15 (2nd Edit.) p. 109. Young chicks may die suddenly without characteristic symptoms but in those of two weeks of age or more, more usually between 3 and 6 weeks, the birds rest on their hocks and the claws curl inwards in a characteristic manner. Chicks may have diarrhœa, they are ruffled and untidy, with delayed feathering and a poor growth rate. Spontaneous recovery occurs in all birds after a time, but losses from smothering occur. Coprophagia in birds kept on solid floors makes the incidence lower than in birds kept on wire. (This is one of the advantages of the deep-litter system of rearing chickens). Enlargement of the sciatic nerves is found on post mortem. In adult birds, lowering of egg yield and hatchability are the main features of the deficiency.

Riboflavine is one of the vitamins which may not be provided by the major components of a ration and must therefore be added as a supplement (Cuthbertson, *loc. cit.*).

Daily nutritional requirements for non-ruminants are approximated in the following table.

Horse:	2·0–4·0 mg. per 100 lb. body weight.
Pig:	3·0–4·0 mg. per 100 lb. body weight or 2·0–3·0 G. per ton of feed.
Dog:	20·0 mg. per lb. body weight.
Fox and Mink:	0·9 mg. per pound of dry food.
Fowl:	0·8–1·7 mg. per pound of feed or 3·0–4·0 G. per ton of feed.
Turkey:	4·5 G. per ton of feed.

Dosage. In prophylaxis of periodic opthalmia in the horse, a tentative dose of 40·0 mg. daily in the food has been suggested, but the efficacy of such therapy has not been established. In dogs, 2·0–10·0 mg. is normally satisfactory.

Pyridoxine Hydrochloride, B.P.C.

Vitamin B_6 or pyridoxine when in the form of the hydrochloride is a white crystalline powder, which is soluble in water but only slightly so in alcohol, and even less soluble in the other common organic solvents.

Sources. Pyridoxine exists naturally and also as its aldehyde, pyridoxal, and as an amine form, pyridoxamine, all of which have vitamin B_6 activity. The sources are typical of the vitamin B group and include yeast, grains, potatoes, cabbage, bananas, legumes, meat, fish, eggs and milk. Synthetic pyridoxine is widely used.

Stability. This vitamin is one of the most stable of the vitamin B complex. Acid solutions keep indefinitely at room temperature and may be autoclaved: they are also light stable unless at a neutral or alkaline pH (solutions are normally about pH 3.). The powder is air stable but is slowly affected by light.

Assay. The assay has been biological, but no international units are established and dosage is in terms of weight of pure substance.

Action. Absorption, storage, and *excretion* are similar to those of other members of the group.

After absorption pyridoxine is utilized, probably as the aldehyde, in the formation of coenzymes. The ester, pyridoxal-5-phosphoric acid, is formed which is the coenzyme for decarboxylase (hence its name co-decarboxylase), and also for transaminase. These enzymes are involved in the metabolism of proteins and amino-acids.

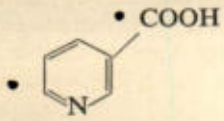
Deficiency results in *acrodynia* which is a dermatitis, characterized by hyperkeratosis and acanthosis of the skin. These features are particularly noticeable on the nose, paws and ears. The muscle action is weak, and nervous symptoms occur. In the dog and pig, microcytic and hypochromic anæmias are seen, and in pigs degeneration of the dorsal root ganglion cells of the spinal cord and axis cylinders of the peripheral nerves, with demyelination, have been reported.

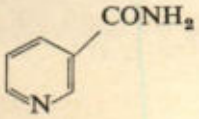
Such lesions and symptoms are rarely met clinically, but pyridoxine has been recommended for vomiting due to excessive stilbœstrol dosage, and to x-ray irradiation in man. This vitamin is also the antidote to cyanacethydrazide (Dictycide) overdosage and should be given on an equal weight for weight basis. This would mean a maximum of 5·0 G. pyridoxine for cattle, and 1·0 G. for sheep, given intravenously. *Dietary* requirements and *dosage* are said to approximate with those of aneurine (*q.v.*).

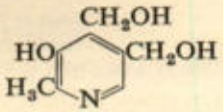
Nicotinic Acid, B.Vet.C. and Nicotinamide, B.Vet.C.

Niacin has been suggested as an alternative name for the acid, and the term *pellagra preventing factor* is applied to both. These two substances are white crystalline, odourless, or almost odourless, powders, the former with a slight acid taste and the latter with an intensely bitter taste. The acid is soluble 1 : 55 in water, but less soluble in alcohol, and almost insoluble in ether: the amide is much more soluble in water (1 : 1) and alcohol (1 : 1·5), but is only slightly soluble in ether.

The formulæ are relatively simple and, in common with pyridoxine, are based on a pyridine nucleus:

(i)  Nicotinic Acid

(ii)  Nicotinamide

(iii)  Pyridoxine

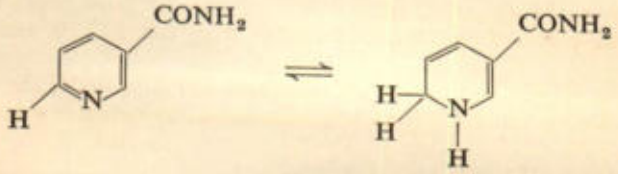
Sources. The majority of these compounds are of synthetic origin often derived from nicotine, but the vitamins are also present in meat, whole grains and their products, yeast, mushrooms, and legumes, particularly soya beans. There are relatively small amounts in milk, green foods and fresh fruit.

Stability. The amide is a little more stable than the acid, but both are reasonably stable, for solutions may be sterilized by autoclaving. Nevertheless, solutions and powders should be kept in airtight and light proof containers.

Assay. Both compounds are assayed chemically, the acid by a straight acid/alkali titration, and the amide by ammonia production.

Action. Nicotinic acid and nicotinamide are both *absorbed* rapidly when given orally, subcutaneously, or intramuscularly, and in the case of nicotinic acid vascular reactions may occur within five or ten minutes of oral administration. Little of the vitamin is *stored* but the liver usually contains appreciable amounts. The vitamin undergoes methylation in the liver, and some is *excreted* in the urine by glomerular filtration and tubular secretion as N, methylnicotinamide.

After the vitamin has been assimilated, the acid is converted into nicotinamide. Nicotinamide enters into combination in the tissues with the protein adenine, the sugar ribose, and phosphoric acid, to form two coenzyme systems, coenzyme I (diphosphopyridine nucleotide, coenzymase, co-dehydrogenase I, or D.P.N.), and coenzyme II (triphosphopyridine nucleotide, co-dehydrogenase II, or T.P.N.). Coenzyme I consists of one molecule each of adenine and nicotinamide with two of *d*-ribose and phosphoric acid, whilst coenzyme II contains an extra molecule of phosphoric acid. These two coenzymes are associated with a number of enzymes which are involved in oxidation processes. The coenzymes appear to function by taking up two hydrogen atoms in the pyridine ring of nicotinamide, with the loss of a double bond. They give up these hydrogen atoms on oxidation and revert to the form which has a double bond associated with the nitrogen atom. This reversible process may be graphically represented by:



The coenzymes containing nicotinamide therefore act as hydrogen carriers in the oxidation-reduction processes of cell metabolism, for which they appear to be essential. These nicotinic enzymes often work in conjunction with those containing riboflavine. They are particularly important in carbohydrate metabolism.

An additional action of nicotinic acid only, is that of causing peripheral vasodilatation. This has little or no clinical application in veterinary medicine.

The essential amino-acid tryptophane is a precursor of nicotinic acid, to which it is converted in the body, and nicotinic acid is not required in

the diet if sufficient tryptophane is present (Cuthbertson, *loc. cit.*, quoting several authors). Pyridoxine and vitamin E are essential for this conversion.

Deficiency results in *pellagra* in man; a rough scaly skin, oral and gastro-intestinal ulceration with diarrhœa, in pigs; perosis, inflammation of the tongue, and dermatitis, in chicks; enlarged hocks in turkeys (Cuthbertson, *loc. cit.*); 'black tongue' or 'brown mouth', in dogs; and a 'feline pellagra' has been described (Heath *et al.*, 1940). Decreased growth rates and fertility are shown in chronic, 'subclinical,' nicotinic acid deficiencies.

Maize (corn) does not contain much available nicotinic acid or tryptophane, and diets consisting mainly of this grain must be fortified with the vitamin. (Cuthbertson, *loc. cit.*, Nat. (Amer.) Res. Council 1944–1954).

Dietary Requirements:

Pig:	12·5 mg. per 100 lb. (50·0 kg.) body weight daily. or 11·0–18·0 G. per ton of feed.
Dog:	0·11 mg. per lb. body weight daily.
Fox and Mink:	4·5 mg. per lb. dry feed.
Fowl:	12·0–20·0 G. per ton of feed.
Turkey:	17·0–20·0 G. per ton of feed.

Dosage:

Calf:	25·0 mg. daily
Pig:	0·1–0·3 G. subcutaneously, 0·2–0·9 G. orally.
Dog and Cat:	5·0–10·0 mg. per kg. (approx. 2·5–5·0 mg. per lb.) body weight given intramuscularly. 10·0–30·0 mg. per kg. (approx. 5·0–15·0 mg. per lb.) body weight given orally.

These doses are tentative. Usually 100·0 mg. two or three times daily by mouth in the pig, and 50·0 mg. three times daily for the dog and cat are sufficient.

The amide should be used on all occasions, for it provides the vitamin in an immediately utilizable form and eliminates any vascular side actions.

Cyanocobalamin, B.Vet.C.

This compound, known as vitamin B_{12}, was isolated simultaneously in Great Britain and America in 1948. It is a dark red, crystalline, hygroscopic powder, which is soluble in water (1 : 80) and alcohol, but insoluble in the normal organic solvents.

Chemically, cyanocobalamin is a complex polyacidic organic base, and has a molecular weight of approximately 1300. It contains, beside carbon hydrogen and oxygen, the metal cobalt (4·5 per cent.), nitrogen, and phosphorus. Cyanocobalamin is one of a series; other members are formed when the *cyano-* group is replaced by other organic groups such as a *nitrito-*,

a *thiocyanato-*, or similar groups. This substitution produces analogues of vitamin B_{12} which have been designated vitamin B_{12a}, vitamin B_{12b}, etc.

Vitamin B_{12a} has been shown to be a hydroxyanalogue of cyanocobalamin, in which —CN is replaced by —OH; it is known as hydroxocobalamin.

Vitamin B_{12b} is very closely related to the B_{12a} analogue, if not actually identical.

Vitamin B_{12c} is nitritocobalamin, whilst *vitamin* B_{12d}, derived by removal of the nitrite group of B_{12c}, is apparently identical with vitamin B_{12b}. The portion of the molecule minus these specific groups is commonly referred to as *cobalamin*, though confusion is added by the generic use of *cobalamins* as a comprehensive name including the whole group of analogues.

Sources. Cyanocobalamin is present in liver (20 tons produces only 1·0 G. of the vitamin), kidney, meat, in fish meals, milk, whey, eggs, ruminant and rabbit fæces, and sewage. Little is present in green food, fruit or yeast.

The majority of the vitamin produced commercially comes as a byproduct of streptomycin and other antibiotic manufacture. Vitamin B_{12} is synthesized by growing moulds and is extracted from the residue remaining after removal of the antibiotic.

Stability. Cyanocobalamin is relatively stable and neutral solutions will withstand autoclaving for 20 minutes at 120°C. Alkalis, strong acids, reducing and oxidizing agents, and heavy metals cause decomposition. The compound is susceptible to light and will decompose in air.

Assay. The compound is assayed electrochemically.

Action. Cyanocobalamin is *absorbed* rapidly following parenteral administration, but gastro-intestinal absorption in man, at least, is dependent on an 'intrinsic stomach factor'. After absorption the vitamin circulates in the blood for a period during which appreciable amounts are *excreted* in the urine. A proportion becomes bound to protein. Small quantities are *stored* in all tissues but most is found in the liver.

The metabolism of cyanocobalamin is complex and is closely associated with that of *folic acid* (another member of the vitamin B complex), and vitamin C., ascorbic acid.

The release of folic acid from conjugated forms, and also the conversion of folic acid to the metabolically active folinic acid, are probably brought about by cyanocobalamin, possibly in conjunction with ascorbic acid. These three are important factors in carbohydrate, protein and nucleoprotein, and fat metabolism.

The synthesis of nucleoproteins is a complex ladder of chemical actions in which cyanocobalamin is required at various stages. The probable sequence of events in the light of present knowledge may be represented as follows:

Conjugated folic acid + B_{12} → folic acid + B_{12} and C → folinic acid + organic precursors (e.g. uracil) → purines and pyrimidines (e.g. thymine) + B_{12} → nucleosides (e.g. thymidine) → nucleotides → nucleic acids.

Through its transmethylating action in the formation of methionine from choline and homocysteine, cyanocobalamin has an effect on fat metabolism, particularly in the liver.

Adequate vitamin B_{12} is also necessary for maintaining the normal sulphydryl level of the blood.

These metabolic actions are reflected in the importance of cyanocobalamin in maintaining normal hæmopoiesis in the bone marrow and elsewhere, in the formation and maintenance of the myelin sheaths of nerve fibres, in the protection of the liver in some species from the fatty changes normally caused by such compounds as the chlorinated hydrocarbons (e.g. chloroform, carbon tetrachloride, tetrachloroethylene), in the maintenance of ovum and sperm production and therefore fertility, in the maintenance of all types of muscle tissue, in the maintenance of healthy skin, brain and pancreatic metabolism; in general, cyanocobalamin plays an important part in the maintenance of all tissues in which protein and nucleoprotein synthesis occurs and where fat conversion proceeds.

It is only to be expected that a compound which affects tissue regeneration will have a marked effect on growth. Even before it was recognized, vitamin B_{12} was referred to as the 'animal protein factor'. This effect has been well recognized in the use of antibiotic manufacturing residues which contain high concentrations of vitamin B_{12}, and also of fish meals and meat and bone meals, in the feeding of pigs and poultry.

The hæmopoietic action was likewise well known before vitamin B_{12} was isolated, when liver extracts were used in the treatment of pernicious anæmia in man: the factor referred to as the 'antipernicious anæmia factor' is now known to be vitamin B_{12}.

Deficiencies of vitamin B_{12} do not occur in ruminants unless cobalt is deficient, when a condition known as 'pine' (Bush Sickness, Nakuruitis, Grand Traverse Disease) occurs. In pigs, skin lesions, hind leg incoordination, anæmia and loss of 'voice' occur; in dogs and cats similar effects might be expected. In all species a loss in appetite occurs which is recovered following administration of the vitamin.

Pine is mainly a disease of sheep in Great Britain, but adult cattle are sporadically affected in established pine areas. The symptoms are similar in the two species and are typified by progressive debility, loss of wool or hair giving the animal a bedraggled ragged appearance, the appetite decreases progressively and emaciation becomes apparent. Lambs fail to grow and have a stunted unthrifty appearance. The animals are usually markedly anæmic. Inco-ordination, particularly in the hind limbs, is followed by collapse. In marginal deficiencies the symptoms are less acute and may be difficult to diagnose. Test dosing is followed by a marked improvement within a week to ten days and soil analysis will normally confirm the condition: for cattle a test dose would be 0·5–1·0 G. in a

single dose, and for sheep about one eighth of this should be sufficient: pasture cobalt content is approximately 0·03–0·04 parts per million in deficient areas. Animals may be given parenteral cyanocobalamin (0·3 mg. per sheep), but this is uneconomic and oral cobalt (8·0 mg. cobalt chloride per week per sheep) or pasture top dressing with 2 lb. (0·9 kg.) per acre are superior. Mineral licks containing cobalt are available.

It should be remembered that in some areas—Western Australia (coast disease) and Florida (salt sickness)—other minerals, especially copper, may also be deficient.

Nutritional requirements have been suggested:

Pig:	Up to 50·0 mg. for weaners and up to 20·0 mg. for pigs over 50 lb. body weight in each ton of feed.
Dog:	10·0 μg. per lb. dry diet.
Fox and Mink:	13·0 μg. per lb. dry food.
Poultry:	Up to 10·0 mg. per ton of food, but this figure may be ignored for chicks in deep litter houses where adequate vitamin B_{12} is obtained from the litter.

Dosage. No exact dosage can be given, for requirements vary in each individual case. As a general tonic, which is the main use of the vitamin 1·0–2·0 μg. intramuscularly per lb. body weight per day may be used as a guide. The normal dose for a dog or cat is 100·0 μg.

Biotin

This vitamin has been known under a number of names—vitamin H, bios IIb, and coenzyme R. It is a white crystalline powder which is soluble in water and alcohol, but not in other solvents. Biotin is present in all animal tissues—liver, meat, in most plants, but is highest in egg yolk; small quantities are found in milk. It is heat stable but is unstable in alkaline solution and in the presence of oxidizing agents: it should therefore be kept in light and air tight containers. The metabolic role of biotin is unknown but may be of a coenzyme nature. Precise requirements are unknown and no definite clinical effects have been proved, although it is frequently claimed to have a beneficial effect on non-specific skin conditions in dogs and pigs. High dosing with egg white which contains avidin, an antagonist, may cause a biotin deficiency, but this is not of much clinical importance. *Doses* of 150·0–300·0 mg. daily have been used experimentally in man.

Para-Aminobenzoic Acid, N.F.

Also referred to as PABA and vitamin H^1, this member of the vitamin B complex is a white crystalline powder which is slightly soluble in water (1 : 170), soluble in alcohol (1 : 8), and in ether (1 : 50). It is stable for all normal purposes but discolours on exposure to light.

This compound is present in the highest concentration in liver and

yeast, but is widely found in animal and plant tissues. It is a component of the folic acid vitamin structure, but otherwise its present importance lies mainly in its antagonism of the sulphonamides (*q.v.*), in that it is an essential growth factor for many bacteria and is displaced by the sulphonamides. It is also an essential growth factor for chickens, and is reported to be useful in countering organic arsenical poisoning. *Dosage* and *nutritional requirements* are unknown, but in man up to 8·0 G. have been given by mouth initially, followed by up to 3·0 G. every two hours, in the treatment of rickettsial infections: antibiotics are more effective and less toxic. These doses however, give some indication as to dosages in arsenical poisoning following tri- or penta-valent compound administration to small animals (e.g. arecoline-acetarsol overdosage during tapeworm eradication.)

Inositol

This vitamin, also known as bios I, is a fine white crystalline powder with a sweet taste. It is soluble in water, but only slightly soluble or insoluble in organic solvents. It is found in quantity in all tissues of animal or plant origin and is manufactured synthetically. It is assayed chemically.

Biochemically, inositol appears to be esterified with phosphoric acid in the tissues, and is associated with fat metabolism, although in a different manner from choline which forms lecithins, amongst other compounds, whereas inositol is found as cephælins.

Clinically its significance is undetermined, but it has a curative action on alopecia in mice and protects the liver of rats from fatty changes. All experimental rations for mice contain 10·0 mg. inositol in 100·0 G. *Doses* of 1·0–3·0 G. by mouth daily in divided doses have been used in man for the treatment of fatty livers and liver cirrhosis, but it is doubtful whether inositol deficiencies will ever occur clinically, in view of the widespread distribution of the compound.

Folic Acid, B.P.

Also known as pteroylglutamic acid, and identical with the *Lactobacillus casei* factor, folic acid has been shown to be the basis of many similarly acting compounds variously designated vitamin B_c, vitamin B_c conjugate, and fermentation *L. casei* factor. These compounds are conjugates of pteroylglutamic acid with extra molecules of glutamic acid attached through peptide linkages

$$(R'(NH_2)COOH + NH_2R^2COOH = R'(NH_2)CO{\cdot}NH{\cdot}R^2COOH + H_2O)$$

Thus vitamin B_c conjugate is a heptaglutamic acid conjugate, and the fermentation *L. casei* factor is a triglutamic acid conjugate.

Folic acid is a yellow or orange-yellow odourless crystalline powder, soluble in acid or alkaline aqueous solutions, but practically insoluble in water and organic solvents. It is stable as a dry powder but in solutions below pH 6 stability is considerably decreased. Alkaline solutions are

stable under normal conditions but are decomposed in the presence of some sulphonamides. Light destroys the compound.

The vitamin is available for injection as *sodium foliate* but is more commonly given orally. The natural *sources* are similar to those of other members of the B complex—yeast, wheat, green foods, meat, including liver and kidneys. Cooking and storage will destroy the vitamin. Intestinal bacteria in all species are probably responsible for supplying some of the needs of healthy animals. The vitamin is also manufactured synthetically.

Folic acid is *assayed* chemically.

Action. Folic acid is *absorbed* fairly well from the intestines, for most species seem to absorb sufficient for normal purposes after synthesis by intestinal bacteria. Metabolism subsequent to absorption is unknown. The inter-relation of folic acid, folinic acid, vitamin C and cyanocobalamin in nucleic acid synthesis has been mentioned under cyanocobalamin (*q.v.*). The acid is also involved in transmethylating actions along with cyanocobalamin, both in nucleoprotein formation and in fat metabolism through methylation in the synthesis of choline and methionine. Through this latter action folic acid and cyanocobalamin reduce nutritional requirements of choline and methionine.

Clinically the symptoms shown in experimentally induced deficiencies are unlikely to occur. These symptoms include macrocytic anæmias with reduction in the numbers of all cellular elements of the blood, diarrhœa, skin lesions, reduced growth rates in pigs, dogs, foxes, mink, experimental animals and birds, which also may show poor feathering and perosis. It should be noted, however, that, as with para-aminobenzoic acid, which is a precursor of folic acid, small quantities of the 'gut active' sulphonamides will promote a deficiency, probably by reducing bacterial numbers and therefore the synthesis of this and other vitamins.

Dietary requirements have not been ascertained, but the U.S.D. (25th Edit. 1955, p. 1979) suggests that 10·0–20·0 G. per ton of feed should be adequate for poultry and fur bearing animals. *Doses* used in man for therapy in anæmia have been up to 10·0 mg. daily in divided doses, either orally or by injection: as much as 100·0 mg. have been given intravenously without harm, though administration was slow and solutions were well diluted. Use in canine anæmia has not given very satisfactory results.

Pantothenic Acid

This complex organic acid is used mainly in the form of calcium pantothenate, a water soluble, white, crystalline, hygroscopic, bitter tasting powder.

Sources. The vitamin is widely distributed in plant and animal tissues, the richest source being royal jelly of the honey bee: yeast, milk, liver, meat, eggs, peanuts, and wheat, also contain appreciable quantities. The calcium salt and pantothenyl alcohol are manufactured synthetically.

Stability. Calcium pantothenate is unstable in solutions outside pH 5–7, and is destroyed by heat. It is probably the least stable of all the members of the B complex of vitamins—stewing meat reduces the pantothenic acid content by two thirds. The alcohol is slightly more stable than other forms.

Action. Pantothenic acid is similar to other members of the B complex in occurring universally throughout all tissues. It is *absorbed* from the gastro-intestinal tract and the alcohol can also be absorbed percutaneously in quantities sufficient to cure deficiencies. Its subsequent metabolism is not well understood. It is probable that pantothenic acid is one of the more important metabolites of the vitamin B group. It is a component of coenzyme A and as such is concerned in acetylation processes throughout the body. In this coenzyme it is probably combined as a phosphorylated ester with adenosine and glutamic acid. Examples of the reactions in which it is involved are the conversion of acetates to sterols, (hence the probable relationship with adrenal cortex necrosis observed in deficiencies), the conversion of choline to acetylcholine, the acetylation of PABA and the sulphonamides, and the conversion of acetate to acetoacetate and oxaloacetate to citrate. Pantothenic acid is also concerned through its incorporation in coenzyme A with carbohydrate and fat metabolism. The conversion of α-ketoglutamic to succinic acid results in the formation of phosphorylcoenzyme A which then co-operates, by transferring the phosphoryl group, in the formation of adenosinetriphosphate, a compound essential for the release of the energy necessary for muscle contraction and other vital processes. The association of this vitamin with ketosis and milk fever through its effect on ketone and phosphate metabolism is very apparent. The vitamin may also be associated with peptide metabolism.

Deficiencies result in dermatitis and loss of hair in all species, particularly in the region of the mouth and eyes. In pigs, ulcerative dermatitis and intestinal necrosis, an exaggerated high stepping leg action, and fœtal resorption have been observed; in calves diarrhœa and weakness are the main symptoms.

Dietary requirements in non-herbivores are:

Pig:	18·5 mg. per 100 lb. (50·0 kg) bodyweight daily or 12·5 mg. per kg. (approx. 6·0 mg. per lb.) of feed. (11·0–13·0 G. per ton of feed.)
Dog:	25·0 μg. per lb. bodyweight (55·0 μg. per kg.) daily.
Fox and Mink:	3·6 mg. per lb. dry food.
Fowl:	10·0–11·0 g. per ton of feed.
Turkey:	11·0–16·0 G. per ton of feed.

Dosage. No adequate dosage scheme has been drawn up. Human dosage indicates a wide margin of safety, the usual range being from 10·0–50·0 mg.,

but doses of up to 1·0 G. have been considered safe. Intramuscularly, 100·0 mg. have been given three times daily, and ointments containing up to 5 per cent. have been applied topically. In chickens the requirement of pantothenic acid increases with the fat content of the diet, and with cyanocobalamin deficiency.

Choline

This vitamin B complex member is a colourless, viscid, strongly alkaline liquid, which is very hygroscopic and is soluble in water, in alcohol, but not in other organic solvents. It is used as the bitartrate, the dihydrogen citrate, the chloride or the gluconate.

Sources. Choline is a component of lecithin phospholipides, which are found in high concentration in nervous tissue and are therefore widely distributed throughout animal tissues: egg yolk, liver, yeast, brain, kidney, heart, wheat, and soya beans, all contain appreciable amounts.

Stability. Choline tends to absorb carbon dioxide when exposed to air. It is also hygroscopic but withstands autoclaving.

Assay. The assay is a chemical one.

Action. Absorption is fairly rapid from the intestines or following parenteral injection. After absorption the compound is distributed widely, a large amount localizing in the liver. Some of the administered choline is *excreted* unchanged but a proportion is converted into trimethylamine and excreted as such by all normal excretory routes.

Choline is concerned in methylation processes and increases the phospholipide metabolism in the liver. It will prevent fatty changes in the liver when the animal is on an excessively fatty diet, and is also thought to mobilize the fat from an already fatty liver. It has been used for this latter purpose in animals and man, but its clinical efficacy has not been fully assessed. Cyanocobalamin and folic acid are also associated with transmethylation and choline will, to a certain degree, 'spare' these vitamins.

Deficiency results in perosis (slipped tendon) in fowls and turkeys. Piglets with a choline deficiency suffer from ataxia, fatty livers, and the mortality rate is high.

Nutritional requirements of choline are high, but methionine, of which it is a precursor, and betaine will offset a choline deficiency.

Pig:	900–1000 G. per ton of feed for piglets up to 50 lb. (22·6 kg.)
Fowl:	1500 G. (optimum) per ton of feed for chickens up to 18 weeks.
Turkeys:	Up to 1700 G. per ton of feed for turkeys up to 8 weeks.

Choline has been used in the treatment of milk fever (Lewis and Price, 1957) and acetonæmia, in both of which conditions fatty livers are

probably responsible for a number of cases which annually resist normal treatment. It has also been used in the treatment of fatty livers caused by chlorinated hydrocarbons and in the treatment of liver conditions in dogs.

Dosage:

Cow: 25·0–50·0 G. by mouth or subcutaneous injection. Good results have been obtained with 25·0 G. given subcutaneously and 25·0 G. at the same time by mouth.

Dog: 20·0 mg. per lb. body weight (44·0 mg. per kg.) daily by mouth.

The members of the vitamin B complex are rarely administered individually for as has been seen in the foregoing monographs many of them are interdependent. For this reason many commercial vitamin preparations contain most of the series in varying amounts. These are usually expensive, and for normal purposes *yeast* and yeast extracts such as Marmite are quite useful.

Dried Yeast, B.Vet.C. is a buff granular powder with a characteristic odour and taste. It contains in each gramme not less than 0·1 mg. aneurine hydrochloride, 0·3 mg. nicotinic acid and 0·04 mg. riboflavine: in many instances the content is nearly twice these figures. Small amounts of pyridoxine and pantothenic acid are present, with appreciable amounts of choline. The aneurine and nicotinic acid are usually present in phosphorylated coenzyme form. Besides the vitamins, about 45 per cent. of yeast consists of protein, 36 per cent. of carbohydrate and in the remainder occurs a number of enzymes. Fresh bakers yeast apparently is less active as a vitamin supplement. Dried yeast and Marmite have been used in piglet scours, in poultry food, and as general 'tonics' for small animals.

Dosage:

Dog and Cat: 120–240 gr. (8·0–15·0 G.) daily. This represents 2·4–4·8 mg. nicotinic acid, 0·8–1·6 mg. aneurine hydrochloride and 0·32–0·64 mg. riboflavine.

In pigs and poultry concentrations of 3–5 per cent. have been incorporated in food rations.

Marmite has been given to piglets at the rate of about one teaspoonful per day for each piglet.

Vitamin C

Ascorbic Acid, B.Vet.C. is not an essential nutritional factor in the domestic animals, for it is synthesized by all species. Guinea pigs, man, and monkeys are, however, unable to synthesize the vitamin, and it is consequently an essential nutritional as well as an essential metabolic factor. The vitamin is a white crystalline powder without odour but with a bitter taste. It is soluble in water (1 : 3) and alcohol (1 : 30), but insoluble in other organic solvents.

Sources. The citrus fruits contain large quantities of vitamin C, but all green foods, meat, especially liver, root crops, tomatoes, and black-currants, contain appreciable amounts. Commercial ascorbic acid is usually synthetic.

Stability. Ascorbic acid in the dry powder form is fairly stable, though it slowly darkens on exposure to light. In solution, however, it is rapidly destroyed by oxidation and by heating in the presence of oxygen. Solutions may be phosphate buffered at pH 6·0–6·5, stabilized with 0·005 per cent. of thiourea, or with 3 parts sodium chloride to each 10 parts of ascorbic acid.

Assay. Ascorbic acid has a chemical assay.

Action. Ascorbic acid is destroyed in the rumen but is readily *absorbed* from the intestines of simple stomached animals. Little is stored, though the liver localizes more than other tissues, with the exception perhaps of the adrenal glands. *Excretion* of any excess occurs in an unchanged form via the kidneys.

The metabolic effects of ascorbic acid are not entirely known. It is essential as a coenzyme in certain oxidative processes, including the oxidation of tyrosine and phenylalanine. It is necessary for normal folic acid function (*q.v.*). Ascorbic acid is also essential for normal wound healing, possibly by inhibiting hyaluronidase-hyaluronic acid activity in the collagen and ground substance of connective tissue: this is also the possible mechanism in maintaining normal capillary function—capillary fragility is one of the main features of scurvy. The role of ascorbic acid in adrenocortical metabolism is unknown, but in times of stress or shock the level within the gland decreases rapidly: following ACTH administration the concentration within the gland increases along with an increase in cholesterol. The significance of these facts is unknown.

The *clinical indications* for the use of ascorbic acid are not determined though the vitamin has been used in the treatment of infertility in cattle. Lowered blood levels in horses, cattle, and dogs, have been reported, though the significance of these findings is not clear. As the site of synthesis in the body is unknown it is difficult to predict the circumstances in which vitamin C deficiencies might occur. However, it is known that vitamin C concentrations are reduced in fever, that the compound is useful in the detoxication of toxins and chemicals, including arsenicals, sulphonamides, salicylates, stilboestrol, and barbiturates: these facts serve to suggest various circumstances in which vitamin C therapy might be useful.

Dosage: (U.S.D. 25th Edit. p. 1947):

Horse: 2·0–4·0 G. by subcutaneous injection.
Bull: 1·0–2·0 G. per 1000 lb. (450·0 kg.) subcutaneously every 3–4 days for up to six weeks.

Cow: 1·0–2·0 G. intravenously and 2·0 G. subcutaneously before mating, or 2·0 G. subcutaneously once or twice a week for up to six doses.

Dog: 25·0–75·0 mg. orally or subcutaneously each day.

Vitamin P.

This is not an established vitamin. It is suggested as a factor responsible for maintaining normal capillary permeability and is said to occur naturally along with vitamin C. Two chemicals extracted from plants and citrus fruits, *rutin* and *hesperidin* are claimed to have similar actions. There is yet no clinical indication for the use of vitamin P analogues.

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CHAPTER 35

THE VITAMINS
(ii) THE FAT SOLUBLE VITAMINS

THIS group comprises vitamins A, D, E and K. A further member was known as vitamin F but this has been shown not to be a true vitamin, and linoleic and linolenic acids, hitherto thought to comprise this vitamin, are now classified with the essential unsaturated fatty acids.

The fat soluble vitamins are more stable as a group than the water soluble ones but even these have individual instabilities, the one perhaps of most importance being the destruction of vitamin E in rancid oils: vitamin A and vitamin D are oxidized when exposed to atmosphere and light.

Other than stability, various factors may influence the intake of fat soluble vitamins; the interference of carotene absorption by prolonged liquid paraffin taken orally and the 'fixing' of vitamin E by excessive quantities of fish oils in the diet are of prime importance, but other circumstances such as excessive amounts of calcium in the diet may also influence fat and fat soluble vitamin absorption. These factors are assuming greater importance as more becomes known. For example there is a tendency to decrease the regularity of cod-liver oil, replacing it either by intermittent supplementation of the food or by the use of concentrated preparations which avoid the feeding of large volumes of unsaturated fatty acids. Greater use is also being made of vitamin 'stabilizers' which are usually antioxidants: these are of particular importance to foodstuff manufacturers, who must ensure that the vitamin content of meals and cakes is adequate, even after months of storage.

Vitamin A.

This is a term applied to several compounds which have 'vitamin A activity'. Pure vitamin A is a complex organic alcohol which exists in two main forms, vitamin A_1 and vitamin A_2, the latter being obtained from freshwater fish livers, whilst the former comes from salt water fish livers. There also exist several less active isomers of vitamin A, quantities of which usually accompany the main compounds. Vitamin A_1 differs from A_2 only in having one less double bond in its molecule and yet is three times as active as the freshwater fish oil extractive. The vitamins are usually found not as the free alcohol, but as the acetate or the palmitate: the palmitate ester occurs in greater quantities than the acetate in the liver oils.

The pure alcohol can be obtained as yellow prisms, the vitamin A acetate as pale yellow prismatic crystals, and the palmitate either as yellow crystals or an amorphous powder. Each has a characteristic melting point and is soluble in fixed oils, which are the usual vehicles for the purposes of administration.

Sources. Vitamin A_1, commonly referred to simply as vitamin A, is derived mainly from saltwater fish livers. The vitamin is extracted in the liver oils, the commonest fish being cod and halibut: tuna and other lesser known fish livers are also used, and whale-liver oil is a potent source of vitamin A. The less active *vitamin* A_2 is obtained from freshwater fish liver but is of little clinical importance. The livers of food animals also contain appreciable amounts, but vitamin A does not occur as such in plants. One of the major sources of vitamin A in the diet of the domestic animals and the only source in herbivores is the group of compounds known as the *vitamin A precursors*. These compounds are *carotenoids*, but only four of the group are important as sources of vitamin A. They are primarily plant pigments known as α, β and γ carotenes and cryptoxanthine: they are present in fresh green foods (associated with chlorophyll), good quality hay, carrots, tomatoes, egg yolk, milk, butter and cheese. These carotenoids, but mainly β-carotene, are converted into vitamin A by enzyme hydrolysis, probably in the liver and intestinal mucosa. Under optimum conditions β-carotene will form two molecules of vitamin A, but, as Cuthbertson (1957) quoting several other authors points out, carotene utilization varies according to the form in which the carotene is presented, the quantities of vitamin A preserving antioxidants present (vitamin E, vitamin C, etc.), and the concentration of the antagonists, such as unsaturated fatty acids, which occur in the food. The carotenes are dark yellow or orange crystalline solids which have a slight odour and little taste. They are fat soluble and dissolve easily in ether but more easily in chloroform and benzene.

Stability. In the absence of oxygen and oxidizing agents vitamin A and its precursors are heat stable, and ordinary cooking does not destroy them. Frozen foods maintain their vitamin content, but rancidity of an oil and exposure to air and light will destroy the vitamin: vitamin C (ascorbic acid), citric acid, and vitamin E (tocopherols), amongst many antioxidant compounds, can be used to maintain stability. In all circumstances the esters—acetate and palmitate—are more stable than the alcohol, and solutions in oil are more stable than the pure, dry compound. Cod-liver oil will keep satisfactorily for many months in a closed, light proof container.

Assay. This was initially carried out by biological methods but modern spectrographic methods have replaced these.

Action. Vitamin A and the carotenes are absorbed from the intestines only when adequate fat, bile salts, and pancreatic enzymes are present. However, too high a concentration of unsaturated fatty acids or liquid

paraffin will decrease the amount of vitamin A absorbed, the former by promoting oxidative destruction of the vitamin, whilst the latter dissolves the vitamin and sequestrates it, preventing absorption. Enteritis will also interfere with absorption. Under normal conditions *absorption* is rapid from both the intestines and sites of parenteral injection. Following absorption the vitamin passes into the lymph and so into the circulation where it may be found as esters of the fatty acids, the free alcohol, and protein bound carotene. The majority of any one dose will be *stored* in the liver, which normally contains about 95 per cent. of the vitamin A in the body: other tissues including the kidneys, adrenals, lungs, and fat, all contain some vitamin A and, or, carotene. Following administration, this storage commences within a few hours, and it has been shown by several groups of workers that rats, for example, will store enough vitamin A from one feed on cod-liver oil or carotene to meet its requirements for the subsequent two months.

The *metabolic effect* of vitamin A is mainly on epithelial tissues, including the retina, skin, and mucosa of the respiratory and urinary systems. The retinal effect relates to the fact that vitamin A is a part of the conjugated protein *visual purple* (rhodopsin), and also of visual violet (iodopsin). The former is concerned with accommodation to light (hence night blindness in deficiencies), whilst the latter is concerned in colour vision: the visual purple is obviously of greater veterinary significance. Young animals are normally born with low reserves, though these reserves are usually proportional to the vitamin A levels in the blood and tissues of the dam, and can therefore be increased by adequate vitamin therapy during pregnancy; after birth, these reserves are usually supplemented by the vitamin in colostrum and milk.

Deficiency symptoms, where the avitaminosis is marked, are mainly those of hyperkeratosis of the skin, including the cornea (xerophthalmia, which once established is almost impossible to cure), blindness, nervous symptoms, decreased growth rates, and a lowered fertility. Details of effect vary in the different species:

The *horse* does not convert carotene to vitamin A very easily, and plasma vitamin A levels are normally lower than those of the cow. Symptoms of deficiency include night blindness, corneal keratinization which results in photophobia, closed lids and lacrimation. The appetite is capricious and, as the condition progresses, respiratory embarrassment, as well as interference with normal mating processes and fertility occur. Interference in hoof formation, with a scaly and encrusted secretion from the perioplic band, has been reported.

Cattle provide perhaps the most spectacular symptoms of vitamin A deficiency, calves showing blindness due to abnormal bone growth around the optic foramina which constricts, and finally causes pressure necrosis of the optic nerve. The calves grow slowly, scouring is common, hyperkeratinization may occur producing a rough, scaly, dry skin which is particularly obvious in the region of the neck, withers, and tail head: the coat is

staring. In older animals, night blindness may result from retinal abnormalities; abortion sometimes occurs, and œdema of the legs and lower parts of the body (anasarca) may be seen. In all cases increased cerebrospinal fluid pressure may cause derangement of motor reflexes, with muscular inco-ordination, a staggering gait, and convulsions. Sterility in young bulls has been attributed to lack of vitamin A during the prepubertal period. Response to treatment is slow, and prophylactic feeding with cod-liver oil is therefore widely practiced.

In *sheep* and *goats* vitamin A deficiency has received little attention, and efforts to identify specific disease syndromes associated with such a deficiency have not had much success. It would seem that, in sheep at any rate, symptoms of vitamin A deficiency follows a pattern similar to that in cattle, but of a less acute nature.

Vitamin A deficiency in *pigs* may occur in intensively reared herds where provision of vitamin supplements is omitted. If large amounts of swill are fed vitamin A deficiencies are more likely. Symptoms may include unthriftiness, slow growth, poor appetite, keratinization of skin and cornea, posterior inco-ordination and paralysis, often with convulsions: adults may be infertile, but where conception is achieved, piglets may be aborted or suffer from weakness and various deformities, including microphthalmia (Goodwin, 1957; Goodwin and Jennings, 1958). Resistance to secondary pathogens is low and enteritis and pneumonia may frequently occur. The condition must be differentiated from swine fever.

Carotene conversion is relatively effective in pigs and access to green foods normally provides sufficient vitamin A. This can be supplemented by cod-liver oil or synthetic preparations, but overdosage with these compounds can be harmful.

Small animals, including the dog, cat, rabbit, fox, mink, etc., apparently require vitamin A in amounts similar to those required by the pig on a weight for weight basis. Symptoms are typical, but deafness due to errors in bone growth similar to those which cause blindness in calves has been reported in dogs: the eighth cranial nerve may also be constricted. Lesions of the oral mucosa, and inadequate kidney function have also been reported in dogs.

Poultry require relatively large amounts of vitamin A, and turkeys more than fowls. Symptoms result after a few weeks on a deficient diet, ducks and turkey poults showing symptoms 3–4 weeks after hatching. These symptoms follow much the same pattern as in mammals and form a syndrome referred to as '*nutritional roup*'. Young birds become lethargic, stand about with ruffled feathers, and when they do move show inco-ordination with a staggering gait. The birds stop growing, become progressively emaciated and, if the condition is untreated they die, usually from secondary infections: the mortality rate in turkeys is very high unless treatment commences within a fortnight or so of symptoms becoming obvious; with chickens the condition is not so acute. Specific lesions occur in

association with the eyes and respiratory system: in the early stages there are watery discharges from the eyes and nose, but later these discharges become inspissated, and cheesy exudates cover mucous membranes and block sinus exits, tear ducts and possibly the bronchi. These birds then show facial swellings as the sinuses fill and swell, and respiratory embarrassment becomes progressively worse. Xerophthalmia (corneal keratosis) is occasionally apparent. Adults will show most of these symptoms, but also a decreased egg yield and poor hatchability. Uric acid crystalline deposits in the kidneys are very common.

Nutritional requirements are not standard, either for species or individuals, but the following will serve as a guide:

Horse, Cow, Sheep and Pig:	3000 i.units per 100 lb. (50·0 kg.) body weight daily.
Small animals:	about 30. i.units per lb. body weight (66 i.u. per kg.) daily.
Poultry:	2,000–4,000 i.units daily per pound of feed.

Pigs may be fed at the rate of 2,500,000 i.units per ton of feed for all but breeding stock, which require between three and four times this quantity. Fowls require about 3,000,000 i.units per ton of feed, though laying and breeding stock require 5,000,000 and 4,000,000 i.units per ton respectively. Turkeys require about 6,000,000 i.units per ton.

Dosage. Vitamin A is commonly given by mouth along with vitamin D as Cod-Liver Oil (Veterinary), B.Vet.C. Less commonly it is given as Concentrated Solution of Vitamin A, B.Vet.C., or as the Concentrated Solution of Vitamins A and D: parenteral injections of these are available commercially. Halibut-Liver Oil, B.Vet.C. is also used.

Cod-Liver Oil (*Veterinary*), B.Vet.C. has characteristics known to all—a clear, yellow, oily liquid with a fishy odour and taste: it contains *not less than* 600 i.units per gramme of vitamin A, and *not less than* 85 i.units per gramme of vitamin D. The *dose* is:

Horse and Cow:	½–2 fl. oz. (15·0–60·0 ml.)
Sheep and Pig:	60 m.–½ fl. oz. (4·0–15·0 ml.)
Dog and Cat etc:	8–120 m. (0·5–8·0 ml.)
Poultry:	½–1% in the food (10–20 pints or approx. 6·0–12·0 l. per ton).

It should not be given to food animals for at least two weeks before slaughter. It is advisable, where food medication is practised, to add the oil as near to the time of use as possible so that vitamin losses from oxidation may be minimal.

Cod-liver oil is used as eye drops and also as a vehicle for skin therapeutics.

A cod-liver oil emulsion and a combination with extract of malt are also detailed in the B.Vet.C., but these are used less frequently than the plain oil.

Halibut-Liver Oil, B.Vet.C., is similar in character to the cod-liver oil but its vitamin content is vastly different: it contains *not less than* 30,000 units vitamin A per gramme, and though no specific limits are prescribed for vitamin D this usually approximates to 3,000 units per gramme. This oil is obviously preferable for the treatment of vitamin A deficiencies, but it is expensive and is rarely used other than in capsules for small animal treatment.

The *dose* for horses, cattle, sheep, and pigs, is 3–5 m. per cwt. (0·2–0·3 ml. per 50·0 kg.) daily, and for dogs and cats: 1–5 m. (0·075–0·3 ml.)—usually one or two capsules daily.

The oil in extract of malt is also official but is not commonly used.

Concentrated Solution of Vitamin A, B.Vet.C. is a fortified fish-liver oil, or a solution of vitamin A in a bland oil, usually arachis oil: it may or may not have a fishy taste and odour, and is normally a golden colour. It contains between 45,000 and 55,000 units of vitamin A per gramme and is therefore superior to halibut-liver oil in its potency.

The dose for all farm animals varies widely but it is usual to give the equivalent of about 45–90 units per lb. (100–200 units per kg.) bodyweight daily—this is approximately 1·0–2·0 G. per day for a 1,000 lb. (450 kg.) cow. Fowls are given 0·07 G. and turkeys 0·1 G. per lb. (0·22 G. per kg.) food—these are equivalent to 3,000 and 4,000 units respectively.

Vitamin D.

As with vitamin A, the term vitamin D is applied collectively to at least ten different anti-rachitic substances, all of which are sterols and therefore related to the sex hormones. Only two of these sterols are of therapeutic significance—*vitamin D_2* or *calciferol*, and *vitamin D_3*, which is a demethylated, dihydro-derivative of calciferol and is the naturally occurring vitamin D found in fish-liver oils. The term vitamin D_1 was applied to a substance later discovered to consist of a mixture of two different antirachitic compounds: it has therefore been deleted from the nomenclature. Other sterols with antirachitic activity are *lumisterol*, *tachysterol*, *toxisterol*, and *suprasterols I and II*, all of which are produced successively during the irradiation of ergosterol—calciferol is also produced, up to 50 per cent. being formed at a stage subsequent to the formation of tachysterol. Calciferol is by far the most powerful anti-rachitic agent of all these sterols, only one other, tachysterol, being of any significance and that only because a derivative—dihydrotachysterol—is a minor treatment for milk fever in cattle. Further antirachitic compounds may be derived from cholesterol: activated 7-dehydrocholesterol or synthetic vitamin D_3 is one of these.

Calciferol, B.Vet.C. is produced by irradiation of ergosterol, which occurs in yeast and moulds in up to 2 per cent. concentrations of the

dried substances. It is a white crystalline, odourless and tasteless powder, which is soluble in organic solvents including fixed oils, and is affected by air and light. Each milligram contains 40,000 units of antirachitic activity as estimated biologically using the effect on bone calcification in rats as the indicator—other methods of assessment may be used.

The chemical relationship with the sex steroids and the adrenocorticosteroids is illustrated on page 629.

Activated 7-dehydrocholesterol, U.S.P., or vitamin D_3, is very similar in all characteristics to calciferol. It occurs in cod-liver and other fish-liver oils, and may be manufactured synthetically from cholesterol by way of dehydrocholesterol. Vitamin D_3 is used as the international reference standard for assays of antirachitic compounds, and is considered to be more effective than calciferol in the same species.

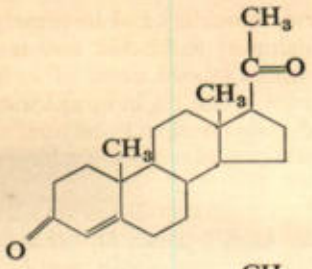
Cod-Liver Oil (Veterinary), B.Vet.C. contains *not less than* 85 i.units antirachitic activity, the majority of which is due to vitamin D_3. Halibut-Liver Oil, B.Vet.C. contains about 3,000 units of antirachitic activity (see vitamin A—*dosage*).

Action. The *absorption* of vitamin D, in common with the other fat soluble vitamins, is related to the absorption of fat, and therefore any factor influencing fat absorption will also affect vitamin D absorption. These factors include lack of bile or pancreatic enzymes, excessive amounts of calcium in the food, and gastro-enteritis. Apart from that obtained by absorption from the intestines, vitamin D is produced by irradiation of sterols when the skin is exposed to the ultra-violet rays of the sun. These irradiated sterols are then absorbed into the circulation and implement the vitamin D reserves. *Storage* of the vitamin D is mainly in the liver, but some is present in the adrenals, lungs, spleen, and kidney.

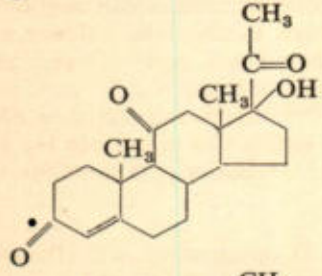
Vitamin D is essential for the absorption of calcium from the intestines, for normal metabolism of calcium and phosphorus in the tissues especially in the bones, and also for normal phosphate excretion (excessive loss of phosphate occurs in deficiency states due to lack of tubular resorption). It is probable that vitamin D is necessary for the activation of alkaline phosphatases—enzymes which are involved in intestinal absorption, bone ossification and tubular resorption of phosphate. Vitamin D is thus closely related to calcium, phosphorus, and magnesium metabolism, and to parathyroid activity.

Deficiencies of vitamin D which lead to conditions known as rickets and osteomalacia are now less common, for most farmers are aware that animals kept in the dark without cod-liver oil or other vitamin D supplement will rapidly develop the disease. Rickets in dogs is not an uncommon condition in Great Britain, but again owners are becoming increasingly aware of the necessity of vitamin D supplementation.

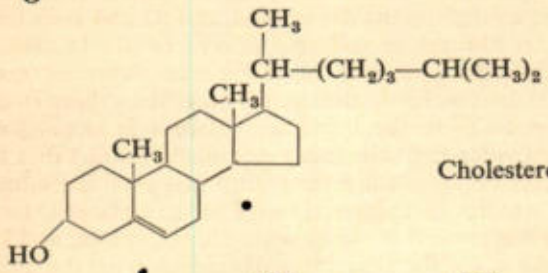
Rickets is a disease of the immature growing animal in which calcium and phosphate metabolism are disturbed and incomplete ossification of the bones occurs. This lack of ossification leads to enlarged painful joints,

(i) 

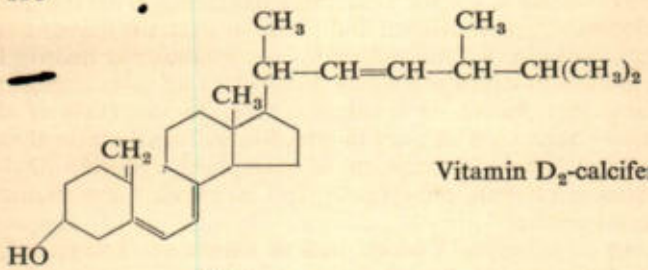
Progesterone.

(ii) 

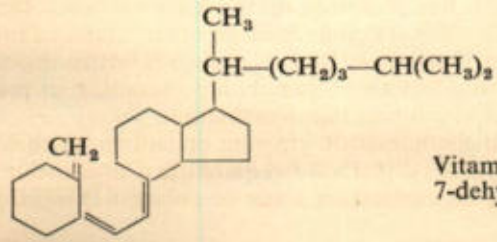
Cortisone.

(iii) 

Cholesterol.

(iv) 

Vitamin D_2-calciferol.

(v) 

Vitamin D_3-activated 7-dehydrocholesterol.

bowed long bones, and 'rickety rosary', which is an enlargement of the costochondral junctions of the ribs: fractures may occur spontaneously. These lesions result in marked lameness. In all cases the appetite becomes capricious: this may cause some temporary recession in symptoms for the growth rate decreases and the demand for vitamin D and, or, minerals remains static—it is always the larger breeds and rapidly growing animals which suffer most.

In *calves* and *lambs*, rickets is commonly due to deficiencies of either calcium, or phosphorus, or both, rather than vitamin D, for irradiation of sterols in the skin plus whatever occurs in the diet will usually provide sufficient vitamin D for normal purposes. It has, however, been reported (Grant, 1955) that vitamin A and its precursors may be the cause of rickets in lambs on pastures adequate in calcium and phosphorus, and where vitamin D deficiency is unlikely: this action is suspected to be due to an effect on phosphorus metabolism.

Pigs are dependent to a greater extent on vitamin D supplies: dogs are similarly dependent, but it is *poultry* which suffer most markedly from vitamin D deficiencies.

Osteomalacia is the equivalent disease in adults. It is characterized by the formation of excessive amounts of osteoid tissue which fails to calcify: this osteoid tissue is mainly confined to the diaphyses of the bones, for it is formed during the normal process of rebuilding the bone, but some is formed in the cancellous bone of the epiphyses of long bones: osteoid tissue under the periosteum, especially at the site of ligament and tendon attachments, and in the Haversian systems, gradually replaces the calcified tissue and weakens the bones. The weakened bones eventually break or become deformed, and in the former case the callus does not calcify so that the bone is unable to support weight.

Recovery of young stock will follow readjustment of the diet although malformations will remain. In adults the prognosis is rarely satisfactory, and where recovery does take place progress is slow and malformations persist.

Nutritional requirements vary widely. There are, for example, species differences, for foxes and mink require very little vitamin D if calcium and phosphorus are present in the diet in correct proportions: other species, dogs, calves, foals and especially poultry, have far greater vitamin D requirements even when the calcium and phosphorus elements are present in the correct ratio. Fast growing breeds of animals require more of the vitamin than the slower growing breeds: this is very well shown in the larger breeds of dog—the greyhound, St. Bernard and Great Dane. Besides these differences it has been shown that breeds with pigmented skins have greater requirements than light skinned breeds, that pregnant and lactating females require more, that animals in northern or southern climates require more than those in temperate or equatorial areas, and that greater quantities of vitamin D are required in the winter than in summer. Of considerable importance is the fact that vitamin D requirements

in all species and individuals is minimal when calcium and phosphorus are present in the diet in optimal proportions (a ratio of approximately 2 : 1). As the ratio changes the vitamin D requirements increase and the vitamin becomes of greater importance, for in many species it tends to overcome the effects of the imbalance and promotes normal utilization. However, though vitamin D will improve the assimilation and use of any calcium or phosphorus present in the food it will not replace an absolute mineral deficiency.

Average *daily minimum requirements* have been assessed as follows:

Horse, Cow, Sheep and Pig:	300–500 units per cwt. (50·0 kg.)
Dog:	5–10 units per lb. (10–20 units per kg.) body weight.

Normally about three times these quantities should be given daily if full requirements are to be met.

Poultry requirements concern vitamin D_3, for vitamin D_2 is relatively inactive. Fowls need about 1,000,000 units vitamin D_3 per ton of food, turkeys 2,000,000 units. Where vitamin D is given to pigs in food up to 8,000,000 units per ton of food has been recommended for piglets of up to 50 lb. weight, and 500,000 units for older pigs though breeding stock may be given 1,000,000 units per ton of food.

Dosages for treatment of deficiencies should approach 10–20 times the minimum daily requirements. According to Hibbs and Pounden (1950 and 1951) doses of 10–30 million units injected or fed daily for five days prior to calving have averted milk fever in cattle. This has been confirmed by Boda and Cole (1956) but Swann (1952) and others have pointed out the toxic effects which may result, and have shown that, if given for longer periods than this, calcification of vessels and heart muscle occurs, as well as deposition of calcium in other sites. This toxicity also affects other species if given in large doses. Single doses of 150,000 to 250,000 units per lb. bodyweight have been reported to cause the death of puppies in a few days to a few weeks, whilst daily doses of about 5,000 units per lb. bodyweight has resulted in chronic toxicity indicated by stunted growth, calcification of heart, kidney and other tissues, malformed teeth and a marked density of bones.

Vitamin E

This is a collective term applied to a group of four organic alcohols known as the α, β, γ, *and* δ, *tocopherols*, of which *alpha-tocopherol* is the most active. Alpha tocopherol is a yellow, almost odourless, viscous oil: it oxidizes very easily and darkens with exposure to air and light. The tocopherols as a group are insoluble in water but soluble in organic solvents, including fixed oils. The acetate esters, which have the same solubilities, are preferred for therapeutic use because of their greater stability.

Sources. Vitamin E is present in green foods, crude vegetable oils, and animal fat: its most potent source is wheat germ oil which has been the main therapeutic source of the vitamin until *d l.* alpha tocopherol was produced synthetically. This has much the same activity as the naturally occurring compound which is dextrorotatory.

Stability. The vitamin E alcohols are rapidly oxidized and destroyed when exposed to air and light. The acetates, however, are less affected by atmospheric oxidation, but are still susceptible to the effects of light, though to a lesser degree than their parent alcohols. Any process which involves oxidation automatically involves the tocopherols which are antioxidants. Thus any oil or fat which is rancid will contain no active vitamin E, for the oxidative processes which result in rancidity will have been restrained by the antioxidant effects of the tocopherols and marked rancidity will only have developed when all the tocopherols have been destroyed.

Assay. The tocopherols are assayed chemically.

Action. Under normal conditions the tocopherols are readily *absorbed* from the intestines, and excess is either *stored* in the fat depots of the body or *excreted*, mostly in the bile but partly in the urine. Where fat absorption is restricted the absorption of vitamin E will be likewise affected.

The predominant action of the tocopherols would appear to be that of regulating the oxidation processes of the body. This antioxidant action links its physiological effect with vitamin A metabolism (it is used for the stabilizing of vitamin A in foodstuffs), and with that of the unsaturated fatty acids. It is probable that it is this antioxidant 'protecting' action on unsaturated fatty acid which is responsible for the 'conditioned' vitamin E deficiency that has occurred fairly widely due to the regular feeding of excessive quantities of cod-liver oil, though Blaxter and McGill (1955) have pointed out that various other factors, including mineral imbalances, influence the course of this type of deficiency.

Blaxter (1957) has also pointed out that, in this 'conditioned' deficiency of vitamin E, the tocopherol content of even severely affected muscles is higher than in normal muscles. He suggests that interference with energy exchanges of cells may occur, due to the formation of abnormal phospholipids on cell interfaces by the excess unsaturated fatty acids. He presumes that tocopherols either prevent the action of such compounds or facilitate their metabolic neutralization. Increased requirements of vitamin E would therefore follow an increased intake of unsaturated fatty acids.

These details add emphasis to the fact that the biochemical status of vitamin E is as yet incompletely known and is probably not simply one of controlling oxidation processes, although investigations now proceeding suggest that the vitamin may be involved in the cytochrome C reductase system (Blaxter, 1957).

Deficiency syndromes which respond to tocopherol therapy have been reported in all domestic species.

It is probable that vitamin E deficiency in all species is accompanied by muscular disorders. These are most marked in calves and lambs, in which extensive investigations have related muscular dystrophy, white muscle disease, and stiff lamb disease (some types), to tocopherol deficiencies. In horses, pigs, and other species, vitamin E deficiencies have not been examined so intensively. The muscle damage results in changes of stance, movement, and general behaviour as the affected animals attempt to transfer the function of affected muscles to other unaffected muscle groups. Lameness is bilateral, and usually numbers of individuals are affected at the same time. The symptoms will vary considerably according to the groups of muscles which are affected, but three main types are described: a skeletal type, in which locomotor and supporting muscles and symptoms are involved; a thoracic type, in which intercostal and diaphragmatic muscles are affected: and a cardiac type, in which the heart muscles are affected.

In addition to muscular involvement other effects such as diminished fertility, œdema, and steatitis, have been demonstrated in some species. In *pigs*, for example, embryonic death occurred in sows maintained on vitamin E deficient diets (Adamstone *et al.*, 1949). In *poultry*, fertility is also affected—cockerels develop testicular degenerations and hatchability of eggs is affected. In *mink* and *pigs*, an inflammation of fatty tissues and a yellow-brown discolouration of the fat, steatitis or 'yellow fat', have been widely reported. In *poultry*, exudative diathesis, which is a generalized œdematous condition resulting from increased vascular permeability (also reported in pigs), and a condition known as nutritional encephalomalacia or 'crazy chick disease', which usually occurs in chicks from three to six weeks of age but has been reported shortly after hatching, are two other ways in which vitamin E deficiency may show itself.

Apart from pigs and poultry no fertility effects have been reliably reported in domestic animals, though such effects in rats and mice have been fully established and were the reason for the early references to vitamin E as the 'anti-sterility' or 'fertility' vitamin.

In lambs and calves the *incidence* of the disease is mainly in spring and early summer, if animals are housed during winter. Increased exercise precipitates an attack of the disease and symptoms occur within two days or so of turning the animals out to grass. Cardiac cases are very acutely affected and are often found dead. With less acutely affected cases a large proportion will recover if treatment is instituted before gross, irreversible muscular damage is caused. The appreciation of the relationship of poor winter feeding and vitamin E deficiencies with muscular dystrophy has now greatly reduced the incidence and mortality rate, but prior to this in some areas of Scotland, Norway, Finland, Canada, and the United States, the morbidity rate was as high as 25 per cent. and the mortality rate was also very high. Annual losses are still appreciable.

Nutritional requirements are not defined. This is possibly because the availability of the vitamin is conditioned by the composition of the diet. Where the level of unsaturated fatty acids in the diet is high, the vitamin requirements will also be high, but it should be remembered that other compounds and conditions besides these acids will depress absorption of vitamin E, including tri-orthocresylphosphate (in some species), possibly sulphaguanidine, and gastro-enteritis: it must also be borne in mind that variations in mineral and carbohydrate concentrations in a diet will modify the symptoms resulting from a vitamin E deficiency or insufficiency. Deficiencies of other vitamins such as choline may predispose muscles to the effects of vitamin E deficiencies. Blaxter *et al.* (1953) found that 0·2 G. α-tocopherol was required daily to prevent muscular dystrophy in calves receiving 1 fl. oz. (30·0 m.) cod-liver oil in their diet, and that from 20·0–150·0 mg. was sufficient to prevent dystrophy in susceptible calves (Blaxter and Sharman, 1953). Requirements for chicks of up to eight weeks old have been variably estimated at between 11·0 and 33·0 G. per ton of feed, whilst for turkeys of up to eighteen weeks 11·0 G. per ton have been recommended, and for breeding stock as much as 45·0 G. or more have been suggested.

Dosage. Therapeutic doses must be increased if the exciting factor is unknown. Should the factor be cod-liver oil, it is advisable to discontinue the administration of this, and supply vitamins A and D in some other form in which unsaturated fatty acids are not present in such high proportions—if at all. Daily doses (U.S.D. 25th Edit.) of Tocopheryl Acetate, B.Vet.C. are:

Calves:	0·3–2·0 G. (5–30 gr.)
Lambs:	0·1–0·5 G. (1½–7½ gr.)
Pigs (weaned):	0·5 G. (7½ gr.) minimum.
Dogs:	30·0–100·0 mg. (½–1½ gr.)

These doses may be given orally, by subcutaneous, or by intramuscular injection.

Wheat Germ Oil, B.Vet.C. has been used but, because of its variable vitamin E content, it is now being largely replaced by synthetic α-tocopherol preparations. The average daily doses recommended are:

Calves:	10·0 ml. (160 m.),
Lambs:	1·0 ml. (15 m.),
Dogs:	1·0–2·0 m. (15–30 m.).

Toxicity. Extremely large doses of tocopherols have produced neither acute nor chronic toxicity and consequently dosage is conditioned more by size of effective dose and expense than by any other consideration.

Vitamin K

The name of this vitamin was derived from *koagulation*, and was suggested by Dam of Copenhagen who, in 1935, demonstrated its presence, though

not its composition, in green leaves. As with other vitamins, the specific vitamin K activity is possessed by a group of compounds, three of which are of significance. All are naphthaquinones. The first to be discovered—that occurring naturally in green foods—was 2-methyl-3-phytyl-1,4 naphthaquinone, and was designated vitamin K_1. The second, discovered in putrefied fish meal, differs only in having a different organic group in place of the phytyl group of vitamin K_1, and has been designated vitamin K_2. Vitamin K_3 is used to designate a synthetic naphthaquinone found after an intensive investigation of a large number of naphthaquinone compounds; it is simply 2-methyl-,1,4-naphthaquinone. Vitamin K_1 is recognized as *Phytonadione* by the U.S.P., and vitamin K_3 as *Menaphthone*, B.Vet.C. or as *Menadione* in the U.S.P.

Menaphthone, B.Vet.C.

This synthetic vitamin is a bright yellow crystalline powder with a faint but characteristic smell. It is insoluble in water, slightly soluble in alcohol and fixed oils, but more soluble in other organic solvents. The powder is very irritant to all mucous membranes, and alcoholic solutions are vesicant. Various menaphthone derivatives are available—acetomenaphthone for oral administration, and a water soluble compound, menaphthone sodium bisulphite for parenteral administration, are the more important ones.

Sources. Menaphthone is synthetic, but vitamin K_1 is present in green leaves—lucerne and horse chestnut leaves being credited with the greatest concentrations—but species of Brassica contain appreciable quantities. Vitamin K_2 is derived mainly from rotted fish, but in common with vitamin K_1 can be manufactured synthetically. Meat and animal products contain little vitamin K.

Stability. The powder is said to decompose to some extent on autoclaving at 15 lb. p.s.i. pressure for 30 minutes, but solutions in oil may be sterilized by heating at 150°C. for 1 hour. Menaphthone is decomposed by light which results in a darkening in the colour of both powder and solutions.

Assay. The assay is chemical.

Action. Ruminants are independent of dietary vitamin K once rumination has commenced, and it is possible that most other species derive some of their vitamin K from bacterial synthesis in the intestines. However, in young ruminants prior to the onset of rumination and in simple stomached species, at least some vitamin K must be supplied in the food. Like all fat soluble vitamins the *absorption* of vitamin K from the intestines is dependent on the presence of bile and fat in the intestines. *Storage* is mainly in the liver and *excretion* is via the urinary system.

Menaphthone and the other vitamin K compounds are essential for the formation of prothrombin in the liver, and lack of the vitamin results

in hypoprothrombinæmia. Lack of prothrombin in the blood breaks the chain of events which results in the formation of blood clots, so that when small contusions occur prolonged bleeding follows with the formation of large hæmatomata, and the development of severe hæmorrhagic anæmia and hæmolytic jaundice. It is only when animals are kept under intensive artificial conditions that deficiencies are likely to occur and, with poultry in particular, it is essential to provide green food either as dried grass or lucerne meal, or better still fresh green foods.

A conditioned *deficiency* exists in cattle and is known as 'sweet clover' disease, in which *dicoumarol* or bishydroxycoumarin elaborated in the sweet clover is absorbed and counteracts the formation of prothrombin in the liver. The same principle applies to the action of *Warfarin*, an anticoagulant rat poison. Vitamin K is the physiological antidote, but in Warfarin poisoning (see p. 210) absorption of the vitamin is usually too slow following oral or intramuscular administration, and slow intravenous injection of menaphthone sodium bisulphite should be tried in pigs, dogs and cats—most other species are resistant to the effects of Warfarin: if possible, menaphthone treatment should be associated with blood transfusions.

Vitamin K is of some value for the treatment of the epistaxis in racehorses associated with the excitement prior to and during races, but the perfect treatment for this condition has yet to be found. Given with vitamin C, menaphthone and other vitamin K analogues are useful in salicylate poisoning; they have also been used beneficially in quinine poisoning and in diseases such as hepatitis and gastroenteritis when vitamin K absorption is restricted, or prothrombin formation impaired.

Dietary requirements have not been generally assessed but it has been suggested that 0·4 G. per ton of food is adequate for chickens of up to 18 weeks of age.

Dosage. No established doses are available but 50·0 or 60·0 mg. have been given intravenously in dogs without any toxic effects. It is probable that in Warfarin poisoning the safe maximum human dose of menapthone sodium bisulphite, which is 100·0 mg. daily, may be taken as a guide for the treatment of dogs, cats and pigs. Intramuscular injections of up to 5·0 mg. of menaphthone have been suggested by the British Veterinary Codex. Commercially, acetomenaphthone has been recommended in daily oral doses of 2·0–10·0 mg. for the dog, and 100·0–400·0 mg. for large animals.

The Unsaturated Fatty Acids

These 'essential' fatty acids were formally referred to as vitamin F, but this name has now been discarded. There are three main groups of unsaturated fatty acids conforming the general formulæ of (i) $C_nH_{2n-2}O_2$ (oleic acid), (ii) $C_nH_{2n-4}O_2$ (linoleic acid), and (iii) $C_nH_{2n-6}O_2$ (linolenic acid). Members of the first group contain one double bond, those of the

second usually 2 double bonds, and of the third three double bonds; the degree of unsaturation naturally increases with the number of double bonds. One or two acids with higher degrees of unsaturation are of some importance.

Linoleic acid, one of the two main essential unsaturated fatty acids, belongs to the second group and contains within its structure two double bonds: it has the empirical formula $C_{17}H_{31}COOH$.

Arachidonic acid, $C_{19}H_{31}COOH$, is the other important acid. It is more highly unsaturated than any of the three main groups mentioned, and contains four double bonds.

The main natural *sources* of these fatty acids are soya bean oil, corn embryo oil (maize germ oil) and lard. The first contains about 50 per cent. linoleic and between 5 and 10 per cent. linolenic acid, the second about the same amount of linoleic but only about 2 per cent. linolenic acid, but lard contains only 10 per cent. or so of linoleic acid.

These acids are relatively unstable but the addition of tocopherols provides a certain degree of protection by virtue of their antioxidant action.

Deficiencies have resulted in stunted growth, skin lesions and tail necrosis in rats but so far little of clinical significance in domestic animals has been demonstrated, though beneficial effects in human skin lesions have been claimed. Linolenic acid is far less important than either linoleic or arachidonic acids in the experimental work so far carried out. Linoleic acid prevents the onset of certain of the lesions associated with pyridoxine deficiencies in rats (acrodynia).

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CHAPTER 36

THE HORMONES

A hormone may be defined as a secretion discharged in very small amounts into the blood stream by an endocrine or ductless gland. Hormones have commonly been described as chemical messengers but their function is usually more autocratic than that of messengers, for they dictate to, control, and co-ordinate the functions of all the organs and tissues of the body. They may have relatively specific actions as with insulin, or act in several ways as with adrenaline: they may be functional hormones such as the œstrogens and progestins which are directly responsible for the changes in an organ, or they may be hormones which cause the production of other hormones and control and co-ordinate their actions: of this latter type the anterior pituitary hormones are the most important. Most functional hormones work in equilibrium with their controlling hormones in the normal body, and an excess of a functional hormone will in turn depress the production of its controller hormone: thus an excess of an œstrogen injected into a normal female animal will depress the production of follicle stimulating hormone by the anterior pituitary gland. In some cases one hormone will antagonize the action of another as with insulin and adrenaline, the first of which causes glycogenesis with the removal of sugar from the circulation whilst adrenaline, which has the function of preparing for and maintaining the body during strenuous action, causes amongst other effects, glycolysis with the mobilization of glucose into the blood. In other cases two hormones will act together as with oxytocin and the œstrogens, the first hormone causing uterine contractions only when that organ is 'sensitized' by the action of œstrogens. Still other hormones will act synergistically in some ways and antagonistically in other ways: thus progesterone will continue the preparation of the mammary gland for lactation after the œstrogens have initiated the preparation, and yet will antagonize the effect of œstrogens in depressing the sensitivity of the uterus to the action of oxytocin: androgens will also antagonize the feminizing effect of œstrogens and yet will act in the same way as the œstrogens in causing growth of the duct system in the mammary glands.

Some hormones are essential for the continuation of life whilst others, though their absence causes modification of body functions, are not

essential. The parathyroid glands are essential, for extirpation results in the development of hypocalcæmic convulsions and death: extirpation of the adrenal glands also leads to death within 1–2 weeks: castration, with the removal of ovaries or testes, causes comparatively little effect on the body even though the organs are the main sources of œstrogens and androgens.

Hormone Classification

Reproductive Hormones.

Female: Ovarian: Follicle:	Natural:	Œstradiol
		Œstrone
		Œstriol
	Synthetic:	Ethinylœstradiol
		Stilbœstrol
		Dienœstrol
		Hexœstrol
Corpus Luteum:		
	Natural:	Progesterone
	Synthetic:	Ethisterone
Male: Testicular: Interstitial cells:		
	Natural:	Testosterone
		Androsterone
	Synthetic:	Methyltestosterone
Male and female gonadotrophins:		
Follicle and Sperm stimulating trophin:		Serum Gonadotrophin
Luteinizing and Interstitial cell stimulating trophin:		Chorionic Gonadotrophin

Pituitary Hormones:

Anterior Pituitary Trophins:	
Gonadotrophins:	
Thyrotrophin:	
Adrenocorticotrophin:	ACTH
Somatotrophin or Growth trophin:	
Lactogenic trophin:	Prolactin
Metabolic trophins:	
Posterior Pituitary:	
Oxytocic factor:	Oxytocin
Pressor factor: } Antidiuretic factor: } Melanophoric factor:	Vasopressin

Adrenal Hormones:

Cortical:	
Mineralocorticoids:	Desoxycorticosterone (D.O.C.A.)
Glucocorticoids:	Corticosterone
	Cortisone
	Hydrocortisone
	Prednisolone
Medullary:	Adrenaline

'Metabolic' Hormones:

Parathyroid Gland:	Parathyroid Extract
Thyroid Gland:	Thyroid Extract
	Thyroxine
	Di-iodotyrosine (synthetic)
Pancreatic Gland:	Insulin

Miscellaneous Hormones: (no present clinical applications)

'Alimentary' hormones: Gastrin, secretin etc.
Thymus, prostatic, and allantoic hormones.

The Pituitary Gland

Fractions of only the anterior and posterior portions of the pituitary gland are available for clinical use. Those fractions obtained from the posterior lobe have already been mentioned in Chapter 18 (*q.v.*).

The Anterior Pituitary Hormones. Six different hormones have been isolated in almost pure forms, and analysis has shown them to be of a protein nature: the somatotrophic or growth hormone, for example, is a sulphur containing protein with a molecular weight of over 44,000, the lactogenic hormone (prolactin) is also a sulphur containing protein and has a molecular weight of about 32,000. However, work which has been carried out on the corticotrophic fraction indicates that corticotrophic activity is due to substances possessing no sulphur, phosphorus, sugars, fats or heavy metals, but having peptide linkages, carboxyl groups and probably at least one basic grouping (Astwood *et al.*, 1951; Quoted by U.S.D. 25th Edit. 1955, p. 367). It is stated that even this may not be the pure hormone. It is probable that the other trophins have a similar composition.

The trophins which have been closely investigated are the somatotrophin or growth hormone; two gonadotrophic hormones (similar in action to the chorionic and serum gonadotrophins), although it has been stated that only one exists in the human; the lactogenic hormone also known as prolactin or luteotrophin; the thyrotrophin also referred to as

TSH (thyroid stimulating hormone); and corticotrophin or adrenocorticotrophic hormone (ACTH).

Twenty or more further hormones have been claimed to occur in anterior pituitary secretions, including the so-called 'metabolic' factors—a diabetogenic, a ketogenic and insulin producing trophins. It has yet to be proved that these factors are distinct entities, and at present they are therefore not of any clinical significance.

In veterinary medicine the only anterior pituitary hormone of clinical significance is the adrenocorticotrophic hormone, for gonadotrophins from other sources are used clinically, and the lactogenic hormone is still of only experimental interest. The thyroid and growth stimulating hormones are not used.

Adrenocorticotrophic Hormone: Corticotrophin, B.P., ACTH

Corticotrophin, B.P. is a white or almost white powder, unless prepared by freeze-drying methods when it exists as fawn flakes or masses. It is a glacial acetic acid/acetone extract which is soluble in water or normal saline and contains not less than 0·75 units per mg. So-called 'long-acting' preparations are either zinc complexes or gelatin suspensions.

Actions. The actions of corticotrophin are essentially those of adrenocortical stimulation, for the hormone has no known actions apart from the stimulation of the adrenal cortex. Following intramuscular or subcutaneous administration the action becomes apparent within a few hours, but intravenous injection produces effects within a few minutes. Non-depot forms lose their effects after a few hours whereas depot injections, though their effects are slower in onset and never reach the maximum achieved by non-conjugated forms, their action is prolonged over a period of 24–48 hours depending on dosage. It has been found in man that intravenous infusion of 20 units over a period of 6–8 hours will equal in adrenal stimulation as much as 150 units given over a 24 hour period in equal, divided doses at 4–6 hour intervals.

The effect of corticotrophin on the adrenal cortex is to produce a rapid decrease in the ascorbic acid and cholesterol levels within the gland. The significance of the loss of ascorbic acid is unknown, but it has been noticed in man that there is a complementary increase in circulating and urinary ascorbic acid. Concurrent with the decrease in cholesterol, there is a rise in the synthesis and output of corticosteroids, and the indications are that the cholesterol is used in the synthesis of these adrenocorticosteroids. Amongst these steroids are hydrocortisone and corticosterone, which constitute about 40 per cent. of the total steroid output of the gland, cortisone, a mineralocorticoid not identified, but probably aldosterone (desoxycorticosterone is probably not produced naturally), various androgens and œstrogens, some progesterone, and precursors of these.

In the rest of the body, the reaction to corticotrophin is the same as

would be expected from the action of mineralocorticoids and glucocorticoids. This includes a decrease in circulating eosinophils which is so marked as to be used as a method of cortrophin assay, and modification of renal, thyroid, skin connective tissue, mineral and carbohydrate metabolism. The metabolic fate and excretion of corticotrophin are unknown but the compound markedly effects the excretion of steroids, causing an increase in the excretion of reducing corticosteroids including hydrocortisone and cortisone. There is also an increase in urinary 17-ketosteroids including androsterone, and also in œstrogen and pregnanolone (an excretory product of progesterone) excretion.

Uses. Corticotrophin has been, and is, widely used in the treatment of bovine primary or post-parturient ketosis. One of the first recorded uses for this purpose was by Fincher *et al.* (1940), who stated that the adrenocorticotrophic principle of anterior pituitary extracts must benefit an animal suffering from ketosis by virtue of its stimulation of glucocorticoid production. This information and comment received little recognition until Shaw and his colleagues (Hatziolos and Shaw, 1950; Shaw *et al.*, 1950) published the first of a long series of reports. These reports have expounded and elaborated the hypothesis that acetonæmia is due to temporary exhaustion of the anterior pituitary gland following prolonged stress during pregnancy, the acute stress of parturition, and the institution of lactation: this pituitary exhaustion results in a lack of glucocorticoid production by the adrenal cortex, a consequent drop in circulating glucose, and an inability to mobilize or synthesize more. Other sources of glucose are then tapped including fat breakdown which is incomplete, possibly due to lack of available glucose and therefore energy, although the true reason is unknown. The total result is an animal with a low milk yield, a loss of appetite and condition, low blood glucose levels and high blood, urine, milk, and breath ketone levels. The whole position, including alternative treatments, has been reviewed by Shaw (1955). The ætiology and treatment of *pregnancy toxæmia* in sheep has not received as thorough an investigation as acetonæmia of cattle, but as the clinical picture has many of the features associated with ketosis, it was anticipated that the toxæmia would respond in a similar manner. However, although cortisone has been reported to give good results (Siegmund *et al.*, 1953), ACTH has not proved as successful in sheep as had been hoped; blood glucose precursors such as propionates, propylene glycol, acetates, glycerin, and glucose, or mixtures of these, often combined with cobalt and other minerals, are as effective. Recent work (McClymont, 1955—high blood œstrogen levels; McClymont *et al.*, 1956—insulin effects; Report (Australia 1955) C.S.I.R.O.,—association with interference in the oxidation of C_2 compounds via the tri-carboxylic cycle; Parry *et al.*, 1956—association with renal dysfunction; Kolesov *et al.*, 1956—association with dietary protein deficiency; Thomson, 1956—unsatisfactory response to blood glucose precursors and ACTH) shows how complex is the condition, and

how unsatisfactory is the response to be expected from treatment now available (Thomson, *loc. cit.*). Published reports on the use of prednisolone in pregnancy toxæmia are not yet available but clinical response during the winter of 1957–58 promises well.

Corticotrophin has also been used in the treatment of skin conditions in cattle (Talsma, 1956), and small animals (Halpin, 1955). In the report on its use in cattle, Talsma quotes considerable benefit from the early use of 40–80 i.units in the treatment of 50 cases with skin lesions due to photosensitization: he also mentions benefit in œdema of the glottis, urticaria and acute laminitis, whilst 20 i.units were of assistance in treating, in conjunction with antibiotics, 20 calves affected with arthritis. In non-specific dermatitis in cats and dogs ACTH is useful, particularly in cases of 'fish', 'flea' or miliary eczema in cats. Pruritis ceases within 24–48 hours and hair begins to grow within 7 days. After a course of ACTH the condition can be expected to return after a period of 6–9 months or less. However, it has been found that testosterone implants, and possibly progesterone implants, in doses of 25·0–50·0 mg., are as effective but more prolonged in action. The implants are preferred in castrates, male or female, but in entire animals ACTH is more useful, for high doses of androgens—or œstrogens—will depress anterior pituitary activity, which in turn will depress gonadal production and aggravate the condition. This is an example where stimulatory therapy is preferable to replacement therapy, and where adrenal steroids can be produced to supplement gonadal steroid activity. The same argument applies if corticosteroids are used in these same skin conditions—single doses have little effect on the pituitary gland, but where dosage is continuous pituitary depression will result with its concomitant adrenal cortex hypoplasia. This must be guarded against by intermittent dosing or periodical injection of ACTH to maintain adrenal activity: pituitary depression is of relatively minor significance for its secretions are not essential to life as are those of the adrenal cortex.

In the field of *mastitis*, corticotrophin has been used as an adjunct to normal therapy to prevent the induration expected to occur in cases of staphylococcal and similar infections (Hindson, 1956). Doses of 100 i.units given intramuscularly, followed by 50 i.units 24 hours later, were claimed to assist recovery without induration in 17 out of 20 cases. This report follows that of Durrell (1954), who used doses of 300 i.units in the treatment of coliform mastitis.

Lawson (1954) reported the use of corticotrophin in the treatment of *arthritis* and *bursitis* in the bull. Since that time ACTH has been frequently used in the treatment of arthritis but has been largely superseded by cortisone, hydrocortisone, prednisolone and prednisone. In the long term view it is probable that stimulation, followed by hypertrophy of the patient's adrenal glands, should be far more beneficial, and the effects longer lasting than intermittent steroid therapy which may be expected to reduce intrinsic steroid production.

Bunce (1954) reports the use of ACTH in conjunction with vitamin B_{12} as a treatment for *neurological diseases* of dogs. Bowers (1954) claimed benefit following ACTH treatment of paralysis following rabies vaccination. Neither of these claims has been substantiated.

Dosage. In *cattle* the doses used in the United States for the treatment of ketosis have varied from 100 to 3000 units given intramuscularly, but the lack of standardization of unit designation has confused the issue and made comparison difficult. Dutch work (Talsma, 1953) indicated that three 50 unit doses given at twelve hour intervals were insufficient. Some American reports refer to the so-called 'crude' corticotrophin injection and it is probable that Talsma also used the short-acting material. Extensive use of the depot or long-acting forms in Great Britain indicate that doses of 80 to 160 or 200 i.units of these compounds are sufficient for all cases, although many respond to a single 80 i.unit dose. This dosage approximates to that used by Rosenberger *et al.* (1956) when obtaining 31 recoveries out of 42 cases using ACTH alone. These workers recommend 100 i.units intramuscularly on one or two occasions, combined with 50·0 G. (1¾ oz. approx.) sodium propionate daily by mouth.

In *sheep*, for pregnancy toxæmia, approximately 40 i.units intramuscularly should be adequate but may be repeated after 24–48 hours if necessary.

For *dogs and cats*, doses of 5–10 i.units of long-acting compounds are given daily to smaller individuals but up to 20 i.units on alternate days have been recommended for larger animals. Personal experience indicates that far larger doses (double) may be used without harm, but it is probable that the extra expense is not offset by an equal increase in benefit.

The intramuscular and subcutaneous routes are recommended. 'Crude' forms may be given intravenously if necessary.

Once made up, short-acting solutions should be used immediately, but long-acting suspension may be kept for about a week.

Toxicity. The toxicity of corticotrophin is essentially that of the steroids which its administration mobilizes into the system. It is unlikely that trouble will be experienced with intermittent dosing but prolonged administration may result in the delayed healing of wounds, lowered resistance to bacterial invasion, with a possible flare up of chronic infections. It should be remembered that infections will not result in a rise in temperature. Electrolyte balance may also be disturbed with sodium and fluid retention, and potassium loss.

The Adrenal Gland and Its Hormones

The Adrenal or Suprarenal glands, located in close apposition to the anterior poles of the kidneys, have two clearly demarcated zones, an internal or medullary zone which is dark brown in colour and an external or cortical zone which is much lighter in colour. These two zones elaborate

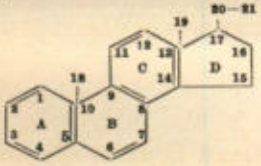
hormones which differ considerably in character and action but which, because they are essential for the continued existence of the animal, make this gland one of the most important in the body.

The *medulla* of the adrenal gland produces adrenaline or epinephrine which is responsible for control of the heart and circulatory system and, by virtue of its production by adrenergic nerve fibres, affects all the structures innervated by the sympathetic portion of the autonomic nervous system. Because of its prime concern with the heart and circulation, adrenaline has been detailed in connection with that system.

From the *adrenal cortex* can be isolated crystalline and amorphous fractions, but as isolation techniques become more selective, the amorphous residue is made to yield more and yet more crystalline compounds. So far about 29 crystalline substances have been isolated, the latest, electrocortin or aldosterone, being reported in 1942. Several androgens and œstrogens are included in the 29, but it is the two groups of steroids known respectively as the *mineralocorticoids* and the *glycocorticoids* that exert the activity specific to the adrenal cortex. Though arbitrarily divided into these two groups it must be understood that each member of one group will possess the actions of the other group but to a varying and lesser degree. Thus the most powerful mineralocorticoid available for clinical use, desoxycorticosterone, (aldosterone is 25–50 times more active in causing sodium, chloride and water retention, but is not yet available for clinical use), has very little glycocorticoid action, whereas corticosterone has both electrolyte and glucose mobilizing effects. The potent glycocorticoid prednisolone has slight mineralocorticoid effects.

Of these two groups, desoxycorticosterone—available as Deoxycortone Acetate, B.P. in Great Britain—is the mineralocorticoid of veterinary interest, whilst cortisone, official in the Veterinary Codex as the acetate, hydrocortisone, prednisone and prednisolone, are the glycocorticoids which have been used.

Chemistry. It must be remembered that steroids of the adrenal cortex are very closely allied to the steroids produced by the ovary and testes, and also that œstrogens and androgens will be produced by the adrenal cortex which may continue sexual activity after removal of the ovaries or testes. These corticosteroids have, therefore, the cyclopentenophenanthrene nucleus (i)

(i) 

cyclopentenophenanthrene
($C_{17}H_{14}$)

Any substitution and changes which occur and any additions to this nucleus will therefore be described in the same way as are the variations

affecting the sex hormones (*q.v.*). The following notes will enable a better understanding of the nomenclature:

1. Any compound with the suffix '-*e*ne' is unsaturated and will possess double bonds in its construction. The number of double bonds is indicated by '-ene', 'di-ene', 'tri-ene' designation, and the site of the linkage is indicated by the number allocated to the first carbon atom in the bond as (ii) and (iia):

(ii)  -'4-ene' (iia)  -'1:3 di-ene'

This double bond position may also be indicated by the Greek Delta Δ and the position indicated as before, the figure(s) being added as in (iii) and (iiia). This is the origin of the Delta- of the many proprietary names for the adrenocortical hormones.

(iii)  -4ene, or Δ^4-ene, or $\Delta^{4:5}$-ene.

(iiia)  -1,3,5,triene, or $\Delta^{1,3,5.}$-triene.

2. The suffix '-*a*ne' indicates a saturated compound.

3. '-ol' indicates a hydroxy-derivative, while '-diol' and 'triol' represent the di- and tri-hydroxy derivatives respectively.

4. '-one' indicates a ketone derivative (double bonded oxygen atom); hence '-dione' and '-trione'.

5. '-ol-one' will then indicate a mixed hydroxyketone derivative.

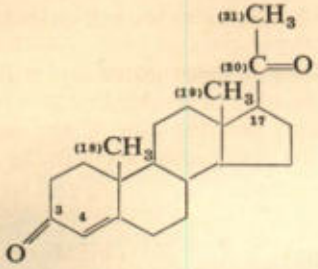
6. Numbers are used to indicate the positions of these groups as for example: 3:17 diol indicating a hydroxyl group attached at both carbons 3 and 17 of the nucleus.

7. Where a particular isomer is designated it may be referred to as 'cis-' or 'α' when the group is orientated to the rear, and 'trans-' or 'β' when the configuration is to the front. The alpha configuration confers a lower activity and these forms are more frequently found as excretory products.

8. It is also important to remember that the prefix 'pregn-' or 'pregna-' indicates progesterone origin: progesterone may be referred to as Δ^4pregnene-3:20-dione.

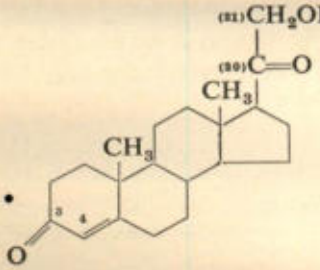
Beginning with *progesterone* (iv) the substitution of a hydroxyl group for a hydrogen atom of the methyl group centred on carbon 21 produces *desoxycorticosterone* (v) also designated 21: hydroxyprogesterone. The addition of a further hydroxyl group for the hydrogen atom at carbon 11 of desoxycorticosterone produces *corticosterone* (vi) which may therefore be designated 11:21 dihydroxyprogesterone.

(iv)



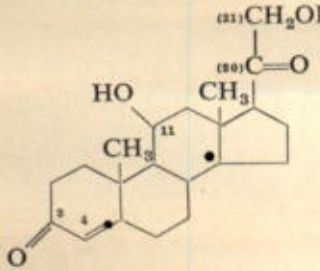
Progesterone, or Δ^4pregnene-3,20-dione.

(v)



Desoxycorticosterone, or 21-hydroxyprogesterone, or Δ^4pregnene-21-ol-3,20-dione.

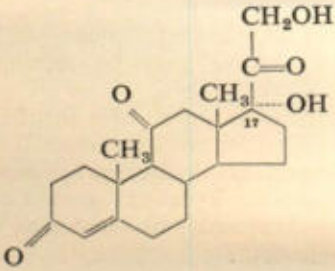
(vi)



Corticosterone, or 11,21-dihydroxyprogesterone, or Δ^4pregnene-11,21-diol-3,20-dione.

If we now change the hydroxyl group at carbon 11 of corticosterone to an oxygen atom (dehydrogenate and therefore '-dehydro-'), and add a hydroxyl group inclined to the rear (α) at carbon 17 we produce *cortisone* (vii)

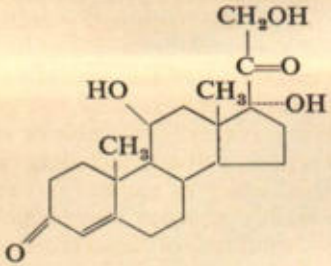
(vii)



Cortisone, or 17-α-hydroxy-11-dehydrocorticosterone, or 11 oxy-17α,21dihydroxy-progesterone, or Δ^4pregnene-17α,21-diol-3,11,20 trione.

If, instead of removing the hydrogen from the hydroxyl group at carbon 11 of the corticosterone, we merely add the hydroxyl group at carbon 17, we have hydrogenated cortisone and produced *hydrocortisone* (viii), that is, a hydrogen atom added to cortisone.

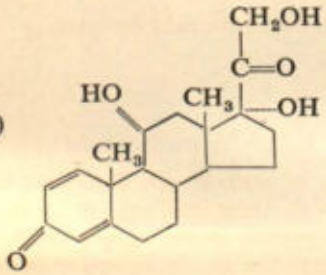
(viii)



Hydrocortisone, or 17α-hydroxycorticosterone, or 11,17α,21-trihydroxy-progesterone, or Δ^4pregnene-11β,17α,21-triol-3,20,dione.

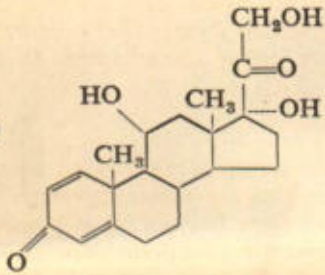
Now if we take cortisone and dehydrogenate it to make another double bond between carbons 1 and 2 in ring A of the steroid nucleus, we produce *prednisone* (ix), and similarly if we dehydrogenate hydrocortisone in the same place we produce *prednisolone* (x). These two new compounds therefore are related to each other in the same way that cortisone and hydrocortisone are related.

(ix)



Prednisone, or $\Delta^{1,4}$pregna-diene-17α,21-diol-3,11,20-trione.

(x)

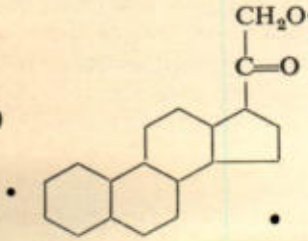


Prednisolone, or $\Delta^{1,4}$-pregna-diene-11β,17,21-triol-3,20-dione.

It will be seen that as the steroid nucleus now has two unsaturated links the indicator in the written formula changes from '*-ene*' or one to '*-diene*' or two double bonds, i.e. $\Delta^{1,4}$-, Delta-one-four.

Physical Characters. Though many of these compounds may be extracted from the adrenal cortex of cattle, sheep and pigs, the yield is too small for economic use and all are prepared synthetically some of the structural modifications being achieved biosynthetically. (The biosynthetic processes used are the enzyme reactions which take place during bacterial fermentation, basic steroids being fed to the fermenting cultures and subsequently recovered in a modified form. An example of this is the introduction of an oxygen atom at carbon 11 of the steroid nucleus to form the hydroxyl group of hydrocortisone and its near relatives.) All are white or off-white crystalline powders, generally insoluble or almost so in water but slightly more soluble in organic solvents including propylene glycol and fixed oils. They may be used either as acetates (xi) or as free alcohols. Veterinary injections are mainly aqueous suspensions (prednisolone, cortisone acetate), but oily solutions of desoxycorticosterone acetate (*Deoxycortone Acetate*, B.P.) and aqueous alcoholic solutions of hydrocortisone (*Hydrocortisone*, B.P.C.) are used. Ointments with and without broad-spectrum or narrow spectrum antibiotics are also available for topical and ophthalmic application.

(xi)



All corticosteroid acetates.

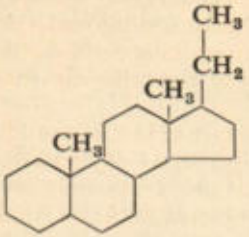
Actions. Although two distinct groups of actions are described and the adrenocorticoids classified according to these actions, it must be remembered that the glycocorticoids all possess some active effect on the electrolyte balance, although hydrocortisone is not so active in this direction as cortisone, and their analogues prednisone and prednisolone are even less active. There is therefore a constant danger that protracted treatment with these glycocorticoids may cause disturbances of the electrolyte balance.

Deoxycortone Acetate, B.P.

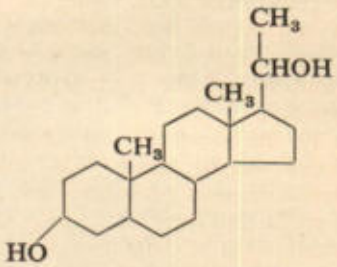
It has not been established that this is the hormone elaborated by the adrenal cortex in the body but it still remains the most active steroid clinically available for influencing the electrolyte balance. It is possible that aldosterone, which has a '-CHO' aldehyde group in place of the methyl group at position 18 and a hydroxyl group at carbon 11 of the desoxycorticosterone structure, will replace this compound for it is 25–50 times more active as a mineralocorticoid. Deoxycortone acetate is rapidly *absorbed* following intramuscular or subcutaneous injection, but it is

poorly absorbed through the skin and is mostly destroyed in the alimentary tract so that oral doses need to be about thirty-five times those for intramuscular injection. *Excretion* is typical of that of all steroids in that part is in the form of the saturated and inactive pregn*ane*-3α,20α-diol (xii) the alpha forms being less active physiologically than beta forms.

(xii)



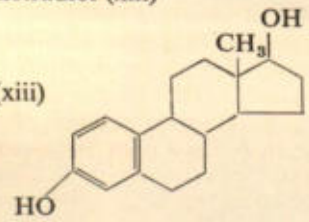
pregn*ane*



pregn*ane*-3α,20α-diol.

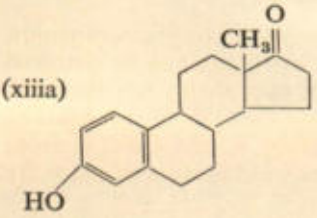
Pregnane-3,20-diol is also the form in which progesterone is excreted. Some is also excreted as 17-ketosteroids, a common urinary form of most steroids in which all groups attached at carbon 17 are replaced by a single oxygen atom, thus forming a '> C═O' or ketone group: œstrone (xiiia) is a typical ketosteroid, produced as a less active excretory product of œstradiol (xiii)

(xiii)



Œstradiol, or $\Delta^{1,3,5}$-œstra-triene-3,17β diol.

(xiiia)



Œstrone, or $\Delta^{1,3,5}$œstra-triene 3-ol-17-one, or 3-hydroxy-17-keto-1,3,5-œstra-triene.

The excretion of steroids in ruminants is not identical with that of non-ruminants (McGirr, 1954), but the manner of excretion and form of the excretory products are not satisfactorily known.

The *mineralocorticoid* action is the major part of the effect of deoxycortone. This action following injection into the normal animal is, in brief, a retention of sodium and chloride ions with water, an excretion of

potassium ions and an inconstant effect on calcium and phosphorus balance. If, however, the sodium intake is restricted there is no effect on either sodium and water retention or potassium loss. Part of the effects of the compound are due to increased tubular resorption of sodium chloride and water and excretion of potassium, but the main effect would seem to be on the cells of the body. Using radioactive sodium (Na^{24} isotope) it has been shown that there is an increase of intracellular sodium and a decrease in potassium. There is also an increase in extracellular fluid due both to water retention and the passage of water from the cells into the extracellular spaces.

Clinically, the effects will be shown by a decrease in urine production, an increase in weight, and a 'filling out' of superficial body hollows.

In normal animals prolonged use of small doses has only an initial transient effect, but large doses may cause an increased water intake and output reminiscent of diabetes insipidus.

Deoxycortone has practically no effect on glucose metabolism, blood eosinophil counts, inflammatory reactions, or allergic œdema, but some progesterone-like activity has been reported.

Though the compound has been used in veterinary medicine no clear indication for its administration has appeared so far.

The Glycocorticoids

The glycocorticoids of clinical interest comprise cortisone, hydrocortisone, prednisone and prednisolone. The activity of these compounds is similar in quality, the only differences being related to degree of effect. In general, prednisone and prednisolone are from 3–5 times more effective than cortisone or hydrocortisone, but this refers only to the glycocorticoid, anti-inflammatory, eosinophil and lymphocyte suppressive actions: the effects on the electrolyte balance are considerably less than those of cortisone or hydrocortisone.

Cortisone Acetate, B.Vet.C.

This, with a few exceptions, may be taken as typical of the glycocorticoids. Originally known as Kendall's Compound E, cortisone can be obtained by extraction from bovine adrenal glands, but is probably not the main glycocorticoid produced naturally, a position thought to be held by hydrocortisone. The material used commercially is not isolated from biological sources, but is prepared by synthetic modification of naturally occurring steroids.

Absorption of cortisone, and hydrocortisone, is poor following subcutaneous or intramuscular injection, and in small animals at any rate the oral route provides a more rapid means of obtaining a clinical effect. In man, intramuscular injections give peak levels in the blood after 8–12 hours, but with oral administration of doses no more than twice as large as parenteral doses, peak levels are achieved in 4–8 hours. For maximum effect doses should be repeated every 8–12 hours with parenteral

dosing, and every 6 hours with oral dosing. Topical application achieves only a superficial action and the same applies to ophthalmic use, in which only structures associated with the anterior chamber are affected. Intra-articular injection provides early local effect. Intravenous injection and subcutaneous implants have also been used for administering cortisone in man but veterinary clinical application is not reported.

After absorption cortisone disappears rapidly from the blood but the further fate is unknown though it is thought that the compound is probably converted into hydrocortisone.

Excretion probably follows the pattern mentioned under deoxycortone acetate.

Cortisone exerts *actions* on the metabolism of carbohydrates, fats, proteins, enzymes, water and electrolytes. In addition, its effects influence the kidneys, adrenal glands, anterior pituitary gland, the skin, joints, connective tissue, and the processes of repair (anti-inflammatory action).

The effects on *carbohydrate, fat and protein metabolism* are not completely understood, but cortisone increases the formation of glycogen from all these sources and normally reduces the metabolic use of carbohydrates. Urinary excretion of nitrogen is increased, probably because of increased renal efficiency, but also may be due to increased protein breakdown.

Enzyme concentrations in the blood and liver increase and the activity of many other enzymes is enhanced, although this action is thought not to be a direct effect but an indirect one due to effects on related substrates and co-factors. Other enzymes such as hyaluronidase are inhibited and the degree of hyaluronic acid polymerization is increased following intra-articular injection: this produces a more viscous intra-articular fluid which has a greater 'cushioning' effect.

Water metabolism is influenced by cortisone in much the same way as it is by desoxycorticosterone, but in the normal animal the effects are variable and inconstant. Extracellular fluid is increased and intracellular fluid is decreased, but the total fluid content of the body may not be changed. In some cases, however, water retention may occur in the first few days of a prolonged course of treatment and be followed later by spontaneous diuresis.

Mineral metabolism is likewise variably affected in animals with normal adrenal function, but usually some tubular resorption and retention of sodium takes place, accompanied by loss of potassium. This effect decreases as administration is continued. Also there is usually some increase in phosphate and calcium excretion and a decrease in magnesium excretion. The total effect is therefore a decrease in intracellular phosphorus and potassium, an increase in intracellular sodium, and a decrease in blood calcium and phosphate. This would seem to discount and contra-indicate the use of these steroids in milk fever which has been advocated on the continent. As these losses of potassium, phosphorus, and calcium are countered by testosterone, the use of this compound would be much more logical.

These effects on mineral balance are considerably less than those caused by deoxycortone, for cortisone is estimated as possessing about 1/30th to 1/50th of the activity of the mineral corticoid.

The influence of cortisone on the *kidneys* of normal animals results in an increase in the rate of glomerular filtration; tubular resorption of sodium also increases and an equivalent decrease in potassium retention occurs. Uric acid and phosphate excretion is also increased.

One of the most important side actions of cortisone therapy is its depressant effect on the production of many of the important *anterior pituitary* trophins and because of their suppression, the decrease in activity of the glands controlled by these trophins.

Of primary veterinary importance is the *depression of adrenocorticotrophin* production (ACTH), for acetonæmia and skin diseases have been correlated with decreased adrenal cortex function. The steroid treatment of these conditions would therefore seem contra-indicated, in that such treatment would tend to depress natural corticosteroid function. However, it is probable that large doses or protracted therapy are more dangerous in this respect (50·0–75·0 mg. daily in man), and it is only in such cases that caution should be exercised—periodic dosing with corticotrophin or gradual withdrawal at the end of a course of treatment are the recommended procedures.

There would seem to be some suppression of thyrotrophin but the action of cortisone in this respect is not clearly understood. There would appear to be no effect on the diabetogenic or growth trophins of the anterior pituitary gland.

The actions on *the skin* are also very important and its use in skin diseases constitutes a major indication. Cortisone induces an increased blood flow through the skin which results in increased warmth and skin moisture. There is a decrease in sebaceous secretions: the increased blood supply also provides better nutrition and removal of waste products. Where inflammatory lesions exist the fibroplasia, exudation, and other processes of inflammation are arrested, and irritation decreases; this in turn reduces self-inflicted tissue damage. To offset these advantages there is a slowing of repair processes and a decreased resistance to infection. Prolonged topical application causes a decrease in epidermal and dermal thickness with an increased collagen density, atrophy of sebaceous glands and a reduction in hair growth.

On the *eye*, the effects are analogous to those on the skin but are of greater importance, for exudation and fibroplasia may result in permanent blindness following corneal scar formation. This can be restricted by the use of cortisone, but antibacterial therapy must be applied concurrently. Only the anterior chamber including the ciliary body, iris, cornea, and conjunctiva are affected by local application: systemic administration must be used if deeper structures are to be affected.

Muscle and bone metabolism are normally unaffected, but during prolonged treatment osteoporosis may develop due to excessive calcium

and phosphate excretion: at the same time there occurs a decrease in the number of osteoblasts and cartilage cells so that the formation of new bone is slowed; this, with the calcium and phosphate mobilization, results in an increase in the proportion of intramedullary connective tissue: in very severe cases spontaneous fractures may follow. Such conditions are only likely to be met in small animals treated continuously over long periods, as in the systemic therapy of arthritis.

The effects on arthritis have achieved great prominence in human orthopædics and increasing use is reported in the veterinary field. The effect on joints following intra-articular or systemic administration is a non-specific anti-inflammatory action (*q.v.*), but an increased polymerization of the hyaluronic acid in the sinovial fluid results in increased viscosity within the first few days of treatment which, in true arthritis, is accompanied by decreased pain and increased mobility. In rheumatoid arthritis in man, it has been observed during histological examination of the sinovial membrane that, as a response to cortisone treatment, fewer lymphocytes and plasma cells, less œdema, less 'papillary tufting', less fibrin deposition and necrosis occur in or on the membrane. Aqueous suspensions are used and the crystals of these are rapidly adsorbed onto the synovial membrane. Following a single injection the results may persist for from three days to several weeks. Joints may be injected repeatedly but any infection in the region of the joint contra-indicates this route of administration.

The effects on *connective tissue* and the *anti-inflammatory* actions of cortisone are very important.

Cortisone depresses the function and production of all connective tissue cells including the reticular embryonic mesenchymal cells, but excluding elastic tissue for some reason as yet not explained. As the cells themselves are depressed the fibres and interfibrillar tissues are also affected, and the production of tissue exudates is decreased, particularly following trauma. Thus, granulation with its high vascularization is inhibited, fibrin production is decreased, leucocytes are fewer and the resistance to infection therefore less, fibrosis is delayed and scar formation is weak and minimal. Epithelial growth is unaffected. This weakening of wound healing can be minimized by increased protein intake.

Systemic and local reactions to all types of injury are suppressed, including febrile, antibacterial, and allergic responses. In *bacterial infections* mobilization of neutrophils at the site(s) of infection does not occur, there is little thrombosis and vascular obliteration with necrosis; liquefaction of caseous material is slowed; capillary permeability is antagonized and fluid extravascation is minimal; more viable bacteria are found both at the infection site and in the blood stream, yet *the febrile and other reactions to bacteræmia, septicæmia and toxæmia are absent*. This factor is of prime importance and must always be considered when contemplating corticosteroid therapy. The effect of the steroids on connective tissue (see above) also slows up the processes of combating the infection and repairing the damage, so that, whilst local reactions are decreased and

marked tissue changes avoided, these advantages are offset by the dangers of bacterial invasion with death from septicæmia. This situation has occurred in people infected with tuberculosis.

Of equal importance in the veterinary field is the antagonism of allergic reactions by the corticosteroids. This includes allergies of natural origin and induced allergic responses, including serum allergy and the reactions to diagnostic allergens such as tuberculin and mallein. There is considerable confusion as to how this action is achieved, but though some inhibition of antibody formation occurs the major part of the action appears to be related not to abolition of tissue sensitivity but to the control of tissue reaction. Thus though skin sensitivity to tuberculin remains, the cortisone prevents the extravasation of fluid, dilation of capillaries, and increased blood flow, so that no appreciable local reaction occurs. The inhibition of allergic response is therefore a part of the anti-inflammatory action of cortisone.

Cortisone also exerts marked effects on the *blood and circulatory system.* The most marked action of cortisone on the blood is the marked decrease in the numbers of eosinophils in the blood. This is frequently used as an indication of the degree of action of the corticosteroid. The action appears to be related to the concentration of cortisone achieved in the blood, for the action is negligible following intramuscular injection whereas it is most marked following intravenous injection or oral administration, when high concentrations will be achieved. In those glycocorticoids which are absorbed rapidly after intramuscular injection an eosinopenic response will follow its administration. This applies particularly to prednisolone.

Lymphocytopenia may occur initially following cortisone administration but continued use does not maintain the decrease. This lymphocytopenia has been used to treat lymphosarcomata and leukæmias but the response is only temporary.

An increase in circulating neutrophils occurs occasionally. The effects on coagulation of blood are variable.

The effects on blood pressure are variable and probably relate to the changes in electrolyte balance, and the effect on kidney and peripheral circulation.

It must not be forgotten that these actions of cortisone are only palliative and not curative. Unless spontaneous resolution occurs, or unless concurrent curative treatment is applied, suppressed symptoms will recur on cessation of treatment. It should also not be forgotten that depression of the anterior pituitary and the adrenal cortex occurs, and sudden withdrawal after prolonged treatment may precipitate severe symptoms of adrenal deficiency, which will in general be the reverse of the actions described above.

Hydrocortisone has the same actions as cortisone but it is more effective following oral, intravenous and topical application. On intramuscular administration it is much less active possibly because the compound is

less soluble in body fluids. The free alcohol is usually more active than the acetate.

Prednisone and *prednisolone* are relatively new and much has yet to be learnt about these compounds. Generalizing, it might be said that the actions of these two compounds are similar to those of cortisone and hydrocortisone, but both are more active (about five times) in all respects except the mineralocorticoid effect, which is far weaker than that of cortisone. Prednisolone is slightly more active than prednisone in respect of glucocorticoid effects.

Uses. The uses of cortisone and the glucocorticoids may be classified into metabolic diseases (acetonæmia and pregnancy toxæmia), arthritic conditions, skin diseases, and to a lesser degree nervous diseases.

Ketosis has been treated with the glucocorticoids since the use of cortisone was first reported in 1950 by Shaw and his colleagues, following an earlier report in 1947 on the effect of adrenocortical extracts. Since that time these and other workers have produced other reports on their effect.

The dose of *cortisone* for cattle has been estimated as lying between 0·5 and 1·5 G. of the acetate injected intramuscularly. The usual response of the primary, uncomplicated case, is a rapid rise of the blood glucose to normal (within 8–10 hours) and beyond, with a return to normal after about 2 days. Eosinophils respond almost in an inversely proportional manner, whilst acetone bodies decrease gradually over a period of about four days (Shaw, 1955). The appetite shows improvement within about 24 hours, and milk yields improve from about the second day after injection. Relapses requiring further doses have occurred. Intravenous administration of the alcohol itself has not been satisfactory (Shaw *et al.*, 1952).

In this last mentioned publication the use of *hydrocortisone* was first reported. It was used in the form of the acetate given intramuscularly in doses of 0·3–1·5 G. Further work showed that hydrocortisone acetate was less effective than cortisone in raising the blood glucose level (Shaw *et al.*, 1954; Gessert, Shaw *et al.*, 1955; Shaw *et al.*, 1955b), although the alcohol was more effective and equal proportions of alcohol and acetate in doses of 0·75–1·0 G. were very effective.

Clinically, hydrocortisone had little to recommend it over cortisone, and ACTH and cortisone were most widely used until the results of trials of *prednisone* appeared. (Shaw *et al.*, 1955a; Morris *et al.*, 1956; Vigue, 1956; Gessert, 1956). This was shown to have effects far superior to those of cortisone and hydrocortisone. Prednisone is between 3 and 5 times more active than cortisone and doses from 0·3 to 0·5 G. have been effective, although the larger dosage was preferred.

At the same time a halogen derivative of hydrocortisone, known as 9 α fluoro-hydrocortisone, was reported to be effective in doses of 0·1 G. of the acetate (Shaw *et al.*, 1955a; Gessert, 1956). This compound, however.

is more active in causing sodium chloride and water retention and potassium loss than even desoxycorticosterone, and is therefore unsuitable as a glucose mobilizer in the treatment of ketosis.

More recently still (Link *et al.*, 1957; Paterson, 1957) reports have indicated that 50·0–150·0 mg. of *prednisolone*, as an aqueous suspension of the alcohol injected intramuscularly, give over 80 per cent. recoveries. Glucose levels rise very rapidly and strongly whilst the eosinophil reduction is equally rapid: in this latter respect prednisolone, as with prednisone, is from 3 to 5 times more active than either hydrocortisone or cortisone. The anti-inflammatory and lymphocytolytic actions are proportionately greater but the effect on the electrolyte balance is less than that of the earlier corticosteroids. Prednisolone is now becoming widely used.

Although these glycocorticoids have now become established as an effective means of mobilizing glucose into the blood, there is no doubt that this is not the end of the ketosis story, nor is the theory of pituitary-adrenal exhaustion entirely accepted as the true explanation of the ætiology of ketosis. Although for nearly a decade this has been the accepted theory, Shaw himself (1956) has foreshadowed modifications of this theory in the light of more recent discoveries, particularly the finding that the circulating glucocorticoid levels are high in ketotic cows whilst the protein bound iodine levels are low.

Pregnancy toxæmia in sheep is similar in many respects, including the incidence of ketonæmia and low blood glucose levels, to acetonæmia in cattle. Other factors, however, serve to show that the diseases are not identical: amongst these are the relationship of the ætiology to a low nutritional plane during late pregnancy, particularly low protein intake, the coincidence of this with the rapid growth of the fœtus, the intensification of symptoms and the increased incidence in twin conceptions (hence "twin lamb disease"), and the rapid recovery of the ewe following abortion.

Despite these differences the glucose mobilization effect of cortisone has been shown of value (Siegmund *et al.*, 1953; Berrier, 1955; Thomson, 1956), but not any more so than less expensive types of treatment. Unpublished clinical reports of the effect of *prednisolone* during the lambing season of 1958 indicate that this compound is as efficient in pregnancy toxæmia as in ketosis of cattle. Nevertheless, the results are not wholly satisfactory. It would seem, as might be expected, that the response of the animal is conditioned mainly by the stage at which treatment is commenced, and the earlier the prednisolone is administered the more rapid and successful the response: other factors involved are the level of nutrition, the stage of pregnancy, climatic conditions and general husbandry. Dosages are also variable and as yet no rational approach can be made: in some cases 50·0 mg. have resulted in abortion, whereas the same doses have been satisfactory elsewhere and in other cases. In the main, with our present knowledge, 25·0–40·0 mg. given intramuscularly, and repeated as necessary, is the recommended dosage routine.

Arthritis in dogs, pigs, cattle and horses has been treated with cortisone which has given temporary improvement, followed by relapse on cessation of treatment. *Doses* have been 25·0–200·0 mg. intramuscularly, or 25·0–75·0 mg. orally, per day in the dog, 500·0 mg. twice daily intramuscularly in the horse, 2·0 G. followed by 1·0 G. daily in the bull, and 0·1 G. intramuscularly per day in pigs. Cortisone is less effective than *hydrocortisone* in the treatment of arthritis and this latter compound is given orally to dogs in initial doses of 20·0–80·0 mg. When the symptoms regress these doses are reduced to daily maintenance doses, which will vary in each individual case. The intra-articular use of hydrocortisone is under investigation and results are so far very encouraging. In horses, intra-articular injections of about 100·0 mg. every 4–7 days have been successful in controlling symptoms, but too little evidence is available as yet. Prednisolone may prove superior to these compounds: for generalized arthritis, doses of 100–150 mg. intramuscularly each day for large animals, and 0·25–0·5 mg. per lb. bodyweight (5·5–11·0 mg. per kg.) intramuscularly each day for small animals, have been recommended commercially as initial doses, followed by gradual reduction to a maintenance dose which will control symptoms. For localized non-infected inflammations of joints, tendon sheaths, and bursæ, injection directly into the cavity of the structure after removal of an equal volume of fluid has been recommended in doses of 20·0–80·0 mg. in large animals and 10·0–20·0 mg. in small animals: these doses can be repeated as necessary, *but this mode of treatment is contra-indicated where infections exist near or in the joint.* It goes without saying that scrupulously aseptic techniques must be used. In dogs, stifle lameness and ossification of the intervertebral discs have been the conditions most frequently treated.

Ophthalmic conditions have been treated with corticosteroids since cortisone was first available, and have proved to be sight saving on occasions. Topical application is effective only in conditions affecting the structures of the anterior chamber. The steroids inhibit fluid effusion, opacity due to cellular infiltration, and scar formation. It must be emphasized that concurrent antibiotic therapy is necessary to control infection. Buffered aqueous suspensions containing 0·5–2·5 per cent. cortisone are applied every 1–2 hours but ointments, usually of 1–2 per cent. concentrations, have a more prolonged action, and should be applied only every 3–4 hours.

Hydrocortisone is superior to cortisone for ophthalmic use and prednisolone will probably prove superior to both. Ophthalmic suspensions and ointments of hydrocortisone, some containing antibiotics, are available and should be applied every two hours or so, and two or three times a day, respectively.

Skin conditions of non-specific or allergic origin respond favourably to oral or topical application of the corticosteroids; pruritis is relieved within 24 hours and inflammatory reactions subside. It is usual to apply the treatment directly to the skin except in severe and generalized conditions.

Eczema and otitis externa of small animals are the main indications for steroid therapy, but 'sweat itch' in horses and similar eczematous and seborrhœic conditions will respond favourably. Ointments of 0·5–2·5 per cent. strengths should be applied two or three times daily. Cortisone preparations, again, are inferior to those of hydrocortisone.

Nervous conditions have been treated by oral or parenteral steroid therapy. The inflammatory reactions and damage caused by the viruses of the distemper complex in dogs (hard pad, etc.) are reduced and the prognosis improved, but care must be exercised, for experimental evidence indicates that the convulsion threshold is lowered by those steroids and acute attacks of convulsions may be precipitated by steroid therapy.

Probably one of the most common uses of the corticosteroids in the future will be in the treatment of diseases associated with acute œdema where vascular permeability is increased: such diseases as fog fever and lung œdema in other species, acute mastitis in cattle, sheep, goats and pigs, serum allergy and other allergic conditions, should all benefit, though simultaneous treatment of specific pathogens must also be carried out. Diseases in which rapid fibrosis interferes with treatment, such as staphylococcal and corynebacterial mastitis, will also benefit from steroid therapy in conjunction with antibiotics.

The palliative effect of the corticosteroids has been stressed repeatedly, but it is very important to remember that relapses will occur at varying periods after treatment has ceased if no attempts are made to destroy or remove the ætiological factors.

Contra-Indications. Little is known about the untoward effects of corticosteroids in animals, but by analogy from human information the following conditions preclude the use of corticosteroids:

Bacterial infections, but particularly chronic infections with acid fast organisms, Johne's disease in cattle, sheep and goats being the main organism involved.
Diabetes mellitus.
Recent abdominal surgery.
Cardiac insufficiencies.

Use in pregnancy should be avoided if possible, for it has been shown that large doses in the rabbit cause fœtal degeneration and abortion: abortion following the use of prednisolone in pregnancy toxæmia cases has also been reported.

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CHAPTER 37

THE HORMONES
(ii) MISCELLANEOUS HORMONES

THE so called 'metabolic hormones' are the only remaining hormones of clinical significance. These are the hormones of the thyroid, the parathyroid and the pancreatic glands.

The Thyroid Gland

This endocrine gland consists in most species of two masses of tissue situated on either side of larynx and upper trachea, with an 'isthmus' joining them anteriorily. From the dried glands of cattle, sheep, and pigs a buff-coloured, amorphous powder with a meat-like odour and saline taste is prepared by defatting with ether and drying (Thyroid, B.Vet.C.). The B.P. stipulates that the powder is standardized to contain 0·1 per cent. iodine as thyroxine but the U.S.P. merely requires 0·2 per cent. in organic combination, which is not necessarily iodine as thyroxine.

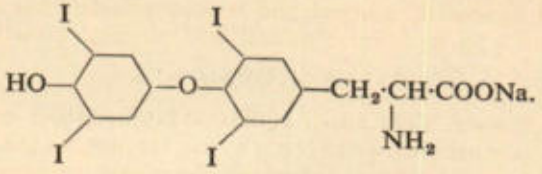
Thyroxine Sodium, B.Vet.C. is the lævorotatory sodium salt of thyroxine which is twice as active as the racemic (*dl.*) form. It is a cream coloured powder which is slightly soluble in water but more so in dilute acids or alkalis. *l.*Thyroxine sodium possesses the activity of thyroid extracts qualitatively but quantitatively 0·1 mg. is approximately equal in activity to 60·0 mg. of the dried extract. Its main advantage is chemical synthesis and lack of need for biological assay.

The active constituent of the thyroid gland has not been definitely determined but is probably thyroxine, an organic iodine compound originally isolated in crystalline form by Kendall (of corticosteroid fame) in 1914. Thyroxine exists within the gland in conjugated form combined with a protein, when it is called thyroglobulin. Thyroglobulins are water soluble. Precursors of thyroxine, di-iodotyrosine, and mono-iodotyrosine, itself a precursor of the di-iodine compound, are both present in the thyroid extracts, but are inactive. More recently (1953) an active compound named tri-iodothyronine has been identified and put forward as the actual hormone.

Metabolism. The metabolism and action of the thyroid hormone and iodine are more or less identical so that an iodine deficiency automatically

constitutes a thyroid deficiency. Reference to the formula of *l*-Thyroxine Sodium, B.Vet.C. (i) will make this readily understandable, for it will be seen that four iodine atoms are contained in each molecule of thyroxine and comprise 504 parts of the molecular weight of thyroxine which is 777; that is, over $\frac{2}{3}$ of the total molecule by weight is iodine.

(ii)



l-Thyroxine Sodium, B.Vet.C.

The thyroid gland selectively extracts iodine from the plasma and concentrations many times those of the circulation are maintained in normal glands. The way in which this is achieved, and the synthesis of the hormone which follows, are imperfectly understood but present theories may be simplified as in (ii).

(ii) Iodine + tyrosine + oxidase + peroxidase (?) enzyme systems →

di-iodotyrosine $\xrightarrow{\text{oxidation}}$ thyroxine → 3,5,3′, tri-iodothyronine.

dehydro-alanine iodine.

The release of thyroxine from the normal gland is controlled by the thyrotrophic hormone of the anterior pituitary gland, and in thyroid insufficiency the plasma content of this trophic hormone increases. Excess of circulating trophin is possibly responsible for the increase in size of the thyroid which occurs in iodine deficiencies and other goitrogenic circumstances. With excessive thyroid secretion thyrotrophic hormone production is suppressed: if this excess is therapeutic and temporary, reactivation of the pituitary gland and consequent stimulation of the thyroid gland follow cessation of the treatment. Following administration of thyroid extracts or *l*.thyroxine sodium about half the oral dose is absorbed, but the effects are not apparent for several days and maximum effect from single doses may not be achieved for as long as ten days; residual effects may continue for as long as a fortnight. Because of this, thyroid hormone must be considered as potentially cumulative.

After absorption thyroxine causes an increase in metabolic rate with increased combustion of carbohydrate which results in depletion of liver glycogen; there is also increased combustion of fat with a mobilization of fat from all depots, and of protein, with increased urinary nitrogen, salt and water. This increased oxidation rate, which is the principal effect of

thyroid substances, is not a direct effect but is probably due to the effect on coenzymes and other intermediate factors involved in intracellular energy transforming processes. These effects are accompanied by increased irritability of the vasomotor centre, increased heart rate and output, and an increased circulatory rate. In addition to these metabolic effects the thyroid hormone works in conjunction with other hormones such as the parathyroid, pancreatic, adrenal, and anterior pituitary hormones, playing an important part in normal mental and physical growth, and sexual maturation.

Iodine Deficiency. Deficiencies of thyroid hormone and iodine are interrelated and have been shown to occur widely throughout the world causing considerable economic losses in herbivorous species, carnivores, and birds. Clinical manifestations take the form of *goitre*, and are most apparent in young animals. In the severest forms young animals may be born dead after prolonged gestation, completely without hair, œdematous and with enlarged thyroid glands—hairless calves and piglets are perhaps the most common instances of the condition in Great Britain, but sheep, goats, horses, dogs, cats, and birds may all be similarly affected.

Adults are affected but the condition is less spectacular and takes the form of unthriftiness, loss of coat colour and character, and sometimes sterility in male and female with loss of sex drive in the male. Goitre may be due directly to iodine deficiency, or be associated with the goitrogenic effect of substances in the diet—thiocyanates, possibly from linseed or clover (Flux *et al.*, 1956), substances in kale (Sinclair *et al.*, 1954; Clements, 1955), and possibly goitrogens in other foods, besides the incidental effects of such drugs as phenothiazine: this last possibility is receiving much attention now that this drug is being supplied in mineral lick forms which results in prolonged intake and therefore a greater exposure to possible goitrogenic effects. Andrews *et al.* (1956) could find no evidence of goitrogenic effect, and this is supported to a certain extent by American work on horses (Trum, Wasserman and co-workers, 1956). In some instances the goitre can be due to both iodine lack and goitrogenic substance intake.

Toxicity. In excessive dosage *thyrotoxicosis* may result with intensification of all these actions. Increased pulse rates and cardiac irregularities, restlessness, and sleeplessness occur: if this dosage is continued osteoporosis may follow excessive mobilization and excretion of calcium and phosphorus. Early manifestations of overdosage are increased and irregular heart action, loss of weight, a tendency towards a higher body temperature and restlessness. In all therapy with thyroid compounds these signs should be watched for and animals checked weekly until a satisfactory maintenance dose has been established.

Use. Both iodine and thyroid substances may be used in the treatment of thyroid deficiency in all species, but it must be remembered that thyroid

deficiencies are not invariably associated with an insufficiency of iodine and in cases where the two are not associated iodine is not a substitute for thyroid compounds. These deficiencies are known under various names, including 'hairless calves', and 'hairless piglets', 'big neck', goitre, and myxœdema. These are the names accorded due to the signs associated with advanced thyroid and iodine deficiencies.

Less obvious conditions for which iodine and thyroid treatment is indicated are unthriftiness, slow growth, lack of 'wire' in wire-haired breeds or straightness in curly coats, poor colour in the coat, lethargy, obesity, œdema, possibly nymphomania in female cattle, loss of libido and depressed spermatogenesis in rams, boars, bulls, etc. where they occur in known iodine deficient areas. The clue to the thyroid and iodine deficiencies may be given by occasional births of goitrous young.

In dogs, a bilateral alopecia, most commonly associated with wire haired breeds, responds well to thyroid treatment. Obesity and urinary incontinence in dogs have also been effectively treated with thyroid, but other hormones and diet regulation are probably more beneficial and safer.

Dosage. In acute fœtal iodine and thyroid deficiencies treatment is often successful in animals which survive for two or three days after birth. Both iodine and thyroid substances may be given but thyroid on its own is too slow in action. Dosage of iodine may be instituted by intravenous injection of sodium iodide in calves, but oral dosage with either sodium or potassium iodide from the onset is usually satisfactory in all species. Doses will vary from a few milligrammes daily in puppies and kittens to a few grains daily in calves and foals. Thyroid may be given additionally by mouth in doses of approximately 1·0 mg. (1/60 gr.) per lb. body weight (1·0–2·0 mg. per kg.) in all species. The average dose for calves is 5 gr. (0·3 G.) twice daily, and for dogs ½–5 gr. (30·0 mg.–0·3 G.) daily.

Deficiencies in *adults*, which are of less acute nature, may be treated initially with thyroid at the rate of 1·0–2·0 mg. per kg. (approx. 1/60 gr. per lb.), and this should be supplemented by iodine feed supplements and salt licks. Adult cattle have been treated—especially bulls with lowered fertility and impaired sex-drive—with *l*.thyroxine sodium, using a dosage of 5·0–8·0 mg. given by subcutaneous injection: this has supplanted the use of iodinated casein, (the original use of which was in the attempted improvement of milk yield in cows: it proved uneconomical). In all cases of thyroid administration, a careful check on the heart should be made weekly until a maintenance dose is established. Any signs of cardiac irregularity should be followed by reduction or temporary cessation of dosage in view of the known cumulative action of thyroid extracts.

Mineral supplements usually contain about 0·03 per cent. of potassium iodide, or the more stable iodate (Chilean Iodine Educational Bureau: Pamphlet No. 47, p. 16)—especially in tropical climates; this is represented

by ½ oz. in 1 cwt. of supplement (15·0 G. per 50·0 kg.). Daily doses of such a supplement should be:

Milking cattle:	1½–5 oz. (45·0–140·0 G.)
Other adult cattle:	2–3 oz. (60·0–180·0 G.)
Calves:	1–1½ oz. (30·0–45·0 G.)
Brood mares:	2–4 oz. (60·0–120·0 G.)
Other horses:	2–3 oz. (60·0–90·0 G.)
Ewes:	½–¾ oz. (15·0–22·5 G.)
Lambs:	⅙–⅓ oz. (5·0–10·0 G.)
Sows:	2–4 oz. (60·0–120·0 G.)
Store pigs and others:	1–2 oz. (30·0–60·0 G.)
Laying hens:	8–15 oz. (220–400 G.) per 100 birds.
Chicks:	1–2 oz. (30·0–60·0 G.) per 100 birds.
Older chickens:	3–6 oz. (90·0–160·0 G.) per 100 birds.

Salt licks should contain about 0·05 per cent., or 1 oz. of potassium iodide in 100 lb. (30·0 G. per 50·0 kg.) salt, but up to 2 oz. per 100 lb. (60·0 G. per 50·0 kg.) have been recommended for dairy cattle (Crichton, 1934).

Antithyroid Substances. Though the development of tolerance to thyroid administered over a period can occur due to the development of antibodies, this is not considered to be of clinical significance.

Apart from the naturally occurring goitrogens already mentioned previously, a group of substances known as the *thiouracil derivatives* have a specific depressant effect on thyroid activity and thyroxine production. They induce hypothyroidism, with a slight goitre, a lowering of the metabolic rate, and improved fattening rates. Excretion rate is rapid and cessation of dosage 24 hours before slaughter is adequate for excretory reduction of these compounds to a safe tissue level. The thiouracil compounds have been most successful in pigs and poultry, but effects have been less successful in ruminants. *Thiouracil*, B.Vet.C. should be given in the last four weeks prior to slaughter at the rate of 0·1–0·15 per cent. in pig food, and 0·1–0·2 per cent. in poultry food. *Methyl thiouracil* is considered more active and less toxic: it is fed at the rate of 0·1 per cent. in pig food, and 0·05 per cent. in sheep food. *Propyl thiouracil* is about four times more active than thiouracil but has not been used to the same extent as the others.

Recently the œstrogens have replaced these antithyroid substances in poultry and cattle, whilst antibiotics have proved at least temporarily better in pigs. The carcases of thiouracil pigs are generally over fat.

Antithyroid substances are not commonly used now for fattening purposes, but find occasional use in the treatment of hyperthyroidism. Approximate *daily doses* of thiouracil are: Cattle, 15–60 gr. (1·0–4·0 G.); Sheep 3–7½ gr. (0·2–0·5 G.); Pigs 3–9 gr. (0·2–0·6 G.); Dogs 1–1½ gr. (50·0–100·0 mg.); Cats, ½–1 gr. (20·0–50·0 mg.). Doses of propyl thiouracil should be about a quarter of these doses.

The Parathyroid Gland

There are four small parathyroid glands which are located at the poles of the thyroid lobes. In some species they are embedded in the thyroid gland but in others they are distinct entities.

A desiccated form of the gland is available and has a pale yellow amorphous appearance; it has a faint meaty odour. A lipid extract of parathyroid gland has recently been discovered (Marnay *et al.*, 1956), and is claimed to counteract the acute symptoms of parathyroid removal. An aqueous extract is described in the 1934 B.P.C., intended for subcutaneous injection in view of the fact that very little of any oral dose of parathyroid escapes destruction in the gastro-intestinal tract.

Parathyroid Injection, U.S.P. is a sterile water soluble extract of parathyroid gland for subcutaneous or intramuscular administration: it contains not less than 100 U.S.P. parathyroid units per ml., and the unit is described as '1/100th of the amount necessary to raise the calcium content of 100 ml. of the blood serum of normal dogs 1·0 mg. within 16 to 18 hours after administration'. Commercially, parathyroid injections are not easily available in Great Britain.

Actions and Uses. The function of the parathyroid secretion is thought to be mainly that of controlling the calcium and phosphate level of the blood. The means by which this is effected is unknown but it has been suggested that parathyroid action causes excretion of phosphate in the urine; this increases the plasma solubility of calcium and the mineral is then mobilized, mainly from the bones. An injection of parathyroid hormone in normal animals causes an increase in urinary phosphate excretion, a decrease in the inorganic phosphorus blood level, an increase in blood calcium, and an increased calcium excretion. The effect on the calcium blood level is seen in about four hours and should reach a peak in about 18 hours, followed by a return to normal levels approximately 24 hours after the injection.

Lack of sufficient parathyroid activity causes the reverse of the above effects, and as the level of blood calcium falls muscle and general nervous irritability increases until the convulsive threshold is reached.

In excess, parathyroid hormone causes a considerable increase in calcium and phosphate excretion, a low serum phosphate and a continuous calcium mobilization. In extreme and chronic cases, decalcification of the bones occurs with loss of bone rigidity, fractures and malformations. In acute excess the blood calcium levels are approximately doubled and the blood phosphorus rises; later the blood calcium falls, vomition and diarrhœa occur; circulatory and renal collapse result in death.

In view of these facts it is interesting to note that Hebel (1955) found that high calcium levels in the blood were associated with small glands and vice versa.

Parathyroid extracts have frequently been given orally in tablet form combined with calcium lactate, but as digestive enzymes destroy the majority of any dose, it is doubtful whether any benefit is derived from this practice. Parathyroid injections in doses of 2–15 U.S.P. units have been used in the acute convulsive stages of calcium deficiency in dogs, but in view of the phosphorus and calcium excretion that occurs the injections should not be used frequently. Injections have been used in the treatment of chronic lead and other heavy metal poisoning in which deposition has occurred in bone tissue. Parathyroid injections are not indicated in rickets or osteomalacia.

In the treatment of experimentally induced hypoparathyroidism it has been found that antibodies against parathyroid extracts develop and the effect of a standard dose is progressively reduced.

The Pancreatic Gland

The pancreas, which lies in the loop of the duodenum, contains two vastly different types of glandular tissue. The greater part of the gland consists of an exocrine gland, which secretes a fluid rich in digestive enzymes via the common bile duct into the small intestine. Dispersed throughout the mass of exocrine gland are the islets of Langerhans which have endocrine functions and secrete a hormone known as *insulin* (from *insular*—'of an island'). A third substance 'glucagon' is said to be produced by the alpha cells of the pancreas. It has glycolytic effects.

Injection of Insulin, B.Vet.C.

The Veterinary Codex, quoting the B.P., describes this injection as 'a sterile solution of the specific anti-diabetogenic principle of the mammalian pancreas'. It is a clear, colourless liquid containing 20, 40 or 80 units in each millilitre: the solvent consists of water acidified with hydrochloric acid, and about 1·5 per cent. glycerin.

Actions. Insulin is rapidly absorbed following injection and produces maximum effects within about 3 hours of administration. More rapid effects are achieved by intravenous or intramuscular injection than by subcutaneous therapy, but the hormone is inactivated in the gastro-intestinal canal and is useless when administered orally. The Protamine Zinc Insulins and Globin Zinc Insulins are effective for about 48 hours and 24 hours respectively, but the plain injection is effective for a period of about eight hours only, and requires injection twice a day.

Following absorption, insulin exerts a powerful effect on carbohydrate metabolism, the general effect being one of removal of glucose from the circulation. The primary effect is to increase the phosphorylation of glucose, with the formation of glucose-6-phosphate: the means by which it achieves this is undecided, but may be one of releasing the enzyme catalyst *hexokinase* inside the cells from the control of corticosteroids and

other hormones; another suggestion is that insulin increases the permeability of the cell membrane to glucose which, following rapid entry into the cell, can be phosphorylated by hexokinase present in the cell. These biochemical effects make phosphorylated glucose available for rapid metabolization and results in the removal of glucose from the blood. Some of the absorbed glucose is used to supply energy for cell metabolism, and the rest is converted into glycogen and deposited in the liver and possibly the muscles. Fat is formed in the liver and fat depots. Protein synthesis from amino-acids is also assisted by insulin, possibly by the provision of the energy necessary for biosynthesis.

Besides increasing glucose conjugation in the tissues and the formation of glycogen, insulin also antagonizes the hyperglycæmic effect of adrenaline. Consequently, in overdosage, although some attempt is made by adrenaline to mobilize muscle glycogen, the effects of insulin are too strong and coma supervenes in some species, whilst convulsions occur in others, due to acute hypoglycæmia.

Uses. In true *diabetes mellitus* in the dog (Wilkinson, 1957 & 1958), which is very similar to that which occurs in man, hyperglycæmia and glycosuria are the dominant clinical features: ketones are also found in the blood and urine. The sugar, present in the blood in large quantities, is obtained from various sources—absorption from the intestines, mobilization of carbohydrate reserves, and breakdown of fat and protein. The breakdown of fat is incomplete and results in the formation of ketones. The sugar content of the blood is maintained at a high level despite the excretion of large quantities in the urine: this is due to the continued demand for more and yet more energy by the tissues, which are unable to phosphorylate the glucose produced in response to this demand, obtain no energy from it, and therefore ask for yet more glucose.

This unproductive drain on carbohydrate, protein and fat reserves is responsible for other diagnostic symptoms: increased appetite and thirst, emesis and diarrhœa, increased urine production and a progressive emaciation with marked muscular wasting and lethargy. Bilateral cataract occurs occasionally. Frequently the condition is complicated by pancreatic enzyme deficiency due to generalization of the pancreatitis: insulin, of course, has no effect on such deficiencies and the symptoms they cause.

Insulin injections will reduce the blood glucose level rapidly by both hepatic glycogenesis and by increasing tissue breakdown of sugar with the release of energy. Glycosuria automatically ceases when the blood level decreases below the renal threshold. Ketone production ceases and the breakdown of proteins and fats is reversed.

In *acetonæmia* in cattle and *pregnancy toxæmia* in sheep, insulin has been used in conjunction with glucose therapy. The ætiology of these conditions would appear to be different from that of diabetes, for though ketones appear in both conditions the blood glucose levels are entirely different. Certainly the therapeutic effect is not satisfactory.

Dosage and Administration:

Dog: 5–100 units or more according to requirements.
Cow: 50–200 units.

The optimum dose of insulin for a diabetic dog is decided by one factor and that is the degree of glycosuria: an adequate dose is one which is sufficient to reduce the urine sugar to only a trace when tested at the time of maximum effect. This time will vary according to the type of insulin used. The sugar should not be completely absent from the urine.

When commencing treatment it is wise to admit the dog into kennels, commence with a dose of 5 units and increase the dose by steps of 2 units. Urine should be tested at the appropriate time after each increase in dosage. Larger increases may be used provided a close watch is kept and glucose solutions are available to counteract any tendency to the development of convulsions and coma.

If 'regular' insulin is used twice daily injections are advisable, but mild cases will respond to restriction of diet and single daily injections. In severe cases combinations of 'regular' and protamine zinc injections are helpful.

A feature of many cases of diabetes appears to be the progressive increase in insulin requirements. One such case responded initially to 12 units of protamine zinc insulin each morning; this caused complete disappearance of sugar and the dose was reduced to eight units. Three weeks after treatment commenced sugar was found in the evening urine after morning doses of zinc protamine insulin. The amount of sugar increased to 4 plus over the next two weeks with deterioration in condition despite the increase of insulin to 20 units of 'regular' and 12 units of zinc insulin (total 32 units) given once daily. Five days later 56 units, consisting of equal parts of the two insulins, produced only a trace of urine sugar. The reappearance of sugar and its control by increased dosage alternated until after a further month 88 units were being used. Five months after the first dose the requirements had become stabilized at 100 units divided equally between 'regular' and protamine zinc insulin.

Normally clients are unwilling to carry out the repeated injections and euthanasia is requested.

The official Injection of Insulin, B.Vet.C. is available with 20, 40 and 80 units per ml., whilst Injection of Globin Zinc Insulin, B.P. and Injection of Protamine Zinc Insulin, B.P. may contain either 40 or 80 international units.

The *exocrine* secretion of the pancreatic gland is a thin watery fluid with the consistency of saliva and contains a number of enzymes which are responsible for the breakdown of protein, fat, and carbohydrate (starches) in the small intestine. These enzymes are active in slightly alkaline pH (7–9); acidity destroys the enzymes. The main proteolytic enzyme is *trypsin*, excreted in the inactive form known as *trypsinogen*.

Activation is mediated by the enzyme *enterokinase*. A related enzyme chymotrypsin, excreted as chymotrypsinogen is activated by the trypsin and both are responsible for splitting the proteins as far as the proteose-peptone stage. Optimum pH is 8–9. A third enzyme *carboxypeptidase* is responsible for hydrolysis of proteoses and peptones, at the end of chains where the free carboxyl groups occur.

The lipolytic enzyme in its inactive form is known as *pro-lipase* but the means of activation to give *lipase* (*steapsin*) is unknown.

The starches are hydrolysed by *amylase* (*amylopsin*) which has an optimum working pH of 7·1.

Pancreatin, B.Vet.C.

This is a standardized, buff amorphous powder with a meat-like odour. It is slightly hygroscopic and is soluble in water but not in the organic solvents: the solution is turbid. It is available as an official compound tablet containing sodium bicarbonate as a buffer to limit gastric inactivation of the enzymes. The official solution is similarly buffered, but is nevertheless unstable and must be prepared not more than 24 hours or so before use. Enteric coated tablets or fresh pancreatic gland are the usual means of administration of the enzymes.

Actions and Uses. The enzymes are essential for normal intestinal digestion. Their absence results in a typical train of events. Some starch and carbohydrate digestion is effected by oral and gastric juices, and similarly pepsin is responsible for some protein digestion. Beyond this, little digestion occurs and voided fæces will therefore contain undigested protein and fat—shreds of meat, and fat which congeals on cooling, are readily recognized in canine or feline fæces. This loss of essential food substances promotes a nutritional crisis, the animal has a ravenous appetite yet continues to lose weight rapidly as its fat reserves, glycogen reserves, and muscle proteins are drawn on to provide the energy necessary to maintain the vital processes. Acute cases of pancreatitis have been described (Coffin *et al.*, 1953; Singleton *et al.*, 1957) but the condition is not ordinarily amenable to replacement therapy owing to tissue destruction and toxæmia; where chronic atrophy without acute systemic disturbance occurs replacement therapy with the enzymes is quite successful. A test to determine the degree of enzyme production using gelatin film (photographic negative) has been described (Davies, 1957), and other tests include test-feeding with lean meat given in small cotton bags, recovered following defæcation and examined. Normally the meat is digested but in pancreatic deficiencies shreds of meat remain in the bag.

Trypsin is gaining favour as a means of liquefying dead tissue—enzymytic debridement—in abscesses, in otitis, hæmatomata, 'foul in the foot' and mastitis. Other enzymes, including pancreatic dornase (desoxyribonuclease), streptokinase and streptodornase have also been used (Bunn and Scheidy, 1955; Leventhal and Easterbrooks, 1956; Jordan, 1957).

These enzymes have been used locally or parenterally, but some are too expensive for routine use. (Leventhal *et al.*, *loc. cit.*). They should be used in conjunction with antibiotic therapy and liquefied material removed periodically. For example, pancreatic dornase in purulent otitis in the dog has been flushed out after 5–10 minutes following the application of 5·0 ml. of an aqueous solution containing 25,000 units: 20·0 ml. of solution containing 100,000 units introduced into the sinuses of horses is flushed out after 24 hours, and the treatment repeated daily as long as required: similar solutions, used daily in the treatment of mastitis, should be milked out with the liquefied material at least once, but preferably twice, daily prior to antibiotic administration.

Pancreatic enzymes may also be used in the preparation of protein hydrolysates and predigested foods. Two of the official tablets are sufficient when dissolved in 5 fl. oz. (150·0 ml.) tepid water to peptonize a pint of milk. Body temperature is the optimum for peptonizing and about fifteen minutes should be sufficient time for adequate peptonization. Enzyme action can be stopped by boiling. Other foods can be treated similarly and given to sick or convalescent animals.

Dosage and Administration. In dogs and cats the dose of pancreatin will vary according to the amount of functional pancreatic tissue remaining in each individual. Doses of up to 90 gr. (6·0 G.) daily have been satisfactory. Trypsin has been injected via the teat canal in mastitis in doses up to 400,000 units daily dissolved in about 150·0 ml. water, or preferably in phosphate buffer solution as this maintains pH and prolongs activity: normally 75 per cent. activity is lost in 3 hours at room temperature. (Bunce, 1954). The fluid should be milked out after about four hours and the treatment repeated daily as required.

The Thymus Gland

Though it is generally believed that the thymus gland has an endocrine function associated with growth and maturation and that it is influenced by the anterior pituitary gland secretions, no positive proof has yet materialized. The thymus gland is also thought to be involved in leucocyte production. Thymus extracts are used empirically but there is no indication of any benefit accruing from their use.

Gastro-Intestinal Hormones

A hormone given the name of *gastrin* was postulated as long ago as 1906, but controversy still persists concerning its existence. At one time it was thought to be identical with histamine, but this has been proved erroneous. The effect of the compound, which is obtained from the gastric mucosa of pigs, is to stimulate the secretion of large quantities of highly acid gastric juice when injected intravenously. It has no clinical applications as yet.

A similar situation exists concerning a substance extracted from

intestinal mucosa named *secretin*. This produces an increase of pancreatic secretion but only on intravenous injection. It has been used as a test for pancreatic function. Bile secretion is also influenced.

Other substances also stimulate or inhibit the activity of the gastro-intestinal tract but none is of clinical significance.

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CHAPTER 38

VACCINES AND ANTISERA

Introduction

THE resistance of an immune individual to the attack of a pathogenic organism or a toxic product of a pathogenic organism, whether it be a helminth, a protozoan, a bacterium, virus or rickettsia or any product of these, is due to a very complex reaction of the cells and fluids of the body. The immunity is due to factors which may be described under two headings (1) Specific immune bodies or antibodies, and (2) Non-specific factors, two of which properdin and immunoconglutinin, were referred to by Coombs in his address on 'Immunology in Biology and Medicine' to the 1957 British Veterinary Association Congress.

Both specific and non-specific factors are now receiving a great deal of intensive examination and great strides are being made, but clinically it is only the specific antibody immunity which is used extensively, although substances which stimulate and develop non-specific immunity are not unknown but so far have been used empirically—in hope.

Immunity may be *active* or *passive*. Where the animal body is stimulated to produce its own antibody, an active immunity is created which may persist for a life time as with canine distemper or swine fever, or for as short a time as a year as with tetanus or swine erysipelas: where the antibody is merely transferred from an immune to a non-immune individual this is passive immunity which may persist for up to three or four weeks, but more usually for 10–14 days.

Both active and passive immunities may be conferred naturally and artificially. Any animal which recovers from an attack of a naturally contracted disease will have developed a *natural active immunity; natural passive immunity* is developed usually by the passage of antibodies in the colostrum during the first few days of suckling the young; a good example is the passive immunity against lamb dysentery gained by lambs during their first few hours of life. *Artificial active immunity* is developed when modified antigen (a non-infective pathogenic organism or its products) is injected artificially to encourage the formation of antibodies: *artificial passive immunity* is created when serum from hyperimmunized animals is injected artificially into the non-immune animal.

All these are examples of *acquired immunity*. Where immunity exists in a species, breed or individual from birth and is unrelated to any acquired immunity the term *inherited immunity* is used. Examples of inherited

immunity are the relative immunity of man, horses, dogs and cats, to foot and mouth disease and rinderpest (cattle plague).

Artificial Immunity

The creation of artificial immunity of either an active or passive type is primarily a means of preventing a disease—prophylaxis, but where a disease is already contracted the use of hyperimmune sera may limit the severity and, or, duration of the disease by providing antibodies to neutralize the pathogenic agents. So far, these principles have been applied only in the field of microbiology, but in 1957 Jarrett, McIntyre, Jennings and Mulligan of the Glasgow Veterinary School reported on the application of similar principles to helminthology when they announced the development of a vaccine for husk in calves consisting of attenuated living *Dictyocaulus viviparus* infective larvæ. No doubt this marks the beginning of a considerable step forward on the control and eradication of all such helminths which have a tissue migratory phase in their life history: strongyles and ascarids are obvious subjects but there are many others which may prove susceptible to similar control measures. (Experimental vaccines are now being investigated which, from preliminary trials, give every hope of controlling Hæmonchus and Nematodirus infestations in cattle and sheep, and the nematodes of dogs and cats.)

Passive Artificial Immunity. This type of immunity is created by the parenteral injection of hyperimmune sera which may be used either prophylactically or therapeutically.

A *hyperimmune serum* is a serum which contains a high concentration of specific antibodies and is obtained by repeatedly injecting the donor animal with either increasing doses of a standard antigen (pathogenic organism), or standard doses of an antigen the virulence of which is increased with each succeeding dose, or by a combination of both these methods. These doses of antigen stimulate first the development of a normal immunity, and later a hyperimmunity in which the circulating antibodies are considerably more numerous. Blood is drawn from these animals and subjected to the various processes necessary to produce a sterile, stable, hyperimmune serum. If the donor animal is of the same species as the animal treated, the serum is known as a *homologous antiserum*, whereas if the serum is from a different species it is known as a *heterologous antiserum*. An example of a homologous antiserum is that used in the control of canine distemper virus, whereas lamb dysentery antiserum is normally a heterologous antiserum prepared from horses for use in lambs. Antibodies from homologous antisera persist in the blood longer than those of heterologous antisera.

In recent years it has been ascertained that serum antibodies are associated with the globulin fraction of the blood and more particularly with the gamma globulin fraction. It is possible to selectively *precipitate* these fractions and from the precipitated globulin prepare an immune

body solution which gives an even stronger protection than a normal or native hyperimmune serum. These are known as *concentrated antisera.* Methods other than precipitation may be used in this concentration process including the use of proteolytic enzymes by which the so-called *refined antisera* are produced. So far the only veterinary gamma globulin is that developed by the Animal Health Trust laboratories for use against the distemper complex in dogs and marketed under the name of Gamahtine.

Antisera. These may be of three types:

1. Antitoxic sera in which the immunity of the donor has been developed by the injection of a modified or unmodified toxin. A *toxin* is a soluble poisonous substance produced by a pathogenic organism and remains in the culture medium after the organism has been filtered out. If a toxin is modified in some way to reduce its poisonous potential it is known as a *toxoid;* toxoids are usually prepared from culture media solutions by formalinization or precipitation with alum, producing a formol toxoid and an alum-precipitated toxoid respectively. Antisera prepared against toxins or toxoids are known usually as *antitoxins;* tetanus antitoxin and botulinus antitoxins are well known examples.
2. Antibacterial sera in which the antigen has been a suspension of bacterial bodies. These antibacterial sera may contain antibodies which induce specific reactions by the bacteria when the two are brought into contact. There are thus *agglutinins* which cause agglutination or clumping together of the bacteria, *precipitins* which precipitate the bacteria present in a suspension to which an antiserum is added, *bacteriolysins* which lyse or liquefy the bacterial bodies, and *opsonins* which are distinguished from those in normal serum by being heat stable and have the attribute of inducing the phagocytosis of bacteria by leucocytes—they are sometimes referred to as *bacteriotropins* to distinguish them from the thermolabile opsonins which occur in normal serum.
3. Antiviral sera which are similar in method of preparation to the other types but the antigen used is a vaccine prepared from a specific virus

Hyperimmune native sera are a light to dark amber in colour but solutions of globulins or their derivatives, including concentrated antisera may vary from colourless through a greenish-yellow to a dark amber. Solutions may become turbid with age. In powder form these sera are white or light buff in colour, but when reconstituted their solutions are the colour of the parent serum. All sera should be almost odourless except when preservatives are incorporated.

All liquid sera should be *stored* in light-proof containers at temperatures above freezing but below 4°C. if maximum shelf-life is to be obtained, and expiry dates stamped on labels are usually estimated on this basis. With officially recognised sera these expiry dates must be determined so that the antiserum contains the stated potency during the whole period between the date of manufacture and the date of expiry.

Toxic effects may arise if sera are used in individuals which are sensitive to 'species factors' present in a particular serum. This sensitivity may be natural or acquired but usually it is propagated by a previous injection of a similar serum. The sensitivity is of an allergic nature and occurs more commonly with heterologous than with homologous antisera. Reactions may be peracute and result in death within a few minutes of serum administration, usually when given by the intravenous route: this type of allergic reaction is referred to as anaphylaxis: it rarely occurs following serum administration to domestic animals. A second type which is less acute, occurs not uncommonly and is typified by increased irritability of the animal, with œdema usually associated with the head, ears and neck. The animals head may become twice its normal size and the ears thickened considerably: other areas may be affected. The greatest danger is that of asphyxia due either to œdema of the larynx or pressure on the larynx and pharynx by œdema of local tissue. This type of reaction develops within a few hours of administration. A third type, rarely recognised in animals, is *serum sickness*, a condition met more commonly in the human field and typified by urticaria (nettle rash), pains in the joints and a fever. It may occur from a few days to a few weeks after injection of the serum.

The mechanics of the reactions are incompletely known. One theory which is commonly held is that foreign protein stimulates the formation of specific antibodies which are closely associated with tissue cells. A further dose of the antigen results in an antibody–antigen reaction which involves tissue cells due to their close association with the specific antibodies. Damage to the cells results in histamine release with increased permeability of cell membranes including those of capillary vessel endothelioid cells, which in turn results in a great increase in extracellular fluids and hence severe œdema, and in peracute cases at any rate, a drop in blood pressure.

All cases other than the peracute ones may be treated with circulatory stimulants and antihistaminics such as adrenaline, mepyramine malleate and promethazine.

Active Artificial Immunity. Passive immunity is satisfactory where a temporary and immediate protection against a disease is required or where antibodies may aid recovery from an established infection, but where a stronger and permanent, or at least prolonged, immunity is required this may only be achieved by the creation of an active immunity.

Active immunity to toxins, bacteria and viruses can be created by the injections of toxoids, bacterial vaccines and viral vaccines respectively. Immunity normally takes a minimum of 10–14 days to develop but in some cases it may be several weeks before full immunity is achieved.

Toxoids. A toxoid is a toxin which has been treated in such a manner that its poisonous properties have been destroyed, or almost so, without

materially affecting its ability to stimulate the formation of antibodies in a non-immune individual.

The basic toxoid is prepared by growing the toxin-producing organism on or in a suitable culture medium, filtering off the organisms and treating the filtrate containing the toxins with formaldehyde. This produces a *formol toxoid* or *anatoxin*. Various purification processes are now applied to decrease the non-toxoid protein content and improve the antibody stimulating properties of the toxoid: the most modern toxoids are formol toxoids treated first with proteolytic enzymes, particularly trypsin, then precipitated with aluminium sulphate (alum precipitated toxoid) and lastly adsorbed onto aluminium hydroxide.

Formol toxoids may be distinguished from alum precipitated toxoids quite easily, for the former are clear, colourless or pale yellow solutions, while the latter are white or off-white 'fluffy' suspensions which settle, giving a white cloud-like deposit and a clear supernatant; the toxoids resuspend very easily.

Aggressin. This term is used less commonly now that whole culture and bacterial vaccines are replacing the natural culture aggressins in clinical practice. Some bacteria, especially members of genus Clostridium produce substances during their growth which in themselves are non-toxic but when injected along with their respective bacteria increase the invasiveness and pathogenicity of those bacteria. These substances occur in bacterial culture or diseased tissue filtrates, and it is these filtrates which increase the 'aggressiveness' of specific bacteria that are called *aggressins*.

Bacterial Vaccines. Compared as a group with toxoids, bacterial vaccines are less successful in their effects just as antibacterial sera are less effective than antitoxin sera. Nevertheless, many antibacterial vaccines are invaluable, especially when whole culture vaccines are prepared so that exotoxins are also included and a combined toxoid and antibacterial vaccine prepared.

Bacterial vaccines may consist of:

1. Suspensions of killed bacteria. These may be formalinized suspensions equivalent to the formol toxoids and called *anacultures*, or alternatively they may be cultures or suspensions of bacteria inactivated by heat. In both cases the antigenicity of the cultures should not be affected. The term *bacterin* is sometimes used to designate a member of this group of vaccines.
2. Suspensions of living attenuated bacteria. The bacteria used in these preparations are in most cases bacteria which have been grown for many generations in conditions which will allow growth but will decrease pathogenicity. Most of these preparations are true vaccines in that they stimulate the production of antibodies which remain long after the vaccine bacteria have disappeared from the body, but in one or two cases such as the B.C.G. anti-tuberculosis vaccine, immunity to infection persists only so long as the bacteria comprising the vaccine remain in the system.

This is an example of the phenomenon known as *premunition* which has already been referred to in connection with immunity to protozoan diseases (see piroplasm chemotherapeutics p. 593).

If a vaccine is prepared using strains of bacteria isolated from the individual which is to be immunized by the injection of this vaccine, it is referred to as an *autogenous vaccine*. Some species of bacteria exist as a number of different strains, each of which varies antigenically from the others. Consequently a vaccine prepared from one or two strains only cannot expect to provide protection against all strains of that particular species of bacterium, whereas a vaccine prepared from strains causing disease in an individual may be expected to stimulate the production of antibodies specific to those strains. To overcome this disadvantage it is now usual to prepare *polyvalent vaccines* (and antisera), in the preparation of which are used as many different strains of the specific organism as can be found.

Viral Vaccines. The principles applying to bacterial vaccines also apply to viral vaccines, with a few differences. Thus, there exist vaccines which are composed of suspensions of killed virus: there are also vaccines which consist of suspensions of live viruses which have been reduced in virulence by growth under conditions that reduce pathogenicity but hardly, if at all, affect antigenicity. There are, however, vaccines consisting of suspensions of virus particles which are fully virulent in one species of animal, but which are intended for vaccination of an entirely different species for which the virus has relatively little pathogenicity: this situation arises because the viruses which affect the two species are similar antigenically but have a rigid and specific host affinity. This cross immunity phenomenon is most marked in the viruses causing the various animal pock diseases.

The method of preparing virus vaccines varies according to the particular virus involved and the tissues for which each has an affinity, but certain details are common to all. The primary factor in the preparation of all viral vaccines is the need of all viruses for living cells, without which they cannot grow. The living cells are provided either by living experimental animals the species of which varies according to the host affinity of the virus, by embryonated eggs, and also by tissue cultures. Where attenuated viruses are used, these may be modified by growing them in an unusual host as with egg adapted canine distemper virus vaccines, or by growing them in tissues (living animals or cultures) and then subjecting them to adverse growing conditions. Such a vaccine is that of swine fever in which the blood of artificially infected pigs obtained at the height of the resultant disease is incubated with ethylene glycol and crystal violet.

Specific Vaccines and Antisera

The method of creating artificial passive immunity is simply one of injecting an antiserum: this passive immunizing can be prophylactic or

therapeutic in its effect. With active immunity however, the methods of achieving it vary according to the disease and the individual preference of the physician so that generalization is difficult: in the main however, live organisms give a stronger immunity than dead organisms and whole cultures provide a wider protection than either bacterial body vaccines or toxoids alone. Where live vaccines are used, greater care is usually required to ensure that the live organisms neither precipitate a clinical infection in the injected animal nor contaminate the area or room, its fittings and instruments, with live, virulent organisms to the danger of animals subsequently entering the area, consulting room, kennel, or wherever it may be. In addition, it must be remembered that the inoculated animal will excrete living organisms for several days subsequent to inoculation and will therefore be infective to susceptible individuals. These remarks apply particularly to canine distemper virus inoculations.

Bacterial Vaccines and Antisera

There are four categories of biological products used against diseases caused by bacteria. They are: 1. antisera; 2. live vaccines; 3. dead vaccines; 4. toxoids: some vaccines combine groups 3 and 4.

Anthrax

This is a disease to which all animals, birds, and man are susceptible, the order of decreasing susceptibility in Great Britain being cattle, pigs, sheep, horses and dogs. It is usually a septicæmic disease in which anthrax bacilli are found in the blood for several hours before death. In some species the disease is more typically associated with subcutaneous œdema. The organism is a large sporulating rod which in blood smears stains typically with methylene blue.

An antiserum and a spore vaccine are available for treatment and therapeutic purposes.

Anthrax Antiserum, B.Vet.C. The serum is prepared normally in horses, though it can also be prepared in other animals, using repeated injections of *B. anthracis* cultures, the virulence of which is increased with each succeeding dose. The potency is officially laid down in the British Veterinary Codex: 1·0 ml. of the antiserum must protect at least three out of twelve standard guinea pigs from 200 lethal doses of a standard virulent spore suspension (Pasteur 11 strain of *B. anthracis*) injected twelve to twenty-four hours after the antiserum.

Actions and Uses. The serum may be used for *prophylactic* and *therapeutic* purposes in all in-contact animals following confirmation of a clinical case. It is not commonly used because of the sporadic nature of the disease and also because of expense, but within recent years several cases have occurred more or less simultaneously on the same farm, and it is in these multiple outbreaks that the serum is of most use. All in-contact

animals showing a fever should be given therapeutic doses immediately, followed by further doses if the fever does not subside. All in-contact animals not showing a fever can be given prophylactic doses of serum or spore vaccine. (Antibiotics are effective in the treatment of anthrax but have been responsible in many cases, particularly in pigs, for inability to obtain positive smears on post-mortem. This has been, in turn, responsible for the increased numbers of carcases opened up before anthrax has been diagnosed.)

There are two important factors to remember in treating anthrax, the first is that all needles and syringes used for the injections must be adequately sterilized (boiling for 1½ hours on one occasion, or for 15–30 minutes on three consecutive days, preferably with a strong bactericide). The second point is that the disease becomes notifiable only on the death of the animal, but any animal suspected of suffering from anthrax that dies whilst under treatment in Great Britain must be reported to the Divisional Office of the Animal Health Division of the Ministry of Agriculture, Fisheries and Food.

Dosage. For *prophylaxis;*	Horse and Cow:	20·0–30·0 ml.
	Other species:	10·0–20·0 ml.
for *therapy;*	Horse and Cow:	100·0–150·0 ml.
	Other species:	50·0–100·0 ml.

Injections are normally given by the subcutaneous route, but in emergency, intravenous injections may be given providing care is taken in avoiding allergic reactions: an initial dose of a few ml. will reveal any acute sensitivity and the remainder can be given an hour later if no reaction has occurred.

Homologous antisera appear to give better protection than heterologous sera. The passive immunity can be expected to last from two to three weeks. The antiserum can be used in conjunction with antibiotic therapy.

Anthrax Spore Vaccine (Living). The vaccine consists of a suspension in normal saline, glycerin and saponin, of living spores obtained by the growth of an avirulent uncapsulated strain of *B. anthracis*, the master culture of which is maintained by the Ministry of Agriculture Veterinary Laboratories at Weybridge. The official vaccine is such that 0·5 ml. will stimulate sufficient antibodies to protect inoculated sheep from a challenge with 100 lethal doses of a virulent strain of *B. anthracis* three weeks subsequent to inoculation.

Actions and Uses. The vaccine is issued in Great Britain only if the order is countersigned by a Divisional Inspector of the Ministry of Agriculture, Fisheries and Food, Animal Health Division. It is intended for the active immunization of animals which are exposed to considerable risk of infection as on those farms where several animals have been affected simultaneously. Immunity is achieved in about two weeks but horses are slow in developing immunity—up to six weeks has been suggested as a

possible interval: as their susceptibility is relatively low this is not of great clinical significance. The immunity lasts for only six to ten months and as spores will remain infective in soil for many years the practical limitations of the vaccine are obvious.

Dosage.

Horse and Cow:	10 million viable spores (usually 1·0 ml.)
Sheep, Goat and Pig:	5 million viable spores (usually 0·5 ml.)

The vaccine should be administered subcutaneously.

Tuberculosis

This is a notifiable disease in many countries of the world and treatment of the disease is not allowed. However, prophylaxis is not restricted and extensive trials with the Calmette-Guérin premunitive vaccine (B.C.G.) have proved its value as a prophylactic. The vaccine is a suspension of living bacteria of the non-pathogenic strain of *Mycobacterium tuberculosis* developed over a considerable number of years by Messieurs Calmette and Guérin.

The methods of preparation and the standards are specified and vigorously applied. The vaccine must be used within fourteen days of preparation and must be stored between 2° and 4° C. during the period elapsing before use.

Actions and Uses. The vaccine is intended for the inoculation of non-infected calves to provide protection against bovine strains of *Myco. tuberculosis*. Normally calves should be vaccinated immediately after birth, but should older calves be presented for premunization only non-reactors to the tuberculin test should be injected. The vaccine may be given either intravenously or subcutaneously, but though animals react to the tuberculin test much longer it is usual to use the subcutaneous route. Following a subcutaneous inoculation a local persistent swelling appears and a sensitivity to the tuberculin test develops which persists for more than eighteen months. Following intravenous administration, a transient respiratory embarrassment may occur: sensitivity to tuberculin develops more rapidly but persists for a shorter time than following the subcutaneous injection (12–18 months following the initial injection). Animals should be revaccinated yearly if the subcutaneous route is used, but twice yearly if intravenous injections are given: sensitivity to tuberculin decreases more rapidly after the second and subsequent inoculations.

It must be emphasized that the immunity persists only so long as bacteria of the *Bacillus Calmette-Guérin* strain remain in the system, and that repeated dosing is essential for continued resistance to tuberculosis infection.

Dosage: Cattle:	5·0–50·0 mg. bacteria intravenously.
	50·0–100·0 mg. bacteria subcutaneously.

Brucella Infections

Infections of cattle with *Brucella abortus* is the main infection due to members of the genus *Brucella* in Great Britain: two vaccines are available. *Br. melitensis* or a melitensis-like organism has also been reported but the infection is notifiable; no treatment was allowed and affected animals were slaughtered*. A third organism known both as *Br. bronchisepticus* and as *Hæmophilus bronchisepticus*, is responsible for a condition in dogs known as kennel cough; a serum is recognized officially and in addition to the serum a vaccine is also available commercially.

Brucella Abortus, Strain 19, Vaccine (Living), B.Vet.C.

The vaccine is a suspension of living *Br. abortus* organisms artificially cultured using a strain developed originally in the United States. This strain, known as *Strain 19*, has a low virulence. The suspension is not robust and should be used as soon after issue as possible, being kept in a refrigerator until it is required. Its life after manufacture is short; no vaccine retains its full virulence for much more than two months after manufacture and this period is therefore the official shelf-life. During the period before use the vaccine should not be submitted to continuous agitation such as may occur during transport for long periods in a car, for this also reduces the antigenicity of the vaccine.

Actions and Uses. The vaccine is intended for use only in female cattle. BULLS SHOULD NOT BE VACCINATED owing to the possibility of establishing a permanent bacterial focus derived from the vaccine. This focus would maintain a continuous blood agglutinating titre, and as nearly all cattle sales regulations stipulate that bulls entered for sale must be offered with a negative response to the agglutination test, vaccination might prevent the future sale of the bull.

The best time for inoculating is at the heifer calf stage when animals are between four and eight months old. If vaccination is carried out before four months the vaccine may not 'take', whereas immunizing after eight months may result in a persistent reaction to the agglutination test, although it is suggested that a second dose prior to the first pregnancy will greatly enhance the protection given by the first dose of vaccine (B.V.A. Handbook Husbandry and Diseases of Calves, 1957 p. 92). This also would continue positive agglutination reactions which would otherwise have disappeared by the time of the first calving. Heifers or cows should be blood tested prior to a primary vaccination. No animal should be vaccinated in late pregnancy. Following vaccination it is not uncommon to notice severe systemic reactions, especially in calves.

The vaccine is available in 5·0 ml. dose vials either from commercial houses or, if vaccination is proceeding through the Calfhood Vaccination

* The Brucella Melitensis Order of 1940 was relaxed in 1956 as no cases of human brucellosis had been associated with the 42 outbreaks recorded to that date. The powers under the Order were retained but heat treatment of milk substituted for eradication by slaughter.

Scheme of the Ministry of Agriculture, Fisheries and Food, through the Animal Health Division of the Ministry.

Dosage: All female cattle: 5·0 ml. subcutaneously.

Dead Brucella Abortus Vaccines are available commercially. They have been recommended for use in all cattle, including bulls, and cows at all stages of pregnancy. Two 20·0 ml. doses given with a fourteen day interval in spring and summer of the first year, but only once in subsequent years have been recommended commercially. It has yet to be proved that such vaccines are of value.

Bronchisepticus Antiserum, B.Vet.C.

The antiserum is usually obtained from horses hyperimmunized by the injection of *Hæmophilus bronchisepticus* (*Brucella bronchisepticus*). The serum must comply with the official standards of potency.

Actions and Uses. The serum may be used prophylactically and therapeutically against kennel cough in dogs. This is a condition which may occur alone, but frequently complicates the various virus infections which comprise the canine distemper complex.

The disease is characterized by tonsilitis, pharyngitis and bronchitis, and the typical symptom is a short harsh, dry, insistently repeated cough.

The serum is useful but broad-spectrum antibiotics are superior in therapeutic effect.

Dosage. For prophylaxis: Dogs—3·0–10·0 ml. subcutaneously.
For therapy: Dogs—5·0–20·0 ml. subcutaneously.

A *vaccine* for active immunization is also available commercially. Three injections at weekly intervals have been recommended, with a dosage scale assessed according to body weight:

5–15 lb. (2·0–7·0 kg.): 0·2, 0·4 and 0·8 ml.
15–35 lb. (7·0–16·0 kg.): 0·4, 0·8 and 1·6 ml.
35–60 lb. (16·0–28·0 kg.): 0·5, 1·0 and 2·0 ml.

Clostridial Diseases

The bacterial genus Clostridium comprises a number of organisms which produce extremely potent exotoxins, and in some cases it is the toxin alone which is of pathological significance. For example, at one extreme, *Cl. chauvæi*, which causes 'blackquarter' in cattle and sheep but only rarely in other species, produces a relatively weak exotoxin, whereas at the other extreme *Cl. botulinum* grows saprophytically in dead carcases or meat products, and it is the toxin alone which produces the rapidly fatal results so typical of 'botulism'. Between these two extremes are organisms which rely partly on tissue invasion and partly on toxin absorption for effect, the relative importance of the two factors varying according to the organism, and in some cases according to the conditions of infection.

In the prophylaxis and therapy of clostridial diseases, as would be expected, the antitoxin sera and toxoids are of considerable importance. Where the toxin is the only factor of pathological significance as in botulism, tetanus, and enterotoxæmia, antitoxins are specific in treating the condition, and antitoxins and toxoids are indicated for the creation of passive and active immunities respectively, although whole culture vaccines may be used as with Botulinum Vaccine, B.Vet.C. Where bacterial invasion is also a factor in the ætiology of the disease, antisera are prepared against whole cultures, and vaccines consist of sterile suspensions of bacterial bodies and toxoids: braxy, black disease, and blackleg vaccines are examples.

Black Disease

This is a condition which occurs mainly in sheep, although cattle and horses suffer from conditions caused by the same organism, *Cl. ædematiens*. The disease in sheep is characterized by sharply defined almost circular necrotic areas in the liver (hence the name for the disease of 'infectious necrotic hepatitis',) and copious amounts of fluid in the body cavities. An attack of the disease is usually precipitated by liver-fluke invasion of the liver. In other species the lesions are more like those of blackleg (*q.v.*).

Black Disease Antiserum, B.Vet.C. This antiserum contains antitoxic globulins capable of neutralizing the toxins of *Cl. ædematiens* type B, and is prepared by the administration of toxoid and toxin to horses by intramuscular injection.

Dosage. For prophylaxis by subcutaneous injection:

Horse and Cow:	10·0 ml.
Sheep:	2·0 ml.

For therapy:

Horse and Cow:	30·0 ml.
Sheep:	10·0 ml.

The first therapeutic dose should be given intravenously but repeat doses, which should be injected every 24 hours, may be given subcutaneously.

Passive immunity may be expected to last about two weeks.

Black Disease Vaccine, B.Vet.C. This is a whole culture vaccine for active immunization against *Cl. ædematiens*.

Dosage.

Cattle:	10·0 ml.
Sheep:	5·0 ml.

To obtain the best immunity two doses should be given by subcutaneous injection at an interval of three to four weeks.

Improved Black Disease Vaccines are also available commercially. These may be whole culture vaccines in which the toxoid has been precipitated with alum in order to concentrate the toxoid and also slow up its

absorption rate, or they may be the alum precipitated toxoid alone. The dosage rate is reduced to 5·0 ml. for cattle and 2·0 ml. for sheep.

Active immunization should be completed about two weeks before the expected onset of the 'season'. Single 'booster' doses in subsequent years should be given at about the same time.

Blackleg

Also known as 'blackquarter' and 'quarter-ill', this is a disease primarily of cattle and sheep; cases in pigs and horses have been reported but are of relatively little significance. The cause is usually *Cl. chauvæi*, but a percentage of cases are due to *Cl. septique* and a few to *Cl. ædematiens* or *Cl. perfringens* (*or welchii*). The condition is typified by a severe gangrenous and gaseous lesion of the muscles and subcutaneous tissues, often of the shoulder, ribs or hindquarters. The vital organs show toxæmic changes and the body cavities contain serous fluid. The disease is usually triggered off by bruising due to a knock or fall and often affects the heaviest and best animal of the herd or flock. Animals of six months to 2 years are the most commonly affected; they are frequently found dead without having shown signs of lameness such as would be expected in subacute cases.

Blackleg Antiserum, B.Vet.C. This antiserum is normally prepared in horses using formolized whole cultures of *Cl. chauvæi*. It is intended for protecting cattle and sheep against blackleg in areas where the organism is known to be present in the soil. It is of little therapeutic value because of the peracute nature of the disease, but, in conjunction with antibiotics, the antiserum has been of value in the early stages of the condition.

Dosage. For prophylaxis following confirmation of a case:

Cow: 10·0–40·0 ml. subcutaneously.
Sheep: 5·0–10·0 ml. subcutaneously.

Where treatment is attempted, up to five times these doses may be required: the serum should be given subcutaneously.

Blackleg Vaccine, B.Vet.C. This is a formolized whole culture *Cl. chauvæi* vaccine which may be given in fluid or implant form. Each implant is equivalent to 5·0 ml. of formol culture. The vaccine is intended to confer active immunity against blackleg in cattle and sheep, and should be administered at least two weeks before exposure to infection (before being turned out to grass in the case of calves and older cattle, or before lambing in sheep).

Dosage. Cow: 5·0 ml.
Sheep: 2·0 ml.

With fluid anacultures it is usual, in heavily infected areas, to administer two doses at an interval of two weeks or more, but if implants are used repetition is not required.

Improved Blackleg Vaccines are usually whole cultures with the toxoid precipitated with alum. Doses are reduced to 2·0 ml. for cattle and 1·0 ml. for sheep.

Braxy-Blackleg Vaccine, B.Vet.C. and *Blackleg-Lamb Dysentery Vaccines* are available. The former is intended for protection against blackleg due to both *Cl. chauvæi* and *Cl. septique* in cattle and sheep, as well as against braxy in sheep. The latter covers blackleg and lamb dysentery in sheep.

Dosages are 5·0–10·0 ml. for cattle and 5·0 ml. for sheep. Two doses are required in heavily infected areas, with an interval of at least two weeks between injections, the last being given about two weeks before the expected onset of the braxy season, or before turning out to grass (cattle). With the blackleg-lamb dysentery vaccine it is common to give 5·0 ml. before tupping and a further 5·0 ml. one to two weeks before lambing. *Improved double vaccines* contain whole cultures with the toxoids precipitated with alum. Their doses are 5·0 ml. in calves and 2·0 ml. in sheep, given with the same routine as the normal vaccines.

Botulism

This is a pure intoxication, all the pathological changes and symptoms stemming from the ingestion of a toxin produced in the tissues of dead animals. This toxin is absorbed following the ingestion of dead animal tissues, a craving for which may result from soil and pasture deficiencies, particularly of phosphorus. The condition, caused by four types of toxin produced by *Cl. botulinum*—types A, B, C and D, is known throughout the world and is responsible for severe losses in cattle, sheep, poultry and wild fowl, fur bearing animals, and less commonly in horses. The disease in cattle is known as 'lamsiekte' in South Africa, 'bulbar paralysis' in Australia, and 'cattle paralysis' in America. In poultry, 'limberneck' and 'western duck sickness' are two names by which the disease is known in America. The symptoms in all species are similar, severe muscle weakness and paralysis: type C toxin is most commonly implicated but type D occurs amongst cattle in S. Africa, and types A and B may be the cause of botulism in poultry.

Although botulinum antitoxin sera are available, once the symptoms of botulism appear the antitoxins are of little use, though they are the best treatment available. Recovery is uncommon.

Botulinum Vaccine, B.Vet.C.

This vaccine is a formol culture of *Cl. botulinum* type C or type D, or a mixture of both types. Two kinds are recognized, an alum precipitated formol whole culture, and a dialysed, aluminium phosphate adsorbed, formolized whole culture.

Dosage. The alum precipitated vaccine is given subcutaneously in doses of 10·0 ml. in cattle, 5·0 ml. in sheep and 1·0 ml. in mink (type C

only) if one type of culture is used alone, but where combined cultures of types C and D are used these doses will need to be doubled. A second dose should be given six weeks after the first. The dialysed vaccine is diluted according to potency and doses will vary from batch to batch and manufacturer to manufacturer, although the dosage for cattle is usually adjusted to a volume of 1·0 or 2·0 ml.

Braxy

This disease of young sheep occurs primarily on hill farms and mountainous areas of Wales, Northern England, Scotland and Ireland; also in Scandinavia and Iceland. It is characterized by a congested œdematous area of the abomasum where it lies next to the rumen, in conjunction with a generalized toxæmia due to toxins produced in this lesion, and copious peritoneal fluid. Symptoms are mainly of fever, ruminal tympany and abdominal pain. The organism responsible for the conditions is *Cl. septique*, which is also responsible for blackleg cases in cattle, sheep and pigs. In braxy, the precipitating factor is grazing on frosted pasture, death frequently occurring within 24 hours of such grazing.

Braxy Vaccine, B.Vet.C. This vaccine is a formolized whole culture intended for actively immunizing sheep against braxy. It is given in 5·0 ml. doses by subcutaneous injection to young sheep in the autumn prior to their first winter: on farms with a bad braxy history it is advisable to give two injections with an interval of from two to four weeks between them. Vaccination should be completed at least two weeks before the expected onset of the braxy season.

Improved vaccines may be whole cultures in which the toxoid is alum precipitated and the bacteria lysed or whole, or they may be alum precipitated toxoids alone. All are given in 2·0 ml. doses.

Combined *braxy-blackleg vaccines* are also available (see Blackleg.)

Lamb Dysentery

This is an enterotoxæmic disease of lambs occurring during their first seven days of life but usually within a few hours of birth. Acute cases may die without showing symptoms but less acute cases show all the symptoms of enterotoxæmia with acute ulcerating hæmorrhagic enteritis: inability to suckle, abdominal pain, arched back, diarrhœa which often contains pure blood, rapid collapse and death. The causal factor is *Clostridium perfringens* Type B, which produces toxins which are common to most of the other strains of perfringens (or 'welchii'). Ewes vaccinated against lamb dysentery secrete antibodies in their colostrum which will give some passive immunity to suckling lambs providing the disease is not contracted before the lamb first suckles: shepherds in lamb dysentery areas try to ensure that lambs suckle immediately after birth. Lambs may also be given antiserum soon after birth, but though this is an extremely effective measure it is not always practicable.

Lamb Dysentery Antiserum, B.Vet.C. This is a serum of horses hyper-immunized by the injection of toxins and toxoid of *Cl. perfringens* type B, although type C and type D toxoids may be included to help reinforce the toxin production. The serum contains antibodies which will neutralize all five of the recognized toxic factors (α, β, γ, δ, ε) produced by the common types of *Cl. perfringens* (A, B, C, and D.) Besides being specific in its protective action against lamb dysentery, this serum can be used in the other 'perfringens' diseases, although the specific sera are preferred if a correct diagnosis can be made. Once symptoms are obvious, the serum is of little value. The serum will also give short term protection against 'pulpy kidney'.

Dosage. 5·0 ml. injected subcutaneously within 12 hours of birth. This dose is equivalent to 2·0 ml. of concentrated lamb dysentery antisera.

Lamb Dysentery Vaccine, B.Vet.C. This is a formol whole culture vaccine intended for active immunization of ewes against *Cl. perfringens* type B, and usually types C and D also. Thus the vaccine will protect against 'pulpy kidney' (type D) and 'struck' (type C), although specific vaccines are recommended in areas where these diseases are rife. It is essential that lambs should take colostrum as soon after birth as possible.

Dosage. Sheep: 5·0 ml. one month before tupping followed by 5·0 ml. one week to ten days before the anticipated lambing date. In the next and subsequent years single booster doses may be given to the ewes just before lambing.

Pulpy Kidney

This is an enterotoxæmia of sheep and lambs in which the lethal factors are toxins elaborated by *Cl. perfringens* type D in the intestine and absorbed. The causal organism is less invasive than that causing lamb dysentery but may nevertheless be recovered from parenchymatous organs on post mortem. It is a common inhabitant of the intestines of normal sheep (Bullen and Battey, 1957), and the condition is triggered off by sudden changes of diet or overeating, especially of rich food. The disease is characterized by sudden death, sometimes after a short illness accompanied by nervous symptoms. Animals post-mortemed immediately after death may show few signs of clostridial toxæmia other than excessive gas formation in the intestines and glycosuria. The typical lesion of 'pulpy kidney', in which the cortex of the kidney is soft and will wash away when held under a running tap leaving glomerular and vascular 'fronds' and networks, may not be seen unless examination is deferred for several hours after death. Treatment consists of avoiding sudden changes in diet, preventing overeating, and routine vaccination.

Pulpy Kidney Antiserum, B.Vet.C. This is usually a heterologous serum prepared in horses using *Cl. perfringens* type D cultures. It is of value in

giving immediate protection to lambs and sheep in flocks where the disease has occurred. The passive immunity may be expected to last for 3–4 weeks.

Dosage. Young lambs 2·0 ml., older animals 5·0 ml. All injections should be given subcutaneously. Double sera, effective against pulpy kidney and lamb dysentery, should be given in 5·0 ml. doses to lambs.

Pulpy Kidney Vaccine, B.Vet.C. This formolized whole culture vaccine may be used for actively immunizing lambs and sheep. It may be given 5·0 ml. at a time subcutaneously in a two dose regime, with or without a dose of serum given simultaneously with the first dose. A period of about four weeks should elapse between injections, the last dose being given about two weeks before the 'season'. The *Improved Vaccines*—usually alum precipitated toxoids—are given in 2·0 ml. doses, but two doses are still needed. In subsequent seasons, one dose only is required.

Struck

This disease of sheep, also known as Romney Marsh disease, is essentially an enterotoxæmia similar to pulpy kidney but caused by *Cl. perfringens* type C. The disease is characterized by acute enteritis, sometimes blackleg-like lesions of the muscles, and toxæmic degeneration of the parenchymatous organs—liver, kidney, spleen etc. Vaccination is the surest means of avoiding the fatalities which can be numerous during late winter and spring.

Struck Vaccine, B.Vet.C. As with the other official perfringens (or 'welchii') prophylactics, this vaccine is a formolized whole culture, given in the same dose and by the same routine as the pulpy kidney vaccine with which it is often combined under the name of 'Enterotoxæmia Vaccine'. Alum precipitated combined toxoids in two doses of 5.0 ml. each, given with an interval of four weeks between injections, are now preferred.

Tetanus

Popularly known as 'lock-jaw', tetanus is a disease of the nervous system in which the symptoms are due to toxins produced by *Cl. tetani* in damaged tissue. The organisms do not penetrate from the site of inoculation but proliferate in the wound, producing toxins which are then absorbed. Prophylaxis is more reliable than therapy and it is usual to inject antiserum in horses, which are the most susceptible species, as soon as possible after the wounding has occurred especially if the wound is on the foot. In sheep, which is the next most frequently affected species, docking and castration with a hot iron is often preferred before other methods because of its sterilizing effect: Burdizzo and elastic band docking of lambs is often followed by numerous cases of tetanus. Wounds containing a focus of tetanus organisms usually fail to heal: stiffness, photophobia, and difficulty in eating and drinking, are the early signs of tetanus; nervous

spasms, succeeded by paralysis and death, follow later. Treatment is best effected by the use of muscle relaxants in conjunction with antibiotics and large doses of antitoxin intravenously. Very good results have followed the use of chlorpromazine (*q.v.*).

Tetanus Antitoxin, B.Vet.C. The antitoxin is prepared in horses using tetanus toxoid. Its main value is as a prophylactic administered at the time of operation or as soon as possible after a wound has occurred. Passive immunity should persist for about one month. Therapeutically, the toxin is of less value, for once the toxin has reached the nervous tissue neutralization is difficult; however, the serum will prevent the absorption of further toxin from the site of inoculation and should always be used.

Dosage: Prophylactic by subcutaneous injection:

Horse and Cow:	1500–3000 units.
Calf, Sheep, and Pig:	500–1500 units.
Dog:	250–500 units.

For therapy, doses 100 times greater than these have been suggested. The initial therapeutic dose should be given intravenously, but thereafter daily doses may be given subcutaneously.

Tetanus Toxoid, B.Vet.C. This may be either a formolized toxin or an alum precipitated toxoid. The alum precipitated form is greatly superior to the simple toxoid, especially in horses. Single injections are quite useful but two further injections are required to provide a lasting immunity. The second dose is given about six weeks after the first injection, and the third six months later. Active immunity in horses takes about six weeks to develop.

Dosage: Horse: Three doses each of 10·0 ml.

Hæmorrhagic Septicæmia

The organism responsible for this disease, also known as 'transit fever' (not 'transit tetany' which is a blood mineral deficiency), is *Pasteurella septica*. Many different strains of this organism exist and polyvalent vaccines should always be used: even so it is not possible to include all strains and variants, and the vaccine proved to be of value in one area may be useless in another. The value of broad-spectrum antibiotics is superior to that of vaccines, and the tetracyclines or chloramphenicol can be used therapeutically in preference to a doubtful vaccine used prophylactically.

Hæmorrhagic Septicæmia Vaccine, B.Vet.C. This is normally a polyvalent vaccine used in actively immunizing against *Past. septica*. Immunity takes two to three weeks to develop and several doses may be advisable,

given at intervals of two to three weeks, to consolidate the immunity.

Dosage: Horse and Cow: 5·0–10·0 ml.
Sheep and Pig: 2·0–5·0 ml.

Antisera are also available, but though polyvalent, are not dependable unless prepared using indigenous strains of Pasteurella. Prophylactic doses of 10·0–20·0 ml. for horses and cattle, and 5·0–10·0 ml. for sheep, have been recommended commercially: therapeutic doses of up to five times these quantities have been suggested.

Leptospirosis

Two types of Leptospira are implicated in the leptospirosis of Great Britain, *L. canicola* and *L. icterohæmorrhagiæ*, whilst a further type *L. pomona* is common elsewhere. Other species exist but are at the moment of little clinical significance. *L. canicola* is mainly implicated in nephritic syndromes of dogs though it may occur in other species.

L. icterohæmorrhagiæ is most commonly associated with a hepatitis and jaundice in dogs and occasionally pigs. Both are transmissible to man, but the latter is of more consequence.

***L. canicola* Vaccine, B.Vet.C.** This formolized culture is used in the active immunization of puppies against *L. canicola* infections. Initial doses should be given at 4–5 months followed by a further dose two weeks later, and a third one month after the second. Single 'booster' doses at yearly intervals have been suggested.

Dosage: Dogs: 1·0 ml. subcutaneously.

***L. icterohæmorrhagiæ* Antiserum, B.Vet.C.** The antiserum is prepared in horses for passively immunizing dogs and pigs against leptospiral jaundice. Protection for two to three weeks may be expected. When used therapeutically, the antiserum must be used as soon after infection as possible and in large doses, preferably given intravenously: all contacts should be given prophylactic doses. Treatment should include antibiotics and glucose injections in conjunction with the antiserum.

Dosage: Prophylactic: 5·0–10·0 ml. subcutaneously.
Therapeutically: 10·0–20·0 ml. intravenously repeated daily.

Combined *L. canicola* and *L. icterohæmorrhagiæ* antisera are available commercially. Suggested doses are the same as for the official antiserum, though it would be anticipated that double doses might be more logical.

***L. icterohæmorrhagiæ* Vaccine, B.Vet.C.** Similar methods to those used for preparing the 'canicola' vaccine are followed in making this vaccine. Two doses of 1·0 ml. each are recommended for dogs, foxes and

pigs, given subcutaneously with an interval of 7–10 days between. Where rats heavily infest premises a third dose one month later assists in confirming the immunity.

Swine Erysipelas

Once associated with hot weather, this disease of pigs now occurs throughout the year. It is caused by an organism *Erysipelothrix rhusiopathiæ*, which, like the clostridia, is a soil saprophyte. The disease appears in various forms ranging from peracute septicæmias causing sudden death, through the mild 'diamond-disease' form to the chronic arthritic and cardiac forms. The disease responds to serum therapy with or without simultaneous administration of antibiotics, and prophylaxis with either serum, dead or live vaccines, provides passive, short and long lasting active, immunities respectively.

Swine Erysipelas Antiserum, B.Vet.C. Horses are used in the preparation of this antiserum, which may be used to promote 2 weeks duration passive immunity in pigs; active immunity follows the combined use of serum and live vaccine. The serum is also effective therapeutically.

Dosage: Prophylactic: 10·0–20·0 ml. subcutaneously.
or 5·0–10·0 ml. when used in conjunction with live vaccines.
Therapeutic: 20·0–50·0 ml. subcutaneously.

Swine Erysipelas Vaccine (A.T.), B.Vet.C. This is a dead vaccine used in the active immunization of pigs against swine erysipelas. It is killed by formaldehyde and the antigen adsorbed onto aluminium hydroxide. In a disease-free herd the vaccine is given alone, but where the animals have contacted clinical cases it should be given along with a dose of antiserum, to protect the animals during the interval between dosing and the development of active immunity. For full immunity, two doses are advisable given six weeks apart, otherwise immunity lasts only 4–6 months. The second injection prolongs the immunity to a minimum of 8 months. Gilts and sows more than three months pregnant should not be vaccinated.

Dosage: 2·0 ml. injected subcutaneously behind the ear at any age after weaning. The second dose should be injected 6–8 weeks later at a different site.

Swine Erysipelas Vaccine (Living), B.Vet.C. The organisms which comprise this vaccine are attenuated by frequent passage through a special medium. Once prepared, the vaccine maintains its potency for about one month when kept between 2° and 10°C., but must be used within 7 days of removal from a refrigerator. The vaccine is intended for use in combination with S.E. antiserum which should be injected simultaneously with the vaccine, though at a different site. The vaccine should only be used in disease-free herds. One dose along with serum will give protection for up

to 6 months, but a dose of vaccine alone 7–10 days after the first injection prolongs the protection for as much as a further six months.

Dosage: All pigs, 0·5 ml. with 5·0–10·0 ml. antiserum, followed by 1·0 ml. vaccine 7–10 days later. The antiserum and vaccine must not be allowed to contact each other and are best injected on opposite sides of the pigs.

It must be remembered that this vaccine is infectious to man and care must be exercised in disposing of unused cultures and in sterilizing needles and syringes. The creation of the carrier state has been suspected following the use of this vaccine and the dead vaccine is most commonly used.

Miscellaneous Antibacterial Vaccines and Antisera

Several vaccines and antisera have been given official recognition, but their value is disputed.

Corynebacterium pyogenes antiserum and vaccine has been used in the treatment and prophylaxis of *C. pyogenes* mastitis and calf pneumonia, amongst other conditions. It is probable that these biologicals may mitigate the severity of an attack but it is doubtful whether stronger claims could be substantiated. Dosage of the *serum* for cattle and sheep is 10·0–60·0 ml. given parenterally. The *official* vaccine is a formol whole culture to be given intramuscularly to cattle as a prophylactic or a treatment in doses of 10·0, 15·0 and 20·0 ml. at three day intervals. *Toxoids* are also available for prophylaxis or treatment and are given in similar doses.

Staphylococcus toxoid has been used against staphylococcal mastitis and other staphylococcal infections with a routine similar to that for *C. pyogenes* toxoid. *Dosage* for cattle is 10·0, 15·0 and 20·0 ml. with a three day interval between doses. Sheep may be given 2·5, 5·0 and 10·0 ml., and dogs 1·0, 2·0 and 5·0 ml.

With both *C. pyogenes* and staphylococcal therapeutics there may be severe reactions following dosage: subsequent doses should be eliminated or reduced if this happens.

White Scour Antiserum, B.Vet.C. is a *Bacterium coli* antiserum prepared by using polyvalent vaccines. Immunity to *Bact. coli* is type specific, and unless indigenous strains are used the serum may be useless in a given area. The same refers to the many *Bact. coli* vaccines that are available. *Dosage* of serum for prophylaxis in calves is 10·0–20·0 ml. intramuscularly as soon after birth as possible. The dose may be doubled and may be given intravenously. Doses of vaccine vary from 10·0 ml. for foals and calves to 5·0 ml. for sows and 2·0 ml. for piglets.

Apart from these, there are many antisera and vaccines prepared for prophylaxis and treatment of most bacteria, including streptococci,

salmonellæ, and various species of staphylococci. They are widely used, but the benefit gained is largely unassessed and is often negligible.

Viral Vaccines and Sera

There are three categories of biologicals available for protection from, and the treatment of, virus diseases. They are (1) antisera, (2) dead virus vaccines and (3) live virus vaccines. The last group may be further subdivided into (a) attenuated virus vaccines and (b) fully virulent virus vaccines.

The Canine Distemper Complex

Until about 1947 there was only one virus disease of dogs recognized in Great Britain: this was 'canine distemper'. About that time a severe epidemic of what was called 'nervous distemper' began: the symptoms, however, were not entirely those associated with distemper and the disease eventually became recognized as a distinct entity and named 'hard pad' or 'paradistemper'. Later, a further disease previously identified in Great Britain with distemper was recognized as Rubarth's disease, named after the man who first described it and also known as 'contagious canine hepatitis'. Canine distemper is classically described as a diphasic febrile disease of dogs, other canine species, and ferrets. Unaccompanied by secondary invading bacteria, the disease is mild; symptoms include serous discharges from the eyes and nose, a temporary anorexia and lassitude, followed by recovery in two to three weeks. Secondary bacterial infection causes pneumonic and enteric complications which may cause death.

Hard pad generally shows a longer incubation period, a lower maximum and often fluctuating temperature, and characteristic thickening and hardening of the keratin layers of the feet and nose: this keratinization is usually indicative of similar proliferative and inflammatory changes occurring in all other tissues of embryonal ectodermic origin, including the brain and spinal cord. Terminal symptoms are usually of a nervous type; often almost continuous convulsions are experienced.

Canine Distemper Serum, B.Vet.C. This is a homologous serum prepared from dogs hyperimmunized against canine distemper (Laidlaw and Dunkin) virus. It may be used to protect canine species passively for about three weeks, to treat clinical cases when given before the purulent ocular stage of the disease, and to protect susceptible animals from a clinical attack during active immunization with live virus (serum-virus simultaneous method).

Dosage: Prophylactic: 5·0–25·0 ml. by subcutaneous injection.
Therapeutic: 10·0–50·0 ml. intravenously or subcutaneously at the rate of 1·0 ml. per pound body weight (2·2 ml. per kg.).

The dose may be repeated on the following day if results and economics warrant a second dose.

Gamma Globulin. Most of the antibodies contained in serum are gamma globulins; if an animal is hyperimmunized and the gamma globulins isolated, an extremely potent preparation is available for the treatment of the disease against which the donor animal has been hyperimmunized. The only such preparation so far available for veterinary use in Great Britain is a gamma globulin developed by the Animal Health Trust laboratories. This preparation, marketed under the name of Gamahtine, is a freeze-dried powder containing antibodies active against the viruses of distemper (Laidlaw and Dunkin strain), 'hard pad', and canine hepatitis, as well as many of the secondary bacterial invaders. The ampoules of dry powder are stable at room temperature; reconstitution with 1·0 ml. solvent per ampoule gives an antibody potency about ten times stronger than a normal antiserum. One ampoule is a prophylactic dose, but therapeutically one ampoule should be used for each 10 lb. bodyweight. Subcutaneous injection is the usual method of administration but the intravenous and intrathecal routes may also be used.

Canine Distemper Mixed Antiserum, B.Vet.C. This antiserum may be either homologous or prepared in horses. It contains antiviral and antibacterial globulins including antibodies effective in neutralizing *Bact. coli.*, *Salm. typhimurium*, *Salm. enteritidis*, streptococci and *H. bronchisepticus* (*Br. bronchisepticus*). It is intended mainly for the therapy of diseases of the canine distemper complex.

Dosage. 10·0–25·0 ml. subcutaneously or intramuscularly. Homologous antisera may be administered intravenously but not the heterologous preparations.

Double and triple virus antisera are also available commercially. They are usually homologous antisera effective against the viruses of classical distemper, hard pad and canine hepatitis. *Dosages* are the same as for the polyvalent sera and the single homologous antiviral sera.

Antibacterial canine distemper antisera are also available.

Canine Distemper Vaccine, B.Vet.C. Following the research of Laidlaw and Dunkin two forms of prophylaxis were devised, the vaccine-virus and the serum-virus method. This is the vaccine developed by these researches; it consists of spleen and lymphatic tissue of dogs killed at the height of an artificially induced attack of the disease: the virus in these tissues is killed with formaldehyde and a brown particulate suspension is produced. The vaccine is intended for the active immunization of all canine species against classical canine distemper: it also gives some protection against 'hard pad'. The vaccine may be given 10–21 days prior to a dose of living, fully virulent virus, or if desired two doses of vaccine and one of virus may be given at intervals of two weeks. The vaccine-virus method is often preferred to the serum-virus method, but necessitates two attendances by

the client or practitioner, and after the virus injection the animal is highly infective to susceptible animals for several days. Puppies under three months of age are resistant to vaccination.

Canine Distemper Virus (Living), B.Vet.C. The virus is fully virulent and is contained in ferret spleen and lymphatic tissue. It is used for reinforcing the immunity given by the vaccine in the vaccine-virus method of immunizing, or for providing active immunity when given along with serum in the serum-virus simultaneous method in which the serum is given within 24 hours after the injection of the virus. Care should be taken in disposing of 'empty' ampoules and in sterilizing needles and syringes, for the virus may produce a clinical attack in susceptible individuals. Inoculated animals should be isolated from susceptible animals for several days, for they excrete live and infective virus.

The virus should be used within 1 week of removal from cold store (at −20°C.).

Canine Distemper Vaccine, Egg Adapted (Living), B.Vet.C. The strain of virus in this live attenuated virus vaccine is the 'egg-adapted' strain grown in living embryonated eggs. It is used to provide an active immunity against both classical distemper and 'hard pad' in canine species, ferrets, and mink of all ages. Inoculated animals are not infective to susceptible animals. Injection should be carried out only after a period of isolation, preferably lasting three weeks: in practice, this is often difficult, for though a particular animal may be kept away from others, it must have exercise and pass over ground that infected animals may recently have travelled.

Contagious Canine Hepatitis

This disease of dogs has only been recognized in Great Britain during the last decade: previously, cases were considered as atypical distemper cases. Elsewhere, however, Rubarth's disease has been known for many years. The disease is often difficult to diagnose, but symptoms (signs) are related to severe damage to the liver and acute hepatic insufficiency. Peracute cases die suddenly without previous symptoms: where the condition is less acute, symptoms vary but are mainly those of severe malaise, a high temperature, and various subsidiary symptoms of hepatitis—subcutaneous œdema, emesis, severe abdominal pain, convulsions, and jaundice, are some of the possibilities. Mild and subclinical cases also occur. The ætiological factor is a virus related to the fox encephalitis virus described in America by Green. Dogs of all ages over about 3 months are susceptible.

Antisera of a homologous type are available for prophylaxis and treatment, at a dosage rate of 1·0 ml. per lb. body weight for prophylaxis and 2·0 ml. per lb. for therapeutic uses (2·2 ml. and 4·4 ml. per kg. body weight, respectively). Injection routes are the same as for the distemper prophylactics.

Courses of vaccination to give cover against classical distemper, hard pad and infectious (contagious) canine hepatitis are now available commercially. The different vaccines may be given consecutively or simultaneously: with the simultaneous methods doubt has been expressed concerning the possible interference of the two viruses with the development of their respective immunities (the so-called interference phenomenon).

Contagious Pustular Dermatitis

Popularly known as 'orf', this is a highly infectious disease of sheep caused by a virus and characterized by extensive ulceration in and around the mouth, nose, coronet and occasionally the udder and teats of ewes. It occurs throughout the year, but is most common in late summer and early winter, affecting sheep of all ages, including lambs shortly after weaning. Economic loss may be considerable, due to the affected animals' inability to graze because of both lameness and mouth lesions.

Contagious Pustular Dermatitis Vaccine (Living), B.Vet.C. The vaccine consists of a glycerinated suspension of skin pulp containing an attenuated strain of virus. Animals are inoculated on the inside of the thigh and suffer from a modified form of the disease which lasts for about 14 days. Vaccinated animals should be segregated during this period and ewes with suckling lambs should not be vaccinated. Animals should be vaccinated so that they are clear two to three weeks before exposure to infection. Inoculation is by infecting two superficial skin scratches of two to three inches in length and at least half an inch apart. The virus is contagious to man and care should be taken in disposing of containers, which should be boiled along with inoculating needles for 10–15 minutes. Immunity lasts about one year but infections subsequent to vaccination are usually mild. About 10·0 ml. vaccine is sufficient for 25 sheep.

Feline Infectious Enteritis

The disease is one which affects cats and related species of almost any age. It is also known as 'infectious panleucopenia' and is due to a virus which causes an ulcerative stomatitis and intestinal lesions. Symptoms are mainly those of stomatitis and gastro-enteritis with salivation, emesis, and either constipation or diarrhœa. Secondary organisms may intensify these signs, including the abdominal pain, acute depression and the craving for water, although affected cats do not drink. Agranulocytosis is present.

Feline Infectious Enteritis Vaccine, B.Vet.C. The formolized vaccine is a suspension of the spleen tissue of cats killed at the height of an artificially induced infection. It is indicated for the immunization of cats over the age of six weeks and two doses, each of 1·0 ml., should be given two weeks apart. This should give protection for at least twelve months, but a third dose of vaccine is sometimes given two or three months after the second injection.

Louping Ill

Sheep are the animals mainly affected by this disease, but cattle are also susceptible. The disease is caused by a virus which is transmitted by the tick *Ixodes ricinus*: it therefore has a strong seasonal incidence, occurring mainly in the spring (March and June) and autumn (September and October), when tick infestations are maximal. The mortality rate in susceptible flocks may be as high as 60 per cent., and prophylaxis is of considerable importance. The virus attacks the nervous system causing the typical inco-ordinated jerky, leaping movements, at periods varying from six to eighteen days after being bitten by infected ticks. Paralysis and death follow. Apart from controlling the tick population by dipping, vaccines may be used to provide at least a partial immunity in sheep and cattle, which is completed by exposure to natural infection. Young lambs are passively protected by antibodies received in the colostrum from their mothers, but in infested areas, lambs which remain in the flock should be actively immunized by a single injection in August followed by a further dose in the following spring: a third dose to increase the colostrum antibody content may be given in the subsequent spring, before lambing. In cattle, the principle is the same, except that two injections are usually given with an interval of two to four weeks between them; the second dose is given about three weeks before the animals are turned onto infested pasture: natural infection reinforcement of immunity may not occur and a further dose is recommended in August.

Dosage. Sheep: 2·0 ml.; Cow: 5·0–10·0 ml. by subcutaneous injection.

Swine Fever (Hog Cholera)

This virus disease of pigs which had almost died out during the late nineteen-forties has been causing considerable losses in recent years in spite of the inroads on the disease made by vaccination. The disease is typified by a septicæmia and ulcerative gastro-enteritis, as well as by nervous system lesions. Peracute and acute forms exist in which no significant symptoms are seen apart from those associated with septicæmias, but the more chronic type is characterized by emaciation, diarrhœa, and a swaying crab-wise walk. The disease is 'notifiable', and herds in which the disease has occurred are subject to 'standstill' and quarantine orders. Nevertheless, in-contact but unaffected pigs may be protected by prophylactic injections of antisera, but it is unwise to use such antisera in affected pigs for chronic carriers may be established thereby. Passive immunity lasts about 14 days. The vaccine must only be used in disease free herds.

Swine Fever Antiserum, B.Vet.C. The antiserum is homologous and is prepared from pigs hyperimmunized by the serum-virus method followed by virulent virus. It may be used for treatment but is largely of value as an

agent for passively immunizing 'in-contact' pigs and, outside Great Britain, is used along with the virus in the serum-virus method for promoting active immunity.

Dosage. 30·0–100·0 ml. subcutaneously according to weight (20 lb.—20·0 ml.; 90 to 120 lb.—45·0 ml.; 180–200 lb. and over—100·0 ml.).

Crystal Violet Swine Fever Vaccine, B.Vet.C. Also known as hog cholera vaccine, this vaccine consists of the defibrinated blood of pigs killed at the height of an artifically induced attack of swine fever: the blood is incubated for fourteen days with ethylene glycol containing 0·25 per cent. of crystal violet. The vaccine retains its potency for about two years when refrigerated and about nine months at room temperature: normally, however, the vaccine is released with a four week expiry date. The vaccine *must* be injected subcutaneously, for injection into fat may influence the absorption rate and reduce the level of immunity achieved. Protection is achieved in about 14 days from the date of injection and lasts for about one year. It must not be used in infected herds.

Dosage. Up to 70 lb. (30·0 kg.) 5·0 ml.; over 70 lb. 10·0 ml.

Poultry Vaccines

Several vaccines for poultry are included in the British Veterinary Codex, but are infrequently used in Great Britain. Some are of doubtful value. They include Fowl Cholera Vaccine, B.Vet.C. which is given in 1·0 ml. doses subcutaneously to promote active immunity against *Pasteurella aviseptica*. It is of limited value for use in flocks which have been in contact with the disease. Fowl typhoid Vaccine, B.Vet.C. consists of a suspension of killed *Salmonella gallinarum* organisms. The vaccine is given subcutaneously in 1·0 ml. doses to create an active immunity to fowl typhoid. It does not interfere with the agglutination test and should be used in conjunction with the test. Field tests seem to indicate that the vaccine may be of value to protect in-contact flocks, but its use in affected flocks is not advised. Fowl-Pox Vaccine, Chick Embryo Virus (Living), B.Vet.C., and Fowl-Pox Vaccine, Pigeon-Pox Virus (Living), B.Vet.C. are both available for vaccination against fowlpox but are not used in Great Britain at the present time. The chick embryo vaccine is for use in birds under 4 months of age, which are inoculated by piercing the skin above the elbow with a needle which has been dipped in the vaccine. Immunity is achieved fully in about 14 days but is more or less complete from about the third day. Immunity lasts about 18 months; 1·0 ml. is sufficient for about 120 birds. The pigeon-pox vaccine is for use in birds of any age; it is applied with a brush to the scarified skin of the thigh except in young birds where a stiff brush avoids the use of a scarifier. Immunity is achieved in 14 days and lasts fully for about four months and partially for 12 months. 10·0 ml. is enough for about 60 birds.

Newcastle Disease Vaccine (Living), B.Vet.C. is a suspension of chick embryo cultured Newcastle disease virus of low virulence. It has a refrigerator life of about 1 month but lives only a few days at room temperature. The vaccine is not used in Great Britain where the disease is notifiable under the Fowl Pest Order (1936). Intranasal instillation of the virus suspension is followed by a mild form of the disease and the birds are solidly immune to a natural outbreak following recovery. Subcutaneous injection, intramuscular injection, and wing-web puncture, inoculation methods are also used and may be similarly followed by a mild attack, occasionally with nervous symptoms. Immunity is also solid on recovery. The duration of immunity varies from flock to flock and also between individuals but is more prolonged than with the dead virus vaccines also available. The use of the live vaccine is not recommended in disease free areas because of the danger of establishing the virus in the area: it must also be understood that all laboratory diagnostic methods are invalidated by administration of the vaccine.

Sera and Vaccines Used Abroad

The British Veterinary Codex includes several sera and vaccines for use in animals elsewhere than in Great Britain.

Contagious Bovine Pleuro-Pneumonia Vaccine (*Living*), B.Vet.C. is a culture of an attenuated strain of the responsible organism. Up to three injections are given, often with increasing virulence. The first injection is given at the top of the tail to assess individual susceptibility: other injections may be given behind the shoulder. There is always a risk associated with the use of the vaccine. *Dosage* is 1·0 ml. by subcutaneous injection if several injections are to be given, but 5·0 ml. if only one dose is administered.

Blue Tongue Vaccine (*Living*), B.Vet.C. is a suspension with crystal violet of egg adapted and attenuated virus strains intended for the active immunization of sheep. Annual inoculation of sheep of all ages is required, although lambs from immune mothers will not 'take' until they are four months old. The *dose* is 1·0 ml. per sheep given subcutaneously three to four weeks before the blue tongue season.

Foot-and-Mouth Disease Vaccine, B.Vet.C. is an inactivated virus preparation—often a formolized skin and lymph suspension adsorbed by an aluminium hydroxide gel, but it may also be a crystal violet defibrinated blood vaccine. Immunity gained by subcutaneous inoculation begins to decrease after 4–6 months and is only effective against the specific strains used in preparing the vaccine. Its use is usually controlled by the state.

Horse Sickness Vaccine (*Living*), B.Vet.C. is a mouse brain suspension obtained from mice dying from attenuated strains of horse sickness virus. It is used in Africa and the Middle East to protect animals from horse sickness. It should be given annually two to three months before the disease season begins and provides maximum immunity about 100 days

after inoculation. Horse species of all ages except the foals of immune mares may be vaccinated, even in-foal mares: the foals may be vaccinated when over 4 months of age. Animals inoculated for the first time should be worked lightly for three weeks after injection. *Doses* are given subcutaneously in quantities of 5·0 ml.

Rabies Vaccine, B.Vet.C. is prepared in rabbits, sheep, or horses, using a rabbit fixed strain of rabies virus. The brains of these animals are removed, macerated, and suspended in saline after the animals have been killed when paralysis has lasted twenty-four hours. The virus is then inactivated with phenol or other suitable agent. The vaccine is used for actively immunizing dogs in countries where rabies is enzootic. The dose is 5·0 ml. *Rabies Vaccine* (*Living*), B.Vet.C. is an egg adapted live virus vaccine. Immunity following intramuscular injection lasts about 12 months. *Dosage* in dogs is usually one ampoule, but for cattle, in which it has been also used the dose is five times that of the dog.

Rift Valley Fever Antiserum, B.Vet.C. is used to protect new-born lambs from the disease and must be given within 24 hours of birth. Natural infection usually converts the passive immunity into an active one. *Dosage* is 2·0 ml. per lamb given subcutaneously.

Rinderpest Antiserum, B.Vet.C., also known as cattle plague antiserum, is prepared in cattle species. It is used in the serum-virus methods of actively immunizing cattle and buffalo against rinderpest virus in which the aim is to reduce the reaction to the virus to a temperature reaction only. The antiserum may also be used therapeutically but is only of value if injected up to the early febrile stage. *Dosage* for therapeutic purposes is at the rate of up to 5·0 ml. per 2 cwt. (100·0 kg.) body weight, but in prophylactic use with the virus the serum dose must be assessed according to virulence of the strain of virus and individual susceptibility.

Rinderpest Vaccine, B.Vet.C. is a dead virus suspension for the active immunization against rinderpest in the same species that the vaccine is prepared from. Three doses of 10·0 ml. given subcutaneously at weekly intervals will provide an immunity within 10 days and lasting about a year. Subsequently an annual dose of 10·0 ml. is sufficient. A longer lasting immunity may follow a 15·0 ml. dose of vaccine with a large dose of virus injected two weeks later. *Rinderpest Vaccine* (*Living*), B.Vet.C. is indicated for prolonged protection against rinderpest. There are a number of vaccines, each prepared in different species, and each varying in virulence according to the method of preparation. Hopes of a standard virulence egg adapted strain are currently held. Dosage is dependent on the type and method of preparation of the vaccine.

Miscellaneous Biologicals

Venom Antiserum, B.Vet.C. This is a comprehensive standard for all antisnake venom serum. The serum may contain the antitoxic globulins capable of neutralizing one or more snake venoms.

Polyvalent antisera should always be used unless the type of snake is

known: they should be injected in large doses intravenously and locally as soon as possible after the bite. Further doses should be given intravenously if no improvement follows within an hour. The dosage is proportional to the amount of venom injected and not to the size of the victim so that the smaller the patient the larger the dose should be proportionately. *Doses* of 20·0 to 50·0 ml. are suggested.

Diagnostic Biologicals. When certain bacterial diseases are contracted the animal becomes allergic to substances produced by cultures of these organisms. This phenomenon is made use of clinically for the diagnosis of the infection. Mallein and tuberculin are the best known, but Johnin and others are used.

Glanders

Pfeifferella mallei is the cause of 'glanders' in horse species and some Carnivora, but not in cattle. It is also a disease which is transmissible to man, in whom it is often fatal. The disease does not occur in Great Britain but horses for export are tested. The disease in horses is usually chronic, the lungs and air passages being most commonly affected: the ulceration of the nasal septum is characteristic. Farcy is a cutaneous form of the disease: this is essentially a lymphadenitis and chronic lymphangitis. Often the disease is subclinical and the allergy test with mallein is used for diagnosis.

Mallein, B.Vet.C. This is a natural or concentrated, bacteria free filtrate of a fluid medium culture of *Pf. mallei*. It may be administered by one of three methods: (1) The *subcutaneous* test in which 1·0 ml. of mallein is injected subcutaneously in the side of the neck and the temperature recorded at the time of injection and every 3 hours between the 12th and 24th hour after injection. The test may not be carried out if the horses temperature is initially over 102°F. If the neck swelling which follows is greater than 3″ in diameter, is hot and painful and does not disappear quickly, and if the temperature rises more than 1°F. in the 24 hours, the animal is a reactor to the test for glanders. In doubtful cases a retest may be carried out 2–3 weeks later. (2) The *intradermopalpebral* test in which 0·1 ml. of concentrated mallein is injected into the dermis of the lower lid, about ¼″ below the lashes of one eye. The other remains as a control. Healthy animals may show slight œdema of the lid which disappears in 12–24 hours: glandered animals show a reaction which is obvious at 12 hours, maximal at 24 hours, and lasts for about three days. This is the most accurate and practicable test of the three and is used most frequently. (3) The *ophthalmic* test, in which a drop of mallein is instilled into the outer canthus of the eye. Glandered animals react strongly with swelling of the lids and sometimes the side of the face; there is an ocular discharge. Occasionally both eyes react, though the non-infected eye less than the other. The test is not as reliable as the other two.

Tuberculosis

The disease is notifiable and is being eradicated from Great Britain area by area. This eradication is scheduled to be complete in March 1961. The tuberculin (intradermal) test is being used as a diagnostic indicator.

Old Tuberculins, B.Vet.C. These tuberculins are heat concentrated filtrates of fluid media on which *Mycobacterium tuberculosis* of human, bovine, or avian type has been grown. The diagnostic dose is 0·1 ml. given intradermally.

Subcutaneous tuberculin is usually a 25 per cent. dilution in normal saline of mammalian old tuberculin. The dose is from 3·0–5·0 ml.

Purified Protein Derivatives of Tuberculins, B.Vet.C. The tuberculin is prepared by precipitating the protein from a tuberculin filtrate and redissolving it in a suitable vehicle after washing. Human and avian preparations are used. The *dose* of each is 0·1 ml.

The tuberculins used in the Tuberculosis Eradication and Attested Herd Schemes are the *standardized human P.P.D. tuberculin* and the Weybridge *standardized avian P.P.D. tuberculin*. They are used in carrying out the single comparative intradermal test, by which 0·1 ml. of each tuberculin is injected intradermally on one side of the middle third of the neck, at two points equidistant from the prescapular lymph gland and about five inches apart. Skin measurements are taken before, and 72 hours after, injection. Reactions are considered in the light of individual and herd history and especially the incidence of 'non-specific' infection, e.g. Johne's disease and skin tuberculosis, both of which may affect the tuberculin allergy test. The caudal fold is used in some countries (N. America): 0·05 ml. is required and mammalian tuberculin only is used.

In N. Ireland the 'Stormont Tuberculin Test' is official. It consists of a double intradermal test using 0·1 ml. mammalian P.P.D. tuberculin injected at the same site on two occasions with an interval of seven days between. A rise of 5·0 mm. in skin thickness twenty-four hours after the second injection is a positive reaction.

Pigs are injected at the base of the ear, mammalian on one side and avian on the other. Poultry are injected in the wattle on one side, using avian tuberculin only.

The subcutaneous test may be used in horses, cattle, dogs, and cats, a temperature rise of 2°F. or more being a positive reaction. The temperatures are recorded every three hours between the 9th and 24th hour after injection of 6·0 ml. in horses, 3·0 ml. in cattle, 0·5 to 1·0 ml. in the dog, and 0·25 ml. in the cat. The Supreme Argentine Test is a modification of the subcutaneous test aimed at overcoming any acquired immunity to intradermal or ordinary subcutaneous tests. Large doses of tuberculin are used.

The ophthalmic test is similar to that with mallein: one drop of tuberculin (concentrated) is instilled into the eye at the outer canthus and followed forty-eight hours later by a further three or four drops. A purulent

conjunctivitis should be present twenty-four hours later if there is a positive reaction. The test is not entirely reliable.

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PART FIVE

MISCELLANEOUS

CHAPTER 39

PHARMACY

THIS is the art and science relating to the manufacturing, compounding and dispensing of drugs. This chapter, however, is intended to deal only with that part of pharmacy now referred to as dispensing, in which medicinal substances are mixed, packed and labelled. It is essentially a practical subject, but as more becomes known of the chemical and physical reactions involved in making some preparations, such as emulsions and dispersions, the theoretical aspect of dispensing is becoming a study in itself. These theoretical aspects will be mentioned only superficially.

Requirements for Dispensing

The first requirement in dispensing is a knowledge of the weights and measures. A reference to Chapter 2 will serve as a reminder that three systems of weights and measures are in use in Great Britain. *Pharmaceutical balances* are supplied with a set of apothecary weights, for it should be remembered that the official Imperial avoirdupois system has no unit between a grain and an ounce, although $\frac{1}{2}$ oz. and $\frac{1}{4}$ oz. weights are available. These fractions of an ounce also involve fractions of a grain ($\frac{1}{2}$ oz. = 218$\frac{3}{4}$ gr.) and they are therefore unsuitable for normal purposes. As the Imperial grain is common to both the avoirdupois and apothecary systems, it is sensible to use the various apothecary units for weighing quantities of less than one ounce. Each balance is usually equipped with weights of $\frac{1}{2}$ gr. (sometimes $\frac{1}{4}$ gr. also), with grain weights from 1 to 6 grains, $\frac{1}{2}$ and 1 scruple, $\frac{1}{2}$ and 1 drachm, 2 drachm and occasionally four drachm weights. Metric weights may be used.

The normal dispensing balance is designed to weigh quantities up to two ounces and has a left hand 'closed' pan to take weights and a right hand 'open' pan, suspended from the beam side only so that powders may be placed on and removed from the pan without the inconvenience of a second suspending bar. Note that the drugs are weighed directly onto the scale pan: an exception is made with metal pans when mercurial and similarly corrosive drugs are to be weighed, but as metal pans are used only on the oldest type of balance this exception will not apply very frequently. There are two types of balance, Class A and class B. Class A balances are accurate to 1/20th gr. (3·0 mg.) and are used for weighing small quantities of toxic drugs—that is quantities of, say, 1–5 gr. (60·0–300·0 mg.). Class B balances are usually accurate to 1/5 gr. (12·0 mg.); greater accuracy than this is not required for drugs other than the potent alkaloids and similar highly active compounds, and Class B balances are therefore used for routine purposes.

The maintenance of a pharmaceutical balance is not involved, but the life of weights and balances can be prolonged by observing two rules—that no weighing of powders shall commence until the weight drawer beneath the platform is closed, and that no powder is added to, or removed from, the scale pan whilst the beam is up: by conforming to these rules the spilling of powder is largely avoided and the corrosion which this frequently causes is also avoided. Weights are manipulated by hand, and beyond an occasional wipe no cleaning is recommended.

For amounts larger than two ounces various types of commercial balances are used.

Fluids are rarely weighed in dispensing and various sizes of *glass measures* are available, calibrated in apothecary volumes—minims, fluid drachms and fluid ounces. Metric measures and combined Imperial and Metric measures are available. All are intended to be read with marks at eye level and volumes are measured using the bottom of the meniscus: in most measures the main calibrations are repeated on the reverse side to assist in level reading.

Manipulation of solids and semi-solids is achieved by the use of different sizes of *spatulæ* graded according to length. These usually have wooden handles though in some of the older types horn was used; the blades are metal and are similar in appearance to painters' palette knives with parallel semi-sharp edges and a rounded end. No metal spatulæ should be used with mercurial compounds; bone or non-corrodable synthetic spatulæ are designed for this purpose.

Where reduction of solids to a finer state (known as trituration) is required this is done by means of a *pestle and mortar*. The mortar is a lipped bowl made of unglazed porcelain for normal purposes and of glass for the management of poisons: the non-porous surface of the glass avoids the contamination of substances by traces of poison which would be left behind from previous triturations with a more porous surface.

Mixing of powders, the making of emulsions, and various other compounding manipulations are also carried out in a mortar.

A special type of mortar has been used in the past for compounding the mass used in pill making by hand. This mortar is double ended; one end is deeply concave and is used for triturating and mixing the powders, whilst the other end is shallow and is used for incorporating the massing fluid which was most commonly syrup of liquid glucose. Pill making by hand is archaic and these mortars are now rarely seen except in teaching schools and museums.

Sieves for ensuring a standard particle size are now rarely used except in manufacturing. They are now made of stainless steel mesh for grades up to 100, but tinned copper was used previously and may still be seen. For grades finer than 100, silk screens are used. The number or grade of a sieve describes the number of meshes which occur along the sides of an inch square of the sieve.

The British Veterinary Codex defines the particle size of powders of various grades:

A *coarse* powder:	All the powder passes through a No. 10 sieve and up to 40 per cent. passes through a No. 44.
A *medium coarse* powder:	All the powder passes through a No. 22 but only 40 per cent. through a No. 60.
A *medium fine* powder:	All passes a No. 44 but not more than 40 per cent. passes a No. 85 sieve.
A *very fine* powder:	All passes a 120 mesh silk sieve.

If a powder is given a number that powder must *all* pass through a sieve of the same number.

All dusting powders should pass a No. 60 sieve, otherwise particles may cause irritation and thereby aggravate any skin condition. This is very important with such powders as sublimed sulphur which have a tendency to be gritty and cause irritation.

Principles of Prescription Dispensing

When dispensing a prescription whether it is to ones own formula or that of a colleague the aim should be to work methodically, accurately, quickly and neatly. Working to a standard method frequently ensures that the remaining three requirements are automatically complied with.

Methods will vary according to individual ideas but the following scheme may act as a guide.

1. Read the prescription and check the doses. Note any incompatibilities and make sure that the prescription complies with the regulations attaching to poisons and Dangerous Drugs.
2. Write the label.
3. Make sure all dispensing utensils are clean.
4. Prepare the ingredients, compound and fill into the required container(s).
5. Recheck the label against the prescription, label and wrap.
6. Clean dispensing utensils and bench.

Dispensing Powders

Trituration and Mixing. Powders used in the veterinary field may be one or several solids mixed together in a finely divided state. They may be intended for direct administration as a powder, as with dusting powders and many small animal medicines; they may be given mixed in water either as a solution or suspension, e.g. cattle drenches; they may be dissolved in a vehicle and administered as a parenteral injection, or they may be used in the preparation of other forms of pharmaceutical compounds such as electuaries, ointments, tablets, pills and horse balls. The manipulation of powders therefore forms a large part of dispensing.

The first stage in dispensing powders is to choose a clean, dry mortar which is suitable for the volume of powder to be triturated and mixed. Commencing with the powder of smallest volume, each powder is tipped into the mortar in small quantities, each addition being thoroughly triturated and mixed before any more is added. When any powder is particularly coarse it may be triturated separately prior to mixing into the combination. If the powder is adhesive, as with kaolin or Armenian bole, trituration is usually unnecessary and should be avoided where possible: during mixing, however, some trituration is unavoidable and the powder will be compressed on the sides of the mortar; should this happen the caked powder must be scraped off with a spatula and thoroughly mixed and triturated with the succeeding powder. If colouring agents such as the Armenian bole are included in a formula or prescription they are usually the smallest volume of powder included: they should be mixed in after the first of the active ingredients has been triturated in the mortar, otherwise a large amount of the colour will be lost on the sides of the mortar. The usual reason for the inclusion of colour, apart from its disguising effect, is to ensure that the powders as a whole are adequately mixed. Where bulky powders are to be mixed into powders of small volume this should be done slowly, a small quantity of the bulk being added at a time with thorough trituration and mixing between each addition.

Note: If the powders to be made are small in volume (2–20 gr. or 0·5–1·5 G.) of innocuous ingredients it is usual to include in the mass quantities of each ingredient sufficient to make one more powder. This allows for losses in trituration and manipulation. It should not be done with toxic drugs.

Crystalline substances should either be very finely ground or dissolved in a volatile fluid and incorporated into the rest of the powder in much the same way as one mixes cement.

If *toxic* drugs are to be included these should be added and mixed in last to avoid duplication.

Division. When triturated and mixed, the bulk may be divided into individual powders in one of two ways. The most accurate method, which should be adopted for all powders containing toxic or highly active drugs, is by weighing each powder individually. This is laborious and time consuming so that where accuracy is not essential division by eye is acceptable. This should be carried out 'scientifically' and not by heaping small quantities onto their respective wrapping papers and adding or subtracting until approximately equal heaps are obtained. If a flat rectangular heap is made of the powder this can be fairly accurately halved with a spatula, the two halves being separated by moving one half laterally; this can usually be done without disturbing the symmetry of the two rectangles. These two main rectangles may now be subdivided at right angles in a similar manner. This can be continued indefinitely

with perhaps a little tidying between each division. With practice accuracy to one grain can be achieved.

Once divided, each powder can be transferred to a wrapping paper using one spatula as a fixed buffer and another spatula to lift. By this means the catapulting of powders across the bench is avoided.

Poisons should be added last, immediately before wrapping, so that again, duplication is avoided: mixing is achieved by repeatedly turning the powders over with a spatula. Poison doses should always be weighed individually if at all possible.

Fractional Doses. It may happen that doses of a drug are required which are fractions of a grain, as for example 1/12 gr. (5·0 mg.) arecoline hydrobromide; this may be incorporated in a capsule with 3 gr. (0·2 g.) chlorbutol for the treatment of tapeworms in a dog. There are several methods of doing this but the following is relatively simple.

Weigh out accurately 1 gr. (65·0 mg.) of the hydrobromide and place it in a three inch glass mortar. Weigh out eleven grains of an 'inert' powder such as lactose and tip it into the mortar. Mix, and weigh out a series of 1 grain powders; there should be eleven complete powders, the twelfth being short due to manipulation losses. Each of the complete 1 grain powders will contain 1/12 gr. (5·0 mg.) of the hydrobromide.

Wrapping. Powders which are intended for administration by a client must be wrapped individually. The methods may be learnt by reference to Milks' Veterinary Pharmacology, Materia Medica and Therapeutics, 6th Edit. 1949, Baillière, Tindall & Cox, Ltd., p. 28. Which of the methods is used is immaterial so long as a sift proof double fold is made with the free edges of the wrapping papers. For neatness it is advisable to use only one method, which ensures uniform shapes and sizes.

Powders not prepared for dispensing as such may be processed further and incorporated in: 1. mixtures and lotions, 2. ointments, 3. emulsions, 4. pills and horse balls.

Dispensing Mixtures and Lotions

In veterinary practice the vehicle for fluid medicines is usually water; lotions, however, may have glycerin, spirit, propylene glycol, polyethylene glycol and any one of a host of other organic solvents.

The method of dispensing the internal and externally applied fluids is the same.

Following the preliminaries of reading the prescription and writing the label, etc. all the powders should be weighed out and prepared. *Soluble solids* should then be dissolved one by one in a portion of the vehicle in a glass measure, solution being hastened by the use of warm water and vigorous stirring. When dissolved the solution is made up to volume and poured into the bottle. *Slowly soluble solids* such as exciccated magnesium sulphate should be triturated in a warm mortar with some of the warmed

vehicle and transferred to the measure when dissolved. *Insoluble solids* if for internal administration may be triturated in a mortar either with 60 m. (4·0 ml.) mucilage of tragacanth per fluid ounce of final mixture, or 10 gr. (0·6 G.) Compound Powder of Tragacanth, B.Vet.C. per fluid ounce of mixture. Some of the vehicle should be added in the latter case until a cream is formed. With a lotion this addition of suspending agent is deleted, a cream being formed with some of the vehicle only. The suspension is diluted with more vehicle and transferred to a measure, and the mortar washed with some of the vehicle, the washings being added to the contents of the measure. The correct volume is made up with more vehicle. *Solid poisons* should be incorporated immediately before adding the vehicle. *Fluid drugs* are added directly into the measure, the measure(s) used for these fluids being washed with some of the vehicle and the washings added to the mixture already in the bulk measure. *Fluid poisons* should be added directly to the bottle just before topping up and corking.

In practice, where speed is more important than great accuracy, it is common to dispense straight into the bottle. In this case the bottle must be dry, and wherever possible the solids should be funnelled into the bottle while it is dry, otherwise clogging of the bottle neck may occur. The *soluble solids* are therefore poured into the bottle after trituration and mixing: some of the vehicle is then added, the cork screwed into the neck and the solids dissolved by vigorous shaking: when this is achieved the bottle is uncorked and the vehicle added until the bottle is filled to the junction of shoulder and neck. *Insoluble* solids should be funnelled into the dry bottle, a little vehicle added and the bottle allowed to stand until the fluid has 'wetted' all the powder; more vehicle can then be added and the bottle shaken vigorously after corking. When evenly dispersed the volume can be made up. If the powder is not first wetted it may clog a corner of the bottle and never be dispersed correctly. Where *soluble* and *insoluble* powders are to be mixed the soluble powders should be dissolved first and the solution added to the bottle after the insoluble solids have been dispersed. Fluid drugs are added in the same manner as for the normal procedure except that they are dispensed directly into the bottle. *Eye lotions* and *eye drops* should be prepared with a sterile vehicle. *Note:* Suspending agents must not be used in the dispensing of any type of veterinary LOTION.

When the mixture is in the bottle the cork should be pressed in with a screwing action and given a final tap on the bench—this should not be a hard knock or the bottle may fracture causing, at the least a flooded bench, and at the worst a severe laceration of the hand holding the bottle.

Labelling and wrapping follow. For wrapping refer to Professor Milks's demonstration previously mentioned. To estimate the size of paper required (this refers to any object to be wrapped, not just bottles) the width of the paper should be 2/3 the width of the base plus the height of the object, plus 2/3 the width of the top—this provides sufficient paper to

overlap at top and bottom and to cover the height of the object. The length of the paper should be 1½ times round the bottle, box, etc. This provides enough to go round the bottle and yet leaves sufficient to fold over and fasten in the free ends of the paper.

Dispensing Ointments and Creams

Next in frequency of dispensing come the ointments, though, along with the general trend away from personal dispensing, the compounding of ointments is left more and more in the hands of commercial manufacturers.

Ointments with a pure paraffin base are not popular now because their immiscibility with body fluids makes them difficult to apply if the skin is wet, though some drugs make this type of base essential for reasons of stability (e.g. penicillin), slow absorption, or slight penetration as with mercuric iodide blisters. The same difficulty of application also applies when 5 per cent. lanolin is included in the base.

The majority of ointments are now made with water miscible bases and differ from creams only in their firmer consistency. These water miscible bases may be of:

1. *A compound type* containing two phases of an emulsion, namely the fat phase, which may be of animal, vegetable or mineral types, or a mixture of these, and an emulsifying phase consisting usually of a detergent.
2. *A compound type* containing all three phases of an emulsion. These emulsions or creams are miscible with water in all proportions, water being the continuous phase of the oil-in-water emulsions (*q.v.*). The consistency of preparations of this kind can be varied by increasing the proportion of water.
3. *A simple type* which is usually a water soluble organic base consisting very frequently of a mixture of polyethylene glycols. An official base of this type included in the United States Pharmacopœia consists of a mixture of equal parts polyethylene glycols 4000 and 400, the latter being fluid and the former a solid with the consistency and appearance of paraffin wax. The consistency of the base can be varied by changing the proportions of the two glycols.

There are two methods of preparing ointments, referred to as (1) the fusion method and (2) the trituration or levigation method. The *fusion method* consists in melting the fatty components of the base on a water bath in decreasing order of melting points to avoid over-heating. Drugs, if fat soluble, should be dissolved in the fat base, whereas insoluble solids should be added just before the base begins to solidify, stirring being continued until the ointment is set. Frequently, however, the insoluble solids are incorporated after the base has set by means of trituration in a mortar or by levigation with a spatula. Ointment making by *trituration* and *levigation* differs only in that with the latter method the mixing and smoothing of the medicaments through the base is done on an ointment slab of marble or glass, using a spatula to turn and rub the base and

drugs. In both cases a small amount of the base must be added to all the powder and mixed and smoothed in before taking a further portion of the base: by this means an evenly mixed ointment is obtained. Fluids should be mixed in drop by drop.

Ointments with the two phase compound type of base are usually prepared by the fusion method, any insoluble drugs being added by levigation or trituration.

Those with the three phase compound base should always be prepared by a mixed method of fusion and trituration. By this method all the fat phase and fat soluble drugs, including the emulsifying agent should be heated on a water bath and melted together in order of decreasing melting points. The water is heated separately to about 60°C. and a mortar warmed with boiling water; the melted fats are then poured into the mortar, the water added and the whole stirred until set. Water soluble components may be dissolved in the water though this may occasionally interfere with correct emulsification; these compounds can therefore be added after emulsification but whilst the ointment is still fluid, or by levigation when cold.

The simple type of ointment base is combined with the medicaments by trituration or levigation.

Eye ointments are prepared by using the official base which has previously been heated for one hour at 150°C. All utensils can be sterilized either by autoclaving or by wetting with alcohol and burning off.

Packing and Wrapping. Ointments may be packed into cardboard boxes—chipette boxes made from twisted card stuck together, or 'corruganza' seamless boxes stamped out of sheets of card. These are cheap and convenient but are neither so serviceable nor hygienic as ointment jars or collapsible metal tubes. The collapsible metal tubes may be filled in the same way that the jars are filled, by pouring while the ointment is still fluid, but once set the ointment can still be filled into them: this is achieved either by introducing the ointment in small quantities and tapping down, or better by wrapping the ointment in a tube of greaseproof paper, pushing the open end of the cylinder into the metal tube as far as the tube shoulder, and flattening the last ¾ inch of the tube with a spatula which is kept in position as the paper is withdrawn leaving the ointment within the tube. The tube end is then sealed by turning the flattened end over twice and corrugating the seal.

Wrapping of an ointment box or jar is achieved in much the same way as for a bottle, the walls of the box or jar being considered as top and bottom for purposes of estimating paper size and of wrapping.

Dispensing Emulsions

An emulsion is a relatively stable mixture of two normally immiscible liquids. If oil and water, the two substances commonly used in veterinary emulsions, are shaken together they will rapidly separate to give an oil

layer above a water layer: this is partly due to the difference in surface tensions between the two liquids but is also associated with their different densities. If a third substance is introduced which will coat the globules of one of these substances preventing their coalescence, and which will form a transitional buffer bridging the physical differences between the two substances, then a dispersal of one substance within the other can be made semi-permanent: this is an emulsion.

The three phases or compounds forming an emulsion are known as:

1. The *disperse or internal phase*, which is the substance split into small globules and dispersed throughout the second phase.
2. The *continuous or external phase* in which the globules are dispersed and which, within limits can be used to dilute the emulsion, and
3. The *emulsifying agent or emulgent*.

Two general types of emulsions can be made with oil and water. The first is the *oil-in-water* emulsion in which the disperse phase is oil and the continuous phase is water. This type of emulsion is the one commonly used in veterinary medicine. The second is the *water-in-oil* emulsion in which the previous position is reversed; some ointments containing lanolin (wool fat) are partly water-in-oil emulsions, the lanolin acting as the emulsifying agent. In the main, water-in-oil emulsions are used internally whilst the oil-in-water emulsions may be used either internally or externally.

Whether an emulsion will be water-in-oil or oil-in-water depends mainly on the emulgent used, and to a lesser degree the methods of preparation. Thus an emulgent which is essentially lipophilic (fat loving) will produce an emulsion with oil as the external phase, and one which dissolves more easily in water will produce an oil-in-water emulsion with water as the continuous phase

Oil-in-Water Emulsifiers

Carbohydrates:	Acacia, tragacanth, pectin, dextrin, malt, agar, and chondrus (Irish moss) mucilage.
Proteins:	Egg albumin and yolk, casein, gelatin, condensed milk.
Soaps:	Monovalent alkali metal soaps (sodium, potassium, and ammonium soaps), soaps of some amines particularly triethanolamine.

Water-in-Oil Emulsifiers

Saponins:	Tincture of Quillaia.
Soaps:	Polyvalent alkaline earth soaps (calcium, magnesium).
Alcohols:	Many of the complex alcohols—alcohols of wool fat, lanolin, cetyl and stearyl alcohols.

In the last few years research has produced several series of new emulsifying agents. Most of these agents are esters of polyhydric alcohols and long chain fatty acids, for it has been found that hydroxyl (—OH)

and carboxyl (—CO·OH) groups are hydrophylic and long chain hydrocarbon groups are lipophilic: if the balance of these two different characteristics is varied, substances predominantly either lipophilic or hydrophilic can be formed, and by combining one substance from each of these groups a compound emulsifying agent can be produced.

Another type of emulsifying agent is the sulphated alcohol derived from long chain fatty acids. Sodium lauryl sulphate is an example. Quaternary ammonium detergents are also used for oil-in-water emulsions.

Methods of Making Emulsions. There are several methods of making emulsions, but the principle involved is the same for all methods. This consists of breaking the disperse phase into the smallest globules possible and dispersing them evenly throughout the continuous phase. This may be done manually with a pestle and mortar, or mechanically as with a colloid mill in which a rotating disc exerts considerable shearing action on the globules, or as with a ram-jet type of homogenizer in which a plunger forces the three phases through a small aperture under high pressure.

The method used in practice on very rare occasions will usually be that of the pestle and mortar. This will produce only medium grade emulsions with a globule size of from 5·0–20·0 μ, whereas a homogenizer will reduce this to less than 2·0 μ. *Internally administered* emulsions will usually contain acacia if prepared in practice. There are two ways in which they can be prepared, a primary emulsion being made first in both cases. The first is the *dry gum* method in which the oil is placed in a mortar and the dry gum lightly and quickly stirred into the oil, followed quickly by the water, vigorous trituration continuing until the emulsion is complete. The second is the *wet gum* method in which a mucilage is first prepared with water and gum, and the oil triturated into the mucilage a few drops at a time.

The dry gum method is rapid but produces a less elegant and less stable emulsion.

To form these *primary emulsions* acacia, water, and oil must be used in proportions which may vary only slightly. These proportions differ according to the viscosity of the oil, for the lower the oil viscosity the higher must be the proportion of gum, and also water, for these last two remain in a permanent ratio of 1 : 2. In some cases better emulsions may be obtained by increasing the viscosity of the water and gum mixture by adding tragacanth, methyl cellulose, or sodium alginate. The proportions of the three phases are:

	Oil	Water	Emulgent (Gum)
Fixed and mineral oils	4	2	1
Volatile oils	4	4	2

With the oleoresin type of oil—turpentine—more acacia is needed, equal parts of oil and gum being used.

If mucilage of acacia is used in the wet gum method, allowance must

be made for the waters contained in the mucilage, and the quantities become:

	Oil	Water	Emulgent (Mucilage)
Fixed and mineral oils	4	¼	2
Volatile oils	4	1	4
Oleoresins	4	2	8

If emulgents other than acacia are used the proportions of the three phases will depend on the emulsifying properties of each emulgent. A guide to these different proportions will be found in the *Pharmaceutical Pocket Book*, published by The Pharmaceutical Society.

It is essential when preparing emulsions that all utensils be spotlessly clean and uncontaminated, for emulsions will 'crack' (break down) very easily if either dirt or chemical contamination is present, especially if volatile oils are the contaminants.

Once the primary emulsion is made drugs may be added either directly or dissolved in a little of the diluting water. The emulsions can then be made up to volume.

Externally Applied Emulsions. These are liniments and are usually prepared in veterinary medicine using soaps as emulgents. These soaps may be used as such or made in the process of emulsification.

The method normally used is the so called 'bottle method', when the ingredients are put into the bottle which is then shaken until emulsification occurs.

The commonest liniment prepared is 'white liniment' or 'ammonia and turpentine liniment,' containing turpentine, ammonium carbonate, ammonia, or ammonium chloride, soap and water. The soap may be hard soap or soft soap but the proportions vary according to which is used, for 15 gr. (1·0 G.) of hard soap, or ½ oz. (15·0 G.) of soft soap, are required to emulsify 1 fl. oz. (30·0 ml.) of a volatile oil or 2 fl. oz. (60·0 ml.) of a fixed oil.

In the liniment mentioned, the oil is poured into a clean cold bottle; the soap is dissolved in water on a warm bath, cooled, poured into the oil, and shaken to mix; the ammonium carbonate in solution is then added and the mixture rocked until the creamy white emulsion forms. Vigorous shaking is unnecessary and, if the emulsion does not form immediately, standing on the bench for a few minutes followed by a gentle rocking will usually achieve the required effect. The volume can then be made up with water.

Emulsions may be prepared by this method on a small scale, or whole winchesters may be prepared at a time.

A typical formula is

℞	Ammonium carbonate	120 gr. (8·0 G.)
	Turpentine oil	1 fl. oz. (30·0 ml.)
	Soft soap (Green)	½ oz. (15·0 G.)
	Water to	8 fl. oz. (240·0 ml.)

In what has been called the *alkaline method* of making liniments, the soap is made first by adding caustic potash to, say, rape oil in the ratio of 1 fl. oz. (30·0 ml.) of oil to ½ fl. oz. (15·0 ml.) potassium hydroxide solution (5 per cent. KOH). This is shaken up and the oils added—approximately 2 fl. oz. (60·0 ml.) of a volatile and 4 fl. oz. (120·0 ml.) of a fixed oil. This is shaken well to form an emulsion and the other drugs added in solution; the whole is then made up to volume after a further shake; shake again and the liniment is complete.

When eggs are used—not a common practice for veterinary liniments—½ fl. oz. (15·0 ml.) of egg yolk will emulsify about 2 fl. oz. of a volatile oil and 4 fl. oz. of a fixed oil (60·0 and 120·0 ml. respectively). One egg yolk is about ½ fl. oz. in volume. To make the liniment, it is usual to triturate the yolk in the mortar, triturate the oil into it and then add the aqueous solutions of the solid constituents in small quantities, triturating continuously. This type of emulsion is stable over a far wider range of pH than other types of emulsion, and acetic acid is often added with the intention of neutralizing any excess caustic used in making the soap.

Stability of emulsions depends on a number of factors which vary according to the emulgent used. The effect of pH on emulsions has been investigated, but without a great deal of information being produced. However, egg yolk emulsions, as already stated, will withstand the addition of relatively high proportions of acid: tragacanth emulsions are most stable at pH 2, whilst acacia emulsions are stable over a range of pH 2–10. The lack of 'creaming' or separation of a supernatant from concentrated emulsions is related to the size of the globule, and for this reason the mechanically prepared emulsions are the most permanent. Complete 'cracking' may be produced by the addition of electrolytes or alcohols. These two types of compounds should therefore be avoided in emulsion making.

Dispensing Pills. Pills are never made in practice now, and the procedure is only of historical interest. The essentials of the procedure consist of pressing the excipient, or binding substances, into the solid drugs in the shallow end of a pill mortar after the solids have first been prepared by trituration and mixing in the deep end of the mortar. The amount of excipient must be very small and can only be gauged with experience; too much will prevent correct rolling, with the pills sticking together, whilst too little will make the pills crack during rolling. When all the excipient has been thoroughly dispersed throughout the powder the mass is rolled into a sphere by hand and transferred to a cutting machine platform. The sphere is then rolled with the back of the cutter, any tendency to stick being prevented by dusting both platform and roller with an inert powder. When the cylinder is long enough to cover the requisite number of flutings on the cutter, it is transferred to the cutter flutings of the platform, the cutter placed over it and tapped down sharply. This cuts the pill cylinder into cachets (small pillow-like masses) which are returned to the

machine platform and rolled together with a wooden, flat cup roller. Pills for coating may then be transferred to a coating machine.

Dispensing Horse Balls. This procedure is also becoming more of historical than practical interest. Horse balls may be prepared either by: 1. A *fusion* method in which fats or resins are melted and other solid ingredients added just before the mass solidifies. Whilst still malleable the mass is rolled into cylinders of $\frac{1}{2}$–$\frac{3}{4}$" diameter and chopped into lengths of about 3 inches. Any tendency of the mass to stick to the ointment slab or spatulæ being avoided by dusting both with an inactive powder: 2. A *trituration* or *levigation* method similar to the preparation of ointments, (*q.v.*).

Horse balls containing aloes are usually prepared by the first method, whilst the once common tonic ball containing ammonium carbonate and powdered nux vomica is prepared by the second method.

When the cylinders have been made they should be wrapped first in grease-proof paper and then in an outer wrapping paper. Only the outer paper is removed before administration.

Horse balls are *wrapped* in a special way. The paper is cut to size allowing twice $\frac{2}{3}$rds the diameter plus the length of the cylinder and approximately twice round. The paper is then folded over at one end and placed on the bench with the fold underneath and away from the dispenser. The ball is then rolled in the paper beginning at the nearest edge and rolling away; this brings the fold on the outside. The ends are then turned in. This type of wrapping is suitable for both internal and external wrapping.

CHAPTER 40

LEGAL OBLIGATIONS

THERE are certain Acts of Parliament which are expressly designed to control the purchase, sale and use of medicines. Those of particular interest to veterinary surgeons and practitioners are:

1. The Dangerous Drugs Act, 1951.
2. The Pharmacy and Poisons Act, 1933 and the Pharmacy Act, 1953.
3. The Therapeutic Substances Act 1956, which incorporates and supersedes the Penicillin Act 1947, the Penicillin (Merchant Ships) Act, 1951; the Therapeutic Substances (Prevention of Misuse) Act, 1953.
4. Methylated Spirits Regulations, 1952, made under the Customs and Excise Act, 1952.
5. The Protection of Animals (Anæsthetics) Act, 1954.

Of these Acts, and the Orders made under them, by far the most important is the Dangerous Drugs Act, 1951.

Dangerous Drugs Act, 1951

This act consolidates those of 1920 and 1950, and is aimed at preventing the misuse of all drugs which are seriously habit-forming in man. The act is divided into five parts, but it is only Part III which applies to drugs used for medicinal purposes and is therefore of significance to veterinarians.

Part III defines the drugs which are controlled, and regulates the aquisition, storage and usage of those drugs.

The Controlled Drugs

In the Act there are thirty-one different groups of drugs but only those of major importance are listed here:

1. Opium.
2. Morphine and its salts.
3. Diacetyl morphine (diamorphine) and its salts. This is heroin.
4. Cannabis Indica, or Indian Hemp, and its preparations.
5. Cocaine and its salts.
6. Pethidine and its salts.
7. Methadone or Amidone, and its salts.
8. Phenadoxone and its salts.

Also included are many derivatives of these substances. Any compound containing less than 0·2 per cent. anhydrous morphine is excluded from the regulations, and also any compound containing less than 0·1 per cent. cocaine, unless the alkaloids are merely diluted with an inert diluent, when all proportions are controlled. All other drugs are controlled in all concentrations.

Certain exemptions are specified in the Schedules of the Act. These compounds are exempted because they cannot be applied in such a way as to satisfy or create a craving, or because they are formulated with substances which are either obnoxious or have an unpleasant pharmacological action. Opium plaster is an example of the first type of formulation, and Dovers Powder or Powder of Ipecacuanha and Opium, B.Vet.C. is an example of the second type.

The Purchase of Dangerous Drugs

With the exception of the masters of merchant ships, farmers and stock owners (tincture of opium only), midwives and certain other authorized persons, no member of the public can obtain supplies of a Dangerous Drug except on the prescription of a medical practitioner, dentist, veterinary surgeon or a veterinary practitioner. Any prescription issued must conform to strict regulations, and no prescription will be dispensed which does not conform to these requirements.

Prescription Requirements. No pharmacist will dispense the prescription unless the following conditions are met:

1. The prescription must be hand-written and in ink, signed with qualifications, and dated, all in the prescriber's own handwriting. The pharmacist must also be familiar with the signature and satisfied that the prescription is genuine.
2. The address of the prescriber and the name and address of the client must also appear on the prescription.
3. The words 'For Animal Treatment Only' must appear on the prescription.
4. The total amount of the Dangerous Drug(s) to be supplied must be stated.
5. If the prescription is to be dispensed a second or third time the interval between dispensings or specific dates must be stated. If no instructions for repeat dispensings are given the pharmacist will retain and file the prescription. In no case will more than three dispensings be allowed and the prescription will be date stamped on each occasion.
6. There should be no alterations or erasures.

The following prescription will serve as a guide:

A. N. Other, M.R.C.V.S.
12, Cardington Road,
Fanfield, Essex.
12th January, 1958.

℞

Eye-drops of Cocaine, B.Vet.C. 1 fl. oz. (28·4 ml.)

Sig. For Animal Treatment Only.
Instil a few drops into the eyes every four hours.

This prescription contains 8½ gr. (0·57 G.) Cocaine Hydrochloride, B.Vet.C.
Repeat on 19th January, 1958.

A. N. Other, M.R.C.V.S.

A. N. Farmer, Esq.,
Leeds Farm,
Fanfield,
Essex.

Supply for Personal Administration. Dangerous drugs may be purchased by a medical practitioner, dentist, a veterinary surgeon or a veterinary practitioner providing members of these professions 1. supply a signed order or 2. sign the pharmacists Poisons Book. In the event of supplying a signed order this must be given to the pharmacist within 24 hours of the purchase; providing this is duly effected the pharmacist may supply the drugs in response to an urgent request by telephone or telegram. If the goods are dispatched by post the package must be registered.

The signed order must incorporate the details included in the example given below:

12th January 1958.

A. N. Other, M.R.C.V.S.,
12, Cardington Road,
Fanfield, Essex.

Please supply for use in the above veterinary practice:

or Please supply for veterinary use:
Injection of Morphine Sulphate 25·0 ml.
(containing 1 gr. Morphine Sulphate in 2·0 ml.)

A. N. Other, M.R.C.V.S.

This order must be in the veterinary surgeon's or practitioner's own handwriting, which must be familiar to the pharmacist.

Records of Purchase. The *pharmacist* will record the dispensing of prescriptions and signed orders, and will keep the prescription or order for a minimum of two years.

The *veterinary surgeon* or *practitioner* must record his purchases on the day of purchase or on the succeeding day. The record must be made in ink and in a bound book, not a loose-leaf book or card index: this is to prevent the removal or loss of a record sheet. The book used must either be specially reserved for this purpose, or a small section only may be used for Dangerous Drug records. The records must be kept for at least two years subsequent to the last entry and produced for inspection by an authorized person. The details recorded in the following examples must appear.

Date	Name of Supplier	Address	Quantity	Drug & Form	Signature
13/1/58	A. Mann Ltd.	2, Walsall Rd. Fanfield, Essex	25·0 ml.	Morphine Sulphate Injection 1 gr. per 2 ml.	A.N.Other

The signature is not a statutory obligation, but is advisable especially in a large practice where several partners and, or, assistants may be involved in purchases. *No alterations of any description may be made to any entry.* Corrections should be made as a separate entry, cross referenced and signed. It is advisable to keep a separate section for each class of Dangerous Drug. This book must be kept for a minimum of two years after the date of the last entry.

Storage of Dangerous Drugs

Subsequent to purchase, all Dangerous Drugs must be kept in a locked, immovable cupboard or drawer except when in use. This storage place must be kept locked and the key must be available only to authorized people. It is advisable—not essential—that if the store is a cupboard the front should be wood or metal, not glass, so that temptation may be less and illegal access more difficult.

The Use of Dangerous Drugs

Veterinarians may dispose of the Dangerous Drugs he purchases either by dispensing them to clients for the treatment of animals, or by administering them himself directly to animals in his care.

In the first eventuality he is obliged by the Act to record the necessary details either on the same day, or within 24 hours subsequently, in a book kept for that purpose, but not necessarily for that purpose alone. The day book or case book is quite suitable but should be kept for the

statutory two years after the last D.D.A. entry. The details required are those necessary to trace and confirm the dispensing of the Dangerous Drug: they will consist of the date, the name and address of the client, the details of the animal (dog, cat, horse etc.) and its complaint, and finally the amount of the drug and the form in which it was supplied.

Date	Client	Address	Animal	Complaint	Quantity	Drug & Form
20/1/58	C. Sawyer	12 Ross Way Fanfield	10 years old fox-terrier Male	Teeth extraction	5·0 mg. tablets	Methadone hydrochloride 6 tablets

This type of entry is normal for all day book entries and should such a record be made the requirements of the Act are met.

In the second eventuality a peculiar anomaly in the Act allows the veterinarian to use any quantity of a Dangerous Drug personally, or have it given under his personal supervision, without making any record. The medical practitioner and dentist are not so exempt. In spite of this omission it is advisable to record all usage of these drugs so that should trouble arise the whole of the incoming and outgoing stock of Dangerous Drugs can be satisfactorily accounted for. There can then be no argument.

The Pharmacy and Poisons Act, 1933
The Pharmacy Act, 1953

These two acts and the regulations made under them aim at preventing the access of unauthorized persons to dangerous poisons as distinct from habit-forming drugs, and to prevent intentional or accidental misuse of such drugs.

The Acts and Regulations define the drugs involved and the degree of restriction placed on their sale. The list of controlled drugs are divided into Schedules of which Schedules I and IV are the most important and to which the most stringent restrictions apply.

The veterinary surgeon or practitioner may obtain these drugs on the authority of a signed order or by signing the pharmacist's Poisons Book. The general public require a prescription in order to obtain substances in schedule IV, but may obtain substances in Schedule I, other than those controlled by the Dangerous Drugs Act or Schedule IV, by complying with certain regulations concerning identity and genuineness of requirements. Any prescription must comply with the general form indicated for the prescribing of Dangerous Drugs but Schedule IV poisons will only be supplied once unless repetitions are indicated: there are no restrictions on the number of repeats which can be specified.

Other requirements are mainly of concern to a pharmacist but some of the labelling requirements apply to poisons dispensed by veterinarians. In general when a poison is dispensed, those for external use should be in fluted bottles for identification by touch, and all should be labelled with the dispensers name and address and bear, preferably in red lettering, the word 'Poison'. The phrase 'For Animal Treatment Only' is also advisable but not obligatory. External applications should be labelled with the words 'For External Use Only'.

A record in the day book must incorporate the same details as those required for a Dangerous Drug (*q.v.*) and be entered on the day of dispensing or on the following day.

No restrictions are placed on the storage of these drugs by a veterinarian but it is advisable to keep them in a locked cupboard.

Schedule I contains the alkaloids and the accepted poisons such as arsenic, antimony, cyanides, mercury salts, phosphorus compounds and cantharides, amongst others.

Schedule IV contains the barbiturates, sulphonamides, antihistamines and dinitrocresols, amongst others of less importance in the veterinary field.

The Therapeutic Substances Act, 1956

This Act applies to Great Britain and Northern Ireland and incorporates the provisions of the Penicillin Act, 1947, the Penicillin (Merchant Ships) Act, 1951, and the Therapeutic Substances (Prevention of Misuse) Act, 1953.

Part I of the Act perpetuates the provisions of previous Therapeutic Substances Acts and applies to 'substances, the purity or potency of which cannot be adequately tested by chemical means': this includes sera, vaccines, toxins, antitoxins and antigens, glandular products, 'arsphenamine and analogous substances used for the specific treatment of infective disease'. This part controls the manufacture and importation of the specified drugs and makes provisions for regulations laying down standards for manufacture and sale. There are also regulations for delegating power to enforce these standards, and penalties for non-observance are specified.

Part II of the Act applies to 'penicillin and such other substances as may be prescribed by regulations'. This phrase now applies to all antibiotics. Sections are included which allow the sale of antibiotics to and by medical and, dental practitioners, veterinary surgeons or veterinary practitioners, and precludes sale to members of the public except on the authority of a prescription signed by one of these. Exemptions apply to wholesale dealing, export, hospital staff, the masters of ships sailing without a doctor, educational and research institutions, and government departments: powers are retained to make regulations varying these exemptions and it is under these powers that antibiotics are incorporated in foodstuffs. Administration may only occur under the guidance of one

of the practitioners or surgeons mentioned above or of a ship's master where no medical practitioner is on board. Provision for enforcement by the Pharmaceutical Society and maximum penalties for non-observance are laid down.

Part III deals entirely with the legal and administrative provisions.

The Diseases of Animals (Therapeutic Substances) Order, 1952 under The Diseases of Animals Act 1950(a), and The Foot and Mouth Disease (Sera and Glandular Products) Order, 1939 provide additional details applying specifically to similar sera and vaccines etc. for use in England, Wales and Scotland.

The Methylated Spirit Regulations, 1952

These regulations are designed to prevent the public obtaining and drinking industrial methylated spirits or mineralized methylated spirits either before or after redistillation.

A veterinary surgeon or practitioner may purchase up to four gallons of mineralized methylated spirits and ½ gallon industrial methylated spirits at any one time; the latter may be obtained only on a signed order. If authorized (on a permit issued by a Customs and Excise Officer) up to 4 gallons of industrial methylated spirits may be obtained from a pharmacist, but should more than four gallons be required at one time this must be obtained from a Methylator on authorization from a Customs and Excise Officer.

Industrial methylated spirits may be prescribed but not more than one pint will be dispensed either undiluted, diluted with water, or as an ingredient of some formulation. Any prescription or signed order must conform to the principles applying to prescriptions for poisons and will be retained by the pharmacist for two years. Any prescription or order will be fulfilled only once and that must occur within seven days of the date on the prescription or order.

There are no regulations governing the quantity of methylated spirits kept on veterinary premises except where local bye-laws limit the stocks of inflammable material on such premises. There is also no regulation to prevent a veterinarian obtaining ½ gallon industrial methylated spirits daily from any or every chemist in an area.

The Protection of Animals (Anæsthetics) Act, 1954

This act repeals the Animals (Anæsthetics) Act, 1919, but its provisions are not applicable to N. Ireland.

The main provisions of the Act are that all surgical operations must be carried out with an anæsthetic, but that the type and method of anæsthesia are left to the decision of the veterinary surgeon and not specified, as previously. The Act states that 'the expression 'Animal' shall not include

a fowl, another bird, fish or reptile' and in its Schedule I section (i) lists a number of 'Excepted operations'. These include:

1. Experiments authorized under the Cruelty to Animals Act, 1876.
2. First Aid emergency treatment.
3 and 4. Docking and dew claw removal in puppies before their eyes are open.
5. Castration of a male dog before 3 months of age and a male cat before 6 months.
6. Castration of a male: horse, ass, mule, bull or sheep under 12 months, goats under three months and pigs under 7 months. Power to vary these ages is retained.
7. Any minor operation performed by a veterinarian normally without an anæsthetic because of the speed or painlessness of the operation.
8. Any minor operation which is not customarily performed only by a veterinary surgeon or practitioner.

APPENDIX

LATIN ABBREVIATIONS

āā: *ana*, of each.
a. c.: *ante cibum*, before food.
ad: up to
add.: *adde*, add thou.
ad lib.: *ad libitum*, at pleasure.
admov.: *admove*, apply; admoveatur, let it be applied.
ad us.: *ad usum*, according to custom.
æq.: *æqualis*, equal.
agit.: *agita*, shake; or *agitatus*, having been shaken.
altern. d.: *alterno die*, every other day.
ante: before.
applic.: *applicandus*, to be applied.
aq.: *aqua*, water.
aquam ad—: water up to—.
aq. dest.: *aqua destillata*, distilled water.
aq. ferv.: *aqua fervens*, warm or hot water.
aq. frigid.: *aqua frigida*, cold water.
aq. steril.: *aqua sterila*, sterile water.
bln.: *balneum*, bath.
b. i. d.: *bis in die*, twice daily.
c.: *cum*, with.
cap.: *capiat*, let him take.
circ.: *circa*, around; or *circiter*, about.
coch. amp.: *cochleare amplum*, a tablespoonful.
coch. mag.: *cochleare magnum*, a tablespoonful.
coch. med.: *cochleare medium*, a dessertspoonful.
coch. min.: *cochleare minimum*, a teaspoonful.
coch mod.: *cochleare modicum*, a dessertspoonful.
coch. parv.: *cochleare parvum*, a teaspoonful.
d. in p. æq.: *divide in partes æquales*, divide into equal parts.
det.: *detur*, let it be given.
dieb. altern.: *diebus alternis*, every other day.
div.: *divide*, divide.
dos.: *dosis*, a dose.
et: and
extempl.: *extemplo*, immediately.
ft.: *fiat* (*fiant*), let it (them) be made, e.g.,
ft. mist.: *fiat mistura*, let a mixture be made.
id.: *idem*, the same.
infric.: *infricetur*, let it be rubbed in; *infricandus*, to be rubbed in.
m.: *misce*, mix.
m. d. u.: *more dictu utendus*, use as directed.
m. et n.: *mane et nocte*, morning and night.
mitt.: *mitte*, send.
mor. dict.: *more dicto*, as directed.
non: not.
o. m.: *omni mane*, every morning.
o. n.: *omni nocte*, every night.
p. c.: *post cibum*, after food.
part. æq.: *partes æquales*, equal parts.
parv.: *parvus*, small.
phial. agit.: *phialam agita*, shake the bottle.
post cib.: *post cibum*, after food.
pulv.: *pulvis*, a powder; or *pulverizatus*, powdered.
Q. R.: *quantum rectum*, the correct quantity.
q. s.: *quantum sufficiat*, *quantitas sufficiens*, *quantum satis*, sufficient.
quat.: *quater*, four times.
rep. or repet.: *repetatur*, let it be repeated.
s.: *sine*, without.
si op. sit.: *si opus sit*, if necessary.
sig.: *signetur*, let it be marked (labelled).
solv.: *solve*, dissolve.
stat.: *statim*, immediately.
suff.: *sufficiens*, sufficient.
t. d. s.: *ter die sumendus*, to be taken thrice daily.
t. i. d.: *ter in die*, thrice daily.
trit.: *tritura*, triturate.
ut dict.: *ut dictum*, as directed.
ut supr.: *ut supra*, as above.

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