

(NEW SERIES)

No 41.

SCIENTIFIC MEMOIRS

BY

OFFICERS OF THE MEDICAL AND SANITARY DEPARTMENTS

OF THE

GOVERNMENT OF INDIA

---

QUININE AND ITS SALTS: THEIR SOLUBILITY  
AND ABSORBABILITY

BY

CAPTAIN A. C. MacGILCHRIST, M.A., M.D., M.R.C.P., I.M.S.

*(Edited by the Director General, Indian Medical Service.)*

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ISSUED UNDER THE AUTHORITY OF THE GOVERNMENT OF INDIA  
BY THE SANITARY COMMISSIONER WITH THE GOVERNMENT  
OF INDIA.



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## QUININE AND ITS SALTS: THEIR SOLUBILITY AND ABSORBABILITY.

THE administration of Quinine, although so old and well tried a remedy, is still beset with many difficulties and feelings of uncertainty on the part of the physician regarding the rapidity and certainty of action of a given dose of the alkaloid, by whichever channel that dose is administered. This is due mainly to our want of knowledge regarding the physical, chemical and, in particular, physiologico-chemical peculiarities of Quinine and its salts. The factors influencing the absorption of Quinine from the gastro-intestinal tract have been neglected; and even the relative therapeutic or prophylactic value of the various methods of administration of Quinine is still unsettled.

By many it is assumed that Quinine is absorbed chiefly from the stomach, the intestines taking little or no part in the absorption. Malanin,<sup>1</sup> in 1868, pointed out the insolubility of the compound formed by Quinine and bile acids, and took for granted that, when this alkaloid was administered by the mouth, as much of it as was not absorbed from the stomach became inert on coming in contact with bile in the intestines and was thus eliminated in the fæces. A similar action was ascribed to bile acids by Kerner.<sup>2</sup> Lauder Brunton,<sup>3</sup> on account of the precipitation from a mixture of Quinine and bile acids of this salt, which is sparingly soluble, except in an excess of bile, recommended clearing out the liver by administering an emetic and a cholagogue purgative before giving Quinine in the treatment of malaria. According to Sollmann,<sup>4</sup> Quinine is fairly readily absorbed from the stomach: Giemsa and Schaumann,<sup>5</sup> however, have come to the conclusion that most of the Quinine given by the mouth is absorbed from the small intestine. Marshall<sup>6</sup> states that most of the Quinine passes into the duodenum: and Dixon<sup>7</sup> is of the opinion that after entering the duodenum Quinine is under ordinary circumstances absorbed rapidly; but, if there is excess of alkali in the duodenum, Quinine is precipitated, forming with the bile acids insoluble salts which are passed unchanged in the fæces.

When there is so little agreement regarding the fate of Quinine in the gastro-intestinal tract, it is not surprising to find an explanation of the marked variations in the absorption of Quinine—so often encountered in clinical practice, sometimes even in the same individual and when using the same salt of this alkaloid—wanting, and the reason of the efficacy of a preparation like Warburg's tincture still shrouded in mystery. Warburg's tincture has been described as "merely Quinine concealed in a farrago of inert substances." To this description Maclean's (Netley) reply<sup>8</sup> was—"I have never seen a single dose of Quinine given alone to the extent of  $9\frac{1}{2}$  grains sufficient to arrest an



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exacerbation of remittent fever, much less prevent its recurrence; while nothing is more common than to see the same quantity of the alkaloid in Warburg's tincture bring about such results." According to Sollmann<sup>4</sup> the substances—aloes, rhubarb, camphor, gentian and aromatic substances which are combined with the alkaloid in Warburg's tincture, "probably aid in the absorption of the Quinine;" and Cushny<sup>9</sup> states that they promote Quinine absorption by acting on the stomach and that capsicum and piperine have a similar reputation as adjuvants in Quinine treatment. The view expressed in the National Dispensatory<sup>10</sup> is that Quinine absorption is hastened by the previous administration of purgatives, of which a combination of rhubarb and aloes acts best.

Regarding the relative value of the various methods of Quinine administration, it will suffice in these introductory remarks to refer to only two—oral and hypodermic. Most authors of text-books of pharmacology and therapeutics assume that Quinine given by the hypodermic method is rapidly and effectively absorbed. Cushny<sup>9</sup> recommends this mode of administration in cases of emergency; Sollmann<sup>4</sup> states that by hypodermic injections, deep into the gluteal muscles, rapid action is secured; Binz<sup>11</sup> is of the opinion that absorption is thorough and quick. Many clinicians have expressed similar views. Recent experiments and clinical observations, however, have cast doubt upon the orthodox belief that hypodermic injections of Quinine, as of other medicinal agents, mean more rapid and more concentrated action than is possible with administration by the mouth. In Italy and Germany attempts have been made to solve this problem by laboratory methods. Kleine,<sup>12</sup> on finding a smaller percentage of Quinine eliminated in the urine when the alkaloid was injected subcutaneously than when given by the mouth, came to the conclusion that absorption was less in the former instance and that the hypodermic method was therefore of less therapeutic value than the oral. Mariani<sup>13</sup> made an intramuscular injection into the leg of a rabbit, with a solution of .201 gramme of the bi-hydrochloride of Quinine in one cubic centimetre of water, and from the muscle of the rabbit which was killed seventeen hours after the injection he recovered .1 gramme of anhydrous Quinine or 66.5 *per cent.* of the amount injected. The results of Giemsa and Schaumann<sup>5</sup> agree with those of Kleine:<sup>12</sup> they found that after oral administration the amount of Quinine eliminated in the urine was 38.5 *per cent.* of the dose administered and that after hypodermic injection the amount eliminated was only 19.2 *per cent.*; but they regard this difference in the elimination of Quinine as due not to less absorption, but to a greater destruction of Quinine in the body when administered by hypodermic injection than when given by the mouth. From the clinical aspect, the subject has been investigated principally in India. Smythe<sup>14</sup> states that Quinine injected hypodermically is slowly absorbed and is eliminated in the

urine for many weeks after administration ; and that 20 grains injected into the flanks will protect an individual from malaria for the following month at least. According to Megaw<sup>15</sup> the temperature of patients suffering from malaria takes about twelve hours longer in coming to normal when treatment is by hypodermic injections (bi-hydrochloride of Quinine in doses of 10 grains) than when Quinine is given by the mouth, and consequently that absorption is slower from the subcutaneous connective tissue than from the mucous membrane of the stomach. Scott<sup>13</sup> regards the hypodermic method (intramuscular) as of no special value in the treatment of acute cases of malarial fever, owing to slowness of absorption ; but he considers this method particularly useful as a preventive of frequently recurring attacks of ague.

The authors of the National Dispensary<sup>10</sup> acknowledge that the tendency of hypodermic injections to produce " pain, inflammation, gangrene and even fatal tetanus more than counterbalances the advantages of facility of administration and promptness of effect " and recommend that this method of administration should be restricted to cases in which delay would be dangerous. The importance of determining whether or not this " promptness of effect " is really obtained by the hypodermic method is obvious.

In an endeavour to throw some light on these debated points regarding the absorption of Quinine, this work has been undertaken. The alkaloid and its salts employed in the various experiments were obtained direct from Merck (Darmstadt) and therefore in unopened bottles.

### Peculiarities of Quinine and its Salts.

Unfortunately, as the composition of many of the salts of Quinine varies with different manufacturers and as the details (temperature, *etc.*) regarding the conditions under which the results given by various analytical chemists have been obtained are not always given, there is much uncertainty regarding the chemical properties, *e.g.*, solubility, of some of these compounds. As those used in my investigations were obtained from Merck, I have, whenever possible, followed his analyses<sup>17</sup> in the following table:—

Table 1.

Quinine preparations.	Percentage of anhydrous Quinine base.	Solubility of 1 part in parts of cold water.	Reaction of solution.	REMARKS.
Q. bi-hydrochloride .	74.8	66	Faintly acid	Recommended for hypodermic injection.
Q. bi-sulphate . .	58.12	10	ditto	Originally called "neutral sulphate."

Table I—*contd.*

Quinine preparations.	Percentage of anhydrous Quinine base.	Solubility of 1 part in parts of cold water.	Reaction of solution.	REMARKS.
Q. bi-hydrobromide .	60.0	7	Faintly acid	Recommended for hypodermic injection.
Q. urea (carbamide) .	70.0	1	ditto	Recommended for hypodermic injection.
Q. hydrochloride .	81.7	37	Neutral	
Q. sulphate . . .	72.8	800	ditto	
Q. lactate . . . .	75.0	10	ditto	Recommended for hypodermic injection.
Q. hydrobromide . .	76.6	45	ditto	Recommended for hypodermic injection.
Q. cacodylate . . .	62.0	under 10	ditto	
Q. phosphate . . .	76.5	784	ditto	Acicular crystals like the sulphate but harder and denser.
Q. quinate . . . .	58.7	under 10	ditto	Recommended for hypodermic injection.
Q. acetate . . . .	84.3	over 2,000	ditto	
Q. carbonate . . .	80.2	over 2,000	ditto	
Q. tartrate . . . .	79.4	1,000	ditto	
Q. tannate . . . .	31.0	over 2,000	ditto	Composition stated to be very variable.
Q. salicylate . . .	68.8	2,30	ditto	
Q. arsenate (basic) .	68.0	over 2,000	ditto	
Q. arsenite . . . .	85.0	over 2,000	ditto	
Q. valerianate . . .	75.8	100	ditto	
Q. benzoate . . . .	72.6	373	ditto	
Q. formate (basic) .	87.5	under 20	ditto	Recommended for hypodermic injection.
Q. alkaloid . . . .	85.7	1,670	Feebly basic	

Practically all of these Quinine preparations require to be kept in well stoppered bottles, because of the readiness with which they part with water of crystallisation or take up moisture from the atmosphere. They also require

to be protected from heat and light. At a low temperature, they keep indefinitely: exposed to heat, they are liable to lose water of crystallisation and to become decomposed. Exposed to sunlight they acquire—whether in the solid form or in solution—a yellowish or brown colour. Flückiger<sup>18</sup> named this brown product “quiniretin” and found it had the same composition as Quinine, but was destitute of its alkaline re-action; and, although soluble in acids, it could not neutralise them. Heat seems to accelerate this change in Quinine; and boiling, whether for purposes of sterilization or of hastening solution, produces this change in some of these Quinine preparations in a few minutes. Quinine hydrochloride, besides being much more soluble than Quinine sulphate, contains a larger proportion of Quinine base and is much less irritating to mucous surfaces (stomach and rectum): its solutions are less likely to become mouldy, but are said<sup>10</sup> to be much less stable than those of the sulphate.

Besides deterioration due to exposure to heat and light, solutions of Quinine salts are prone to become infected with moulds. In the literature on the subject solutions of Quinine sulphate alone are spoken of in this connection. According to Marshall,<sup>6</sup> “Quinine in general is fatal to moulds, but on standing exposed to the air solutions of Quinine sulphate quickly become infected with the common *Penicillium*, which grows rapidly.” Solutions of the various Quinine salts were kept in stoppered tube-bottles in the laboratory (Edinburgh University) for over three months, the bottles being opened and examined periodically. The sulphate solutions were the most liable to mould infection. The solution of Quinine sulphate with tartaric acid became infected very quickly and showed luxuriant mould growths under two weeks. Flavouring agents, such as syrupus aurantii, still further favour the growth of moulds, especially *Penicillium glaucum*. In these experiments the growth of moulds was not limited to the solution of Quinine sulphate and the genus of fungus was not confined to *Penicillium*. In luxuriance of mould growth, solutions of Quinine quinate and Quinine bi-hydrobromide ranked next to those of the sulphate. Growths were also present, but scanty, in solutions of bi-hydrochloride, bi-sulphate, urea bi-hydrochloride, lactate and arsenite. The genus *Mucor*, as judged from zygosporangium formation, was present in one or two instances, but the *Perisporiaceæ* predominated. Both genera, *Aspergillus* and *Penicillium* with their respective gonidiophores were in evidence, the former being almost as common as the latter. Perithecia, indicating the less frequent mode of reproduction, were observed in solutions of bi-hydrobromide, lactate and arsenite. It would appear therefore that Quinine is not so inimical to the higher members of fungi as to the lower yeast forms, which are said<sup>6</sup> to be as susceptible as bacteria to its action.

### Compatibility of Quinine Salts with Blood-Serum.

With the object of obtaining some information as to what actually happens when solutions of Quinine salts are injected subcutaneously or enter the blood stream, the behaviour of such solutions with ox blood-serum was investigated *in vitro*.

If .01 gramme of a Quinine salt, *e.g.*, bi-hydrochloride, bi-sulphate, bi-hydrobromide, urea bi-hydrochloride, lactate, *etc.*, is added direct in the form of a powder to one cubic centimetre of ox blood-serum in a test tube, a coarse curdy precipitate takes place. This precipitate, produced by adding one part of Quinine salt to 100 parts of ox blood-serum is not merely precipitated alkaloid, as it is insoluble in excess of serum.

As no further progress could be made by adding the dry Quinine salts to the serum, solutions of various strengths of the Quinine salts were prepared and the effects produced by adding one cubic centimetre of these solutions to one cubic centimetre of ox blood serum observed. The following table gives the results, one cubic centimetre of Quinine salt solution being in each instance mixed with one cubic centimetre of blood-serum. The upper line opposite each salt indicates the results got immediately on mixing Quinine salt solution with serum; the lower line the effects produced after standing 24 hours:—



Curdy precipitate produced by adding a Quinine salt in powder form to ox blood-serum.

Table II.

Chief Quinine salts used for hypodermic injection.	DILUTION OF QUININE SALT SOLUTION.				
	1-2.	1-10.	1-50.	1-100.	1-200.
Q. bi-hydrochloride.	Gray syrupy liquid.	Precipitate	Precipitate	Faint haze	No change.
	Gelatinous mass	Gelatinous mass	Deposit	Faint deposit	Haze.
Q. bi-sulphate		Precipitate	Haze	Faint haze	No change.
		Deposit	Deposit	No deposit	Mere cloudiness.

Table II—*contd.*

Chief Quinine salts used for hypodermic injection.	DILUTION OF QUININE SALT SOLUTION.				
	1-2.	1-10.	1-50.	1-100.	1-200.
Q. bi-hydrobromide.		Precipitate .	Precipitate .	Faint haze .	No change.
		Gelatinous mass	Deposit .	Faint deposit .	Haze.
Q. urea (carbamide)	Gray syrupy liquid.	Precipitate .	Precipitate .	Faint haze .	No change.
	Gelatinous mass	Curdy mass .	Deposit .	Faint deposit .	Haze.
Q. hydrochloride . . .			Precipitate .	Faint haze .	No change.
			Deposit .	Faint deposit .	Haze.
Q. lactate . . . . .		Precipitate .	Precipitate .	Faint haze .	No change.
		Deposit .	Deposit .	Faint deposit .	Haze.
Q. hydrobromide . . . .			Precipitate .	Faint haze .	No change.
			Deposit .	Faint deposit .	Haze.
Q. quinate . . . . .		Precipitate .	Precipitate .	Faint haze .	No change.
		Deposit .	Deposit .	No deposit .	Faint haze.
Q. cacodylate . . . . .		Precipitate .	Precipitate .	Faint haze .	No change.
		Deposit .	Deposit .	No deposit .	Faint haze.
Q. formate . . . . .			Precipitate .	Faint haze .	No change.
			Deposit .	Faint deposit .	Haze.

Solutions of Quinine hydrochloride prepared with the addition of antipyrine, urethane or sodium chloride, respectively, as recommended for

hypodermic or intravenous use, were tested in the same way, but they showed no greater compatibility or miscibility with ox blood-serum than did simple solutions of Quinine hydrochloride itself.

Using dilutions of Quinine salts of 1 in 20, the results were the same as under 1 in 50 in above table, only more pronounced, with the exception of Quinine bi-hydrobromide which even in this dilution of 1 in 20 produced a thick semi-solid mass of jelly consistence. This behaviour of the bi-hydrobromide is the more remarkable as it contains a comparatively low percentage of anhydrous Quinine base. The bi-hydrobromide therefore appears to be the least compatible with ox blood-serum.

The above re-actions were carried out at laboratory temperature (12°C.). The effect of incubating the mixture of Quinine salt solution and serum at 37°C. was tested in a few instances and the result was an acceleration of the changes that were seen to occur at laboratory temperature.

Giemsa and Schaumann<sup>5</sup> having observed the behaviour *in vitro* of saturated solutions of some of these salts of Quinine with (1) pig blood-serum and (2) human blood-serum have recorded very similar results.

A series of tubes was next prepared to compare the relative amount of precipitate and deposit formed by adding solutions of the strength of 1 in 80 of each of these Quinine salts to ox blood-serum. Two tubes showed no deposit, but only a flocculent precipitate in suspension—quinat and cacodylate: of the tubes presenting a deposit, the bi-sulphate showed the least deposit and the least opacity of the supernatant fluid. On referring to the table giving the percentage of anhydrous Quinine base in Quinine salts it will be noticed that the quinate, cacodylate and bi-sulphate are exactly those salts which contain the smallest percentage of Quinine base. A second series of tubes were therefore prepared using solutions of the same salts having a strength of 1 of Quinine base in 80. Judging from the amount of deposit and the degree of transparency of the supernatant fluid, the acid salts of Quinine seemed the most compatible with the serum; but the re-actions of the mixtures containing the acid salts were found to be very faintly acid. Of the neutral salts of Quinine there seemed to be slightly greater miscibility with serum on the part of the quinate and cacodylate.

As the salts used for these re-actions have been specially chosen as those generally recommended for subcutaneous injection, the results tabulated strongly suggest an utter unsuitability, especially in the dilutions usually employed, of Quinine salts for hypodermic injection. The three salts most frequently used, bi-hydrochloride, urea bi-hydrochloride and bi-hydrobromide, and in the dilutions most frequently employed produce in a few minutes at body temperature when mixed with ox blood-serum a gelatinous mass.

It was considered desirable to determine whether the Quinine in these mixtures of blood-serum and Quinine salt solutions was present (1) in solution in the supernatant fluid, (2) in the suspended precipitate, or (3) in the deposit.

The tube containing the mixture of blood-serum and Quinine bi-sulphate 1 in 80 was taken and its contents filtered. The clear filtrate gave an intense emerald green colour on the addition of chlorine water and ammonia, so that the filtrate contained Quinine in solution. The deposit was examined next. It was thoroughly washed with water till the washings no longer gave any colour re-action with these reagents, and then treated with weak sulphuric acid. The deposit was not dissolved, but some of the supernatant fluid was placed in a clean test-tube and the reagents, chlorine water and ammonia, added. An intense deep-blue colour resulted. This blue solution was divided between two test-tubes, one of which was heated and the other kept at laboratory temperature. The solution in the tube that was heated turned green in a couple of minutes; the solution in the tube left at laboratory temperature turned green in three days. These results suggest that Quinine was present in the deposit but in an altered form, and probably as an oxidised product.

A quantitative estimation of the Quinine in solution and in suspension was carried out as follows:—

A mixture of serum and Quinine hydrochloride solution was specially prepared by dissolving 1 gramme Quinine hydrochloride in two cubic centimetres of boiling water which on cooling was added to two cubic centimetres of ox blood-serum. After half-an-hour this mixture was filtered through cotton wool with the aid of a water-suction pump. The filtrate was made strongly alkaline with liquor potassæ, when a heavy white precipitate of Quinine alkaloid took place. This milky suspension was then extracted three times with ethyl æther and the æthereal extracts filtered. The æther was evaporated from the filtrate and the residue dissolved in alcohol. The alcoholic solution was then filtered and the filter-paper washed with a little alcohol, the filtrate and washings being received into a weighed porcelain capsule. The alcohol was evaporated on a water-bath and the residue dried at 120° C., when the capsule and residue were weighed. The calculation was as follows:—

Capsule + dried extract	.	.	.	.	.	= 12.484 gm.
Capsule	.	.	.	.	.	= 12.440 „
						<hr/>
∴ dried extract	.	.	.	.	.	= 0.044 gm.

The dried extract is, of course, anhydrous Quinine base. Now, Quinine hydrochloride contains 82 *per cent.* anhydrous base; therefore 0.044 gramme

anhydrous base corresponds with 0.0536 gramme Quinine hydrochloride. It follows therefore that 0.0536 gramme Quinine hydrochloride was in *solution* in the mixture.

Next a similar mixture—1 gramme Quinine hydrochloride dissolved in two cubic centimetres of boiling water which after cooling was added to two cubic centimetres of ox blood-serum—was prepared and allowed to stand till the deposit had settled. The supernatant fluid was pipetted off and (in order to lose as little as possible) the residue was filtered through fine meshed cloth, a thick yellow creamy deposit being left behind on the cloth. The fluid pipetted off and that filtered through the cloth were mixed and made strongly alkaline with liquor potassæ. The resulting suspension was thrice ætherised; the æther extracts filtered; the æther evaporated; the residue dissolved in alcohol; the solution filtered and the filtrate and washings evaporated in a weighed capsule on a water-bath; and the residue, dried at 120° C., weighed—in the manner already described. The results were as follows:—

Capsule + dried extract	.	.	.	.	.	= 12.0435 gm.
Capsule	.	.	.	.	.	= 11.995 „
					<hr style="width: 50%; margin: 0 auto;"/>	
∴ dried extract	.	.	.	.	.	= 0.0485 gm.

Now, 0.0485 gramme anhydrous Quinine base corresponds with 0.0591 gramme Quinine hydrochloride; so that the amount of Quinine hydrochloride in *solution and in suspension* in the mixture amounts to 0.0591 gramme.

It is evident therefore that in such a mixture as that prepared above, out of 1 gramme Quinine hydrochloride contained in it, there was (1) in solution, 0.0536 gramme, (2) in the suspended precipitate, (0.0591—0.0536) gramme, *i.e.*, 0.0055 gramme and (3) in the deposit, (1—0.0591) gramme, *i.e.*, 0.9409 gramme of Quinine hydrochloride respectively. In other words slightly over half the Quinine was in solution and slightly under half was contained in the deposit—probably transformed (oxidised), combined with proteids and therapeutically useless. The importance of this observation in connection with the hypodermic administration of Quinine salts is obvious. In this particular instance the strength of the Quinine salt solution that had been added to the blood-serum was about 1 in 20, which is much more dilute than the solutions generally used for hypodermic injection. It will be evident, on referring to the table giving miscibility of Quinine salt solutions with ox blood-serum, that the greater the dilution of the Quinine salt solution the less is the deposit that forms, and therefore presumably, the greater is the proportion of Quinine in solution until finally in extreme dilution no deposit takes place and all the Quinine is in solution.

The action of Quinine salt solutions on blood-serum reminds one strongly of that of alcohol, which in greater concentration than 33 *per cent.* is quite incompatible with blood-serum but in greater dilution perfectly miscible.

#### Solubility of Quinine Alkaloid in Ox Blood-Serum.

With 25 cubic centimetres of ox blood-serum, fresh and centrifuged, .1 gramme crystalline Quinine alkaloid was shaken up in a flask and incubated at 37° C. for two hours, during which time the flask was frequently shaken. After these two hours, the flask and its contents were allowed to cool at laboratory temperature (12° C.), and then the contents were filtered through cotton wool with the aid of a water-suction pump. The amount of alkaloid in solution in the clear filtrate was determined as follows:—

The filtrate was made distinctly alkaline with liquor potassæ and the resulting suspension thrice shaken up with ethyl æther. The æther extracts were then filtered and the æther evaporated. The residue was dissolved in 60 *per cent.* alcohol and this solution filtered into a weighed porcelain capsule. The filtrate and washings were evaporated on a water-bath, avoiding boiling, and the residue dried at 120° C. and weighed. The following figures were obtained:—

Capsule + dried residue = 12.474 gm.

Capsule = 12.440 „

∴ dried residue = 0.034 gm. (anhydrous Quinine base).

Now, crystalline Quinine alkaloid contains 85.7 *per cent.* anhydrous Quinine base; therefore, 0.034 gramme anhydrous Quinine base corresponds with .0397 gramme crystalline Quinine alkaloid. Thus .0397 gramme crystalline Quinine alkaloid was dissolved in 25 cubic centimetres of ox blood-serum,—*i.e.*, practically 4 parts in 2,500 parts of serum or 1 in 625. Crystalline Quinine alkaloid is therefore nearly three times as soluble in ox blood-serum as in water.

#### Solubility of Quinine Alkaloid in Ox Bile.

Malanin<sup>1</sup> in 1868 demonstrated the insolubility of the compounds formed by the union of Quinine and bile acids and assumed from this that the intestines took little or no part in the absorption of Quinine. A similar action was attributed to bile acids by Kerner.<sup>2</sup> Lauder Brunton,<sup>3</sup> while acknowledging the sparingly soluble character of the precipitate obtained by adding Quinine to bile acids, refers to its solubility in an excess of bile. The opinion expressed by Dixon<sup>7</sup> is that after entering the duodenum Quinine is under ordinary circumstances absorbed rapidly; but if there is excess of alkali in the duodenum Quinine is precipitated, forming with the bile acids insoluble salts which are passed unchanged in the fæces. It is, however, pointed out by

Marshall<sup>6</sup> that the precipitate of Quinine glycocholate which is obtained by adding a solution of Quinine to bile, although very insoluble, is easily decomposed by carbonic acid and alkaline carbonates, and under ordinary circumstances probably plays little part in the absorption of Quinine.

The solubility of crystalline Quinine alkaloid in fresh ox bile was determined by me in the following manner:—

With 15 cubic centimetres of fresh ox bile (the re-action of which tested with red litmus paper, was faintly alkaline) .2 gramme crystalline Quinine alkaloid was shaken up in a flask. To ensure small division of the Quinine the alkaloid was first triturated in a test-tube with a little of the bile by means of a glass rod. The flask after being well shaken was incubated at 37°C. for three hours, and shaken frequently during this period. The flask and its contents were then cooled at laboratory temperature (12°C.). The contents of the flask were filtered through cotton wool with the aid of a water-suction pump, the residue on the cotton wool being washed with a small amount of cold water and the washings added to the filtrate. The clear filtrate was made distinctly alkaline with liquor potassæ. The resulting suspension was shaken up three times with ethyl æther. The æther extract was filtered and the æther evaporated from the filtrate in a stream of hot air (80°C.). The residue was dissolved in 96 *per cent.* alcohol and this solution filtered. The filtrate and washings were evaporated to dryness on a water-bath. The residue was then dissolved in weak sulphuric acid and the resulting solution filtered, the filter being washed with a little of the sulphuric acid. The filtrate and washings were made distinctly alkaline with liquor potassæ and the resulting emulsion thrice shaken up with æther. The æther extract was filtered into a weighed porcelain capsule and the æther evaporated in a stream of hot air (80°C.). The extract was then further dried at 120°C. and weighed—with the following results:—

Capsule + dried extract = 12.065 gm.

Capsule = 11.996 „

∴ dried extract = 0.069 gm. (anhydrous Quinine base).

As crystalline Quinine alkaloid contains 85.7 *per cent.* anhydrous Quinine base, .069 gramme anhydrous Quinine base corresponds with .082 gramme crystalline Quinine alkaloid. Therefore, 15 cubic centimetres of ox bile dissolved .082 gramme crystalline Quinine alkaloid; *i.e.*, 15,000 cubic centimetres of ox bile can dissolve 82 grammes of crystalline Quinine alkaloid; *i.e.*,

183 cubic centimetres of ox bile can dissolve one gramme crystalline Quinine alkaloid. Crystalline Quinine alkaloid is therefore about nine times as soluble in ox bile as in water. This result differs considerably from that of Giemsa and Schaumann<sup>5</sup> who, using *amorphous* Quinine alkaloid instead of the *crystalline* form used by me, give the amazing solubility of 1 in 83;—*i.e.*, Quinine alkaloid (amorphous) is twenty times as soluble in ox bile as in water. The amorphous form would certainly dissolve more quickly than the crystalline, so the solubility may be under-estimated in my experiments. It is worthy of note also, in this connection, that the Quinine alkaloid that is precipitated on Quinine salts coming in contact with alkali in the duodenum must be of the amorphous variety.

### Absorption of Quinine.

Hitherto, experimenters have taken the amount of Quinine eliminated in the urine as a measure of the amount that has been absorbed and entered the circulation. It is, therefore, necessary to examine the reliability of this gauge.

Until the beginning of the last decade the views held regarding the elimination of Quinine appear to have been quite erroneous; there was a lack of harmony in the results obtained by different investigators not only regarding the proportion of Quinine eliminated but also regarding the chemical characters of the Quinine or its derivatives that were eliminated. According to Kerner<sup>2</sup> and Merkel<sup>19</sup> most of the Quinine was eliminated unchanged in the urine, the remaining part being excreted in the form of transformed products. Personne,<sup>20</sup> however, affirmed that only about half the Quinine administered is eliminated unchanged in the urine and that the other half is destroyed in the body and not excreted as transformed products. Schmitz<sup>21</sup> and also Giemsa and Schaumann<sup>5</sup> have confirmed Personne's observation that only unchanged Quinine is eliminated in the urine; and they maintain that there is no Quinine derivative with alkaloidal characters present in detectable amount in the urine after Quinine administration.

Practically speaking, only traces of Quinine are eliminated by channels other than the kidneys. Mariani<sup>13</sup> was able to detect traces in the milk of nursing mothers and in sweat, in the latter only after the secretion had been concentrated by evaporation. From the bitter taste experienced for a long time after taking Quinine in wafers, Giemsa and Schaumann<sup>5</sup> are of opinion that probably a very little is excreted in saliva. In the fæces, under ordinary circumstances, very little is eliminated: after administration by the mouth, Kerner<sup>2</sup> could find traces only; Merkel<sup>19</sup> could find no Quinine; Kleine,<sup>22</sup> 3 *per cent.* at most; Flamini,<sup>23</sup> using the insoluble tannate of Quinine, 8—15 *per cent.*, Schmitz<sup>21</sup> traces only; and Giemsa and Schaumann,<sup>5</sup> even after the administration of the insoluble alkaloid itself, traces only—amounts so small that they

could not be weighed. So far therefore as elimination by other channels is concerned, Quinine excretion in the urine is quite a feasible gauge of absorption.

Regarding the rate and amount of elimination of Quinine in the urine there is commendable harmony in the results of recent investigators. After medium doses (*e.g.* one gramme) of Quinine administered by the mouth while fasting, the average amount eliminated in the first 24 hours has been given by Kleine<sup>22</sup> as 21.9 *per cent.*, by Mariani<sup>13</sup> as 24.7 *per cent.*, by Flamini<sup>23</sup> as 24.6 *per cent.*, by Schmitz<sup>21</sup> as 19.5 *per cent.*, and by Giemsa and Schaumann<sup>5</sup> as 25.8 *per cent.*, and under the same conditions the average total elimination (*i.e.*, the amount eliminated during the two or three days Quinine excretion lasted) according to the same authorities is about 40 *per cent.* It would appear therefore that under these circumstances about 60 *per cent.* of Quinine is destroyed in the body. That the amount of Quinine eliminated in the urine should vary, as a rule, between fairly narrow limits when the mode of administration and other conditions are similar is what one would expect. But even, under such conditions, Giemsa and Schaumann,<sup>5</sup> who regard the amount of Quinine elimination in the urine as the best practical measure of the amount absorbed, acknowledge that in particular individuals there are considerable variations from the normal, and that even in the same individual there might be striking variations on different days even when examination of the *fæces* showed that absorption was similar on all the days. Further, even granting that under similar conditions as regards mode of administration, state of gastro-intestinal tract, *etc.*, the amount of Quinine eliminated in the urine is fairly constant, it cannot be assumed that under altered conditions the relative amounts of Quinine eliminated in the urine will be proportional to the corresponding amounts of Quinine absorbed. To show that such an assumption would be wrong it is only necessary to compare the average amounts of Quinine eliminated in the urine after intravenous administration on the one hand and intramuscular or oral on the other. Mariani<sup>13</sup> gives the following averages:—

Table III.

	Intravenous injection.	Intramuscular injection.	Oral administration (fasting).
1st day . . .	20.54%	18.47%	24.70%
2nd day . . .	6.33%	9.60%	?
3rd day . . .	1.07%	4.91%	?
4th day . . .	—	2.45%	?
TOTAL . . .	27.94%	35.43%	40.88%

These figures show that after intravenous injection less Quinine (totals) is eliminated in the urine than after either intramuscular injection or oral administration. As with intravenous injection there can be no doubt about the Quinine entering the circulation, it is evident that Quinine elimination in the urine cannot be directly proportional to the amount of Quinine that has entered the blood. Further, on referring to the amounts of Quinine eliminated during the first day, it is quite obvious that there is no direct relationship between the amount of Quinine that has entered the circulation and the amount that has been excreted: if it be said that elimination varies directly with absorption, then more Quinine entered the blood after oral administration than after intravenous; if it be said that elimination varies inversely with absorption, then more Quinine entered the blood after intramuscular injection than after intravenous.

In reality, the amount of Quinine absorbed must be equal to the amount of Quinine eliminated in the urine *plus* the amount that has undergone cleavage in the body. The determination of the amount of Quinine eliminated in the urine cannot possibly give us any idea of the amount absorbed unless we are able to determine at the same time the amount that has undergone cleavage or to satisfy ourselves that the amount that has undergone cleavage is constant. Under different conditions of Quinine administration, each of these three factors varies; and as there is no means of estimating the amount of Quinine that has undergone cleavage in the body the amount of Quinine eliminated in the urine is quite fallacious as a universal gauge of the amount of Quinine that has entered the circulation.

There is, however, another method, namely, that of determining the minimum-lethal dose—which hitherto seems to have escaped notice—which is capable of giving us a rough estimate of the amount of absorption, especially when comparing different methods of administration of Quinine. The toxicity or lethality of a substance must be proportional to the *rapidity* and *thoroughness* of its absorption, no matter by what channel or under what conditions the substance is administered. And, as in calculating the minimum-lethal dose, death must occur within twenty-four hours, *rapidity* may be taken as a constant, so lethality varies directly with thoroughness of absorption.

### Oral Administration.

As already noted, many assume without any definite proof that Quinine is absorbed chiefly from the stomach. In their opinion Quinine, in whatever form administered, is converted to some extent into the soluble hydrochlorides

in the stomach, and almost all the Quinine that passes into the duodenum is immediately and permanently rendered inert by the bile acids and alkaline fluids, the alkaloid precipitated by the alkaline juices being very insoluble in water.

For determining the seat of absorption, the following points have to be considered:—(1) the time interval between administration and the first appearance of Quinine in the urine; (2) the period of maximal elimination in the urine; (3) the period during which subjective symptoms, *e.g.* tinnitus, are at their worst; and (4) the period of manifestation of symptoms in cases of poisoning (suicidal in man and experimental in animals).

As regards the stomach, it must be conceded that Quinine is very soluble in gastric juice; but gastric juice is likely to be present in a stomach only during digestion, when little of it can be spared for Quinine. In fact, recent investigators are in harmony regarding the retardation of Quinine absorption when administered with or soon after a meal. According to Mariani,<sup>13</sup> the maximal elimination of Quinine, given while food is in the stomach, takes place between the sixth and twelfth hours after administration; but, given when no food is in the stomach, between the third and sixth hours. As food does not, under normal circumstances, remain in the stomach more than five hours, it follows that most of the Quinine given with food is absorbed from the small intestine. Subjective symptoms moreover, just like the maximal elimination of Quinine in the urine, are at their height between the third and sixth hours when Quinine is given while fasting and between the sixth and twelfth hours when given with a meal. That some absorption may take place from the stomach cannot be denied, for the following reasons, but such absorption is probably very insignificant. Kerner<sup>2</sup> found traces of Quinine in the urine 15 minutes after administering Quinine hydrochloride by the mouth; Lewin<sup>24</sup> has confirmed this, giving the time as 13 to 17 minutes; Giemsa and Schaumann<sup>5</sup> found traces in the urine 25 to 30 minutes after giving the sparingly soluble Quinine alkaloid by the mouth.

In the small intestine, the alkaline secretions of the liver, pancreas and intestine itself in all probability precipitate the alkaloid. Reference has previously been made to the insolubility of Quinine glycocholate, and Lauder Brunton's<sup>3</sup> advice to clear out the liver by administering an emetic and a cholagogue purgative before giving Quinine. That such measures as Lauder Brunton recommends are useful in enhancing the therapeutic value of Quinine in obstinate cases of malarial fever is well recognised by experienced physicians. This beneficial result, however, is probably obtained, not by preventing bile from coming in contact with the Quinine, but by actually favouring contact of as much bile as possible with the Quinine. It has been shown above that, accord-

ing to my calculation, Quinine alkaloid is about nine times as soluble in ox bile as in water, and according to that of Giemsa and Schaumann<sup>5</sup> about twenty times. Further, the glycocholate of Quinine is soluble in excess of bile and is easily decomposed by carbon dioxide and alkaline carbonates. Lastly, as pointed out by Kerner,<sup>2</sup> Quinine salts are much more soluble in aerated than in ordinary water, and carbon dioxide is possibly of importance in the process of absorption of Quinine from the intestine.

From the large intestine probably little Quinine is absorbed. The results of recent workers show a great falling off in the amount of Quinine eliminated subsequent to a period of twelve hours after administration. Peristalsis, moreover, being less active and the contents of the bowel having acquired greater consistence, there is less contact between alkaloid and mucous membrane. Lastly, the elimination of Quinine after administration in the form of an enema is relatively small. Kleine<sup>12</sup> after administering two grammes of Quinine hydrochloride in 100 cubic centimetres of water as an enema found only 17.55 *per cent.* eliminated in the urine in the first 24 hours, as compared with 25 *per cent.* in the same period when the same salt in the same dose was administered by the mouth.

Kobert<sup>25</sup> relates a case of suicide on the part of a schoolmistress who swallowed four drachms of Quinine followed by the juice of two lemons. Unfortunately, the interval of time between her last meal and her taking the Quinine is not mentioned; but the periods at which the different toxic symptoms appeared are interesting from two points of view. In the first place, the minimum lethal dose for man being about four drachms,<sup>25</sup> the correspondence between the periods at which the various symptoms in this case of suicide and in the minimum-lethal dose experiments in guinea-pigs is striking: secondly, if in the case of suicide the stomach was empty at the time of swallowing the Quinine, then absorption was chiefly from the small intestine. The minimum-lethal dose experiments were carried out for testing the relative absorption after oral and hypodermic administration and not for determining the seat of absorption of Quinine. For the latter purpose such experiments are of limited value until it is known how long food usually remains in the guinea-pig's stomach. But this much can confidently be said—that the Quinine could not have reached beyond the small intestine when toxic symptoms were fully developed. Two series of feeding experiments were carried out with guinea-pigs, (1) after fasting 24 hours, and (2) immediately after food. The guinea-pigs were fed by passing the Quinine solution (Quinine bi-hydrochloride 1 in 30) through a No. 3 gum male catheter into the stomach. As gravity was insufficient to pass the solution into the stomach, a Record syringe was used instead of a reservoir to hold the solution and

force it through the catheter into the stomach. The sequence of events is given in the accompanying table alongside that in the case of suicide—

Table IV.

Time after ingestion.	GUINEA-PIGS, MINIMUM-LETHAL OR SUB-LETHAL DOSE OF QUININE BI-HYDROCHLORIDE 1-30 BY MOUTH.		Case of suicide. Quinine 4 drachms + 2 lemons swallowed.
	After meal.	Fasting (24 hours).	
2½ hrs.	...	Giddiness (unsteadiness).	Giddiness and pallor.
3 "	Giddiness (unsteadiness).	.....	.....
3½ "	...	Twitchings	.....
4 "	Twitchings	.....	Unconsciousness and convulsions.
4½ "	...	Convulsions	Convulsions.
6 "	...	Convulsions	Convulsions and death.
6½ "	Convulsions	Death if lethal dose; signs of recovery if sub-lethal.	

There is therefore reason to believe that, under ordinary circumstances, most of the Quinine administered by the mouth is absorbed from the small intestine; a small amount possibly from the stomach, especially if administered while fasting and in the form of a salt easily soluble in water; and also a relatively small amount from the large intestine. As already mentioned, the absorption of Quinine is normally very complete, very little being passed with the faeces after medium doses.

#### FACTORS INFLUENCING ABSORPTION FROM THE GASTRO-INTESTINAL TRACT.

1. *Food contents of the gastro-intestinal tract.*—There seems no doubt that, if Quinine is administered with or soon after a meal, absorption and elimination are retarded (Kleine,<sup>22</sup> Mariani,<sup>13</sup> Giemsa and Schaumann<sup>5</sup>). When administered with a meal, Giemsa and Schaumann found traces of Quinine in the urine only after two hours; when given fasting, they could detect traces in 20 to 30 minutes. Regarding total Quinine elimination see under (4) below.

2. *Affections of the gastro-intestinal tract.*—The frequency with which purgatives (not necessarily cholagogue) are administered before Quinine is evidence that experience has taught physicians that a sluggish or loaded bowel is not favourable to Quinine absorption. Marshall<sup>6</sup> reports that in diseased conditions of the heart or kidney absorption is delayed: this no doubt is due

to a catarrhal condition or chronic venous congestion of the gastro-intestinal tract and liver.

3. *Affections of the liver.*—The probable adjuvant action of bile in Quinine absorption has already been discussed. Carrive<sup>26</sup> has reported a case of hepatic insufficiency in malaria (diagnosed by blood examination), and supposed to be due to malaria, in which there was complete cessation of bile secretion and diminished liver dulness. Under such circumstances Quinine by the mouth would probably have very little therapeutic effect.

4. *The solubility of the Quinine salt employed.*—Mariani,<sup>13</sup> who has made a thorough investigation of the effects on elimination of Quinine of the solubility of the salt administered and of the food contents of the gastro-intestinal tract, came to the conclusions that the total Quinine elimination is greater after administering insoluble than after administering easily soluble salts; and that the total Quinine elimination is also greater when Quinine is administered with a meal than when fasting. Giemsa and Schaumann,<sup>5</sup> using Quinine hydrochloride and Quinine alkaloid, likewise conclude from the urine analyses that the less soluble preparations of Quinine are at least as energetically absorbed from the gastro-intestinal tract as are Quinine salts easily soluble in water.

As it seemed reasonable to doubt the validity of inferring more energetic absorption from the fact of the total Quinine elimination being greater, I determined the minimum-lethal dose of Quinine bi-hydrochloride for guinea-pigs (1) after fasting 24 hours and (2) immediately after food.

Table V.

MINIMUM-LETHAL DOSE OF QUININE BI-HYDROCHLORIDE FOR GUINEA-PIGS  
BY ORAL ADMINISTRATION.

*A.—After fasting 24 hours.*

Weight of animal in grammes.	Actual dose in grammes.	Dose per kilogramme of animal weight in grammes.	Result.
550	0.165	0.3	Recovery. Distinct effects.
620	0.217	0.35	Recovery. Distinct effects.
510	0.204	0.4	Recovery. Very severe effects.
610	0.244	0.4	Recovery. Very severe effects.
600	0.240	0.4	Died in 6--7½ hrs.
470	0.2115	0.45	Died in 8 hrs.
520	0.234	0.45	Died in 6 hrs.
500	0.25	0.5	Died in 2½ hrs.

*B.—Immediately after food.*

Weight of animal in grammes.	Actual dose in grammes.	Dose per kilogramme of animal weight in grammes.	Result.
630	0.252	0.4	Recovery. Slight effects.
630	0.2835	0.45	Recovery. Slight effects.
660	0.295	0.45	Died in 11 hrs.
500	0.25	0.5	Died in 6½ hrs.
500	0.25	0.5	Died in 6—7 hrs.

The minimum-lethal dose per kilogramme when Quinine is given with food is larger (about .5 gramme) than when given after a fast of 24 hours (about .45 gramme). We must conclude, therefore, that, so far at least as guinea-pigs are concerned, absorption is more energetic when the animal is fasting. The same most probably holds for man, the reason for the greater total elimination of Quinine in the urine when Quinine is administered with food being a slower and more gradual absorption of Quinine, with a consequent smaller amount of cleavage of the alkaloid. When Quinine is administered during a fast, there is probably an early abrupt and energetic absorption with proportionate cleavage of the alkaloid. Rapid and energetic absorption is most likely best obtained, therefore, by giving a soluble Quinine salt during a fast; a slow, gradual but persistent action by giving insoluble salts of Quinine with meals.

Soluble salts of Quinine, if given in capsules, are apt to form temporarily local concentrated solutions in the stomach and cause gastric discomfort and even serious injury to that organ. It is also worth noting that, where the ordinary salts of Quinine cause gastric irritation, the difficulty may be overcome by administering one of the insoluble salts, *e.g.*, the tannate, which is practically insoluble till it reaches the intestine.

5. *Carbon dioxide (CO<sub>2</sub>)*.—It has been shown by Kerner<sup>2</sup> that Quinine and its salts\* are much more soluble in aerated than in ordinary water. When Quinine sulphate is dissolved in aerated water, no immediate precipitate is produced by adding an equivalent amount of sodium carbonate; and, no precipitate is produced by adding a concentrated Quinine solution to a dilute solution of sodium bicarbonate in aerated water. These results suggested to

\* NOTE.—Water saturated with carbonic acid dissolves Quinine sulphate freely.

Kerner that carbonic acid probably plays an important part in dissolving Quinine, both in the process of absorption and in the blood. The results of his experiments also seem to show that aerated water, swallowed with Quinine or injected with Quinine as an enema, facilitates the absorption of the alkaloid. Further support is given to Kerner's idea of the importance of carbonic acid as a solvent by the following experiment, reported by Wood.<sup>27</sup> The amount of pure Quinine that 1,000 parts of blood defibrinated and deprived of its gases at 36° C. can dissolve is only .398 part, which gives a solubility of about 1 in 25,000. It has been shown above that Quinine alkaloid is soluble 1 part in 625 of ordinary ox blood-serum.

6. *Single large doses of Quinine or the same amount in divided doses in the course of the day.*—Giemsa and Schaumann<sup>5</sup> have shown that, with the daily administration of one gramme of Quinine in one dose, 23.8 per cent. was eliminated daily in the urine; with the daily administration of .2 gramme every two hours till five doses were given, the corresponding figure was 27.8 per cent. From this they conclude that Quinine in divided doses is of greater therapeutic value than in single large doses, as in the former case less Quinine is destroyed in the body. They therefore support the treatment of malaria by fractional doses of Quinine, as recommended by Nocht<sup>28</sup> and Ufer.<sup>29</sup>

With the single large dose the absorption of Quinine for a certain period of time must have been much greater than could occur at any time after administration in divided doses. With the abrupt accentuated absorption from the single large dose, it is reasonable to expect greater cleavage of Quinine by the protective forces of the body, hence the diminished elimination in the urine. Further, there is no reason to suppose that the Quinine which undergoes cleavage is of no therapeutic value before cleavage has occurred; so the inference of Giemsa and Schaumann that greater elimination in the urine connoted greater therapeutic value is unwarranted. With single large doses Quinine absorption is accentuated for certain intervals of time; with the small frequently repeated doses absorption is never accentuated, but continues evenly at a moderate average. The only way to settle the relative therapeutic value of these two methods of administration is by actual clinical results. Nocht seems to have obtained good results by giving four grains of Quinine every two hours, day and night (if awake), but the great majority of physicians have by experience come to rely more on 15 grains three times daily; in the former instance about 48 grains are given daily, in the latter 45 grains. According to Wood,<sup>27</sup> large doses at intervals have been found in practice better than small amounts frequently, and this conclusion is supported by observations made by Councilman<sup>30</sup> that large doses entirely destroy the parasite whereas fractional doses do not.



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Quinine in the form of Warburg's tincture has often been found efficient when Quinine administered in the ordinary way has been unavailing. It will be interesting, therefore, to examine its constitution in an attempt to explain the secret of its efficacy. It is composed of Quinine sulphate with aloes, rhubarb, gentian and aromatics digested with proof spirits. It is recommended that the bowels be first evacuated by any convenient purge.<sup>31</sup> This preliminary purgation removes any obstacle to the progress of the Quinine along the intestinal canal, prevents dilution of the Quinine by the previous contents of the intestine, permits more ready contact between the Quinine and the mucous membrane of the intestine, and increases the general tone of the whole intestinal tract. It will be observed also that the tincture contains two cholagogue purgatives—aloes and rhubarb. These can help absorption in two ways, (1) by increasing the flow of bile, and (2) by increasing peristalsis which favours contact of Quinine with the intestinal mucous membrane. To prevent any griping, due to these two purgatives, aromatics are present in abundance. There is still another possible action of these two purgatives which has to be guarded against besides griping. It is not desirable that the Quinine should pass too rapidly along the intestinal tract. For this purpose prepared chalk and a little opium are generally included in the composition of the tincture: these tend to diminish the intestinal secretions, and so impede the progress of the Quinine in the intestine. Two other recommendations<sup>31</sup> generally accompany the tincture: (1) it is to be taken alone without dilution, and (2) all drinks are withheld after its administration: these precautions, besides preventing dilution, which would diminish contact of Quinine with intestinal mucous membrane, probably help to retard the progress of the Quinine along the intestinal tract. These latter effects are also favoured or aided indirectly by a further recommendation—that the patient should be well covered after the administration of the tincture and diaphoresis encouraged.

### **Subcutaneous (including Intramuscular) Administration.**

Until quite recently no one ever doubted or questioned the alleged advantages of the hypodermic injection of Quinine,—rapidity and accentuation of action as in the case of other medicinal substances that are commonly administered in this way. And, even now, all authoritative books on pharmacology and therapeutics, while noting its drawbacks and dangers, recommend the hypodermic administration of Quinine in malignant types of malaria. Binz<sup>11</sup> states that the satisfactory results obtained by this method of treatment show that the Quinine is thoroughly absorbed. Some medical officers would even go the length of giving Quinine hypodermically as routine practice in preference to oral administration. According to the National Dispensary,<sup>10</sup> however, the

tendency to produce "pain, inflammation, gangrene and even fatal tetanus" more than counterbalances the advantages of facility of administration and *promptness of effect*, and the use of this method of administration should be restricted to cases in which delay may be dangerous.

The behaviour of those Quinine salts that are used for hypodermic injection, in different strengths of solution, when mixed with ox blood-serum, has already been described. It should be noted also that solutions of Quinine hydrochloride prepared with the addition of antipyrine, urethane and sodium chloride, respectively, as recommended by some for hypodermic and intravenous use, were tested in the same way and showed no greater miscibility with ox blood-serum than did simple solutions of Quinine hydrochloride itself. The ordinary Quinine hypodermic injection, as recommended by Squire,<sup>32</sup> is not more dilute than 1 in 6; the strength of Burrough's and Wellcome's Quinine bi-hydrochloride Vaporoles is 1 in 5; and the strength of extemporaneous Quinine injections generally borders on 1 in 1½. Solutions of Quinine of such strengths must of necessity result in a coagulum and precipitation of much of the Quinine at the seat of injection. It has already been shown that the addition of a 1 in 20 solution of Quinine hydrochloride to an equal volume of ox blood-serum throws about half the Quinine, temporarily at least, out of solution. An examination of Table II strongly suggests that the more concentrated the solution of Quinine salt, the more alkaloid will be precipitated in the mixture with serum; and the more dilute the solution of Quinine salt, the less alkaloid will be thrown out of solution. One would expect therefore from these serum experiments that much of the Quinine contained in the *ordinary* Quinine hypodermic injection would be thrown out of solution at the point of injection, but that, if the Quinine injection is sufficiently dilute (1 in 150), little or no Quinine would be deposited in the tissues.

It will be remembered that the substance separated by adding dilute sulphuric acid to the coagulum (formed by adding Quinine hydrochloride 1 in 20 to serum), after the latter had been washed free from all traces of Quinine, gave a blue colour when treated with chlorine water and ammonia, and that this blue colour changed to green rapidly on heating, but after a few days if left at laboratory temperature. This substance is probably an oxidation product of Quinine, and the ease with which it can be re-converted into Quinine suggests that, although much Quinine is thrown out of solution at the seat of injection apparently as a transformed product in combination with albumen (compare with Rossbach's<sup>33</sup> investigations), Quinine may be gradually liberated from the coagulum for two or three days after injection. Reference will again be made to this coagulum in connection with the occurrence of tetanus after Quinine injections.

Giemsa and Schaumann<sup>5</sup> state that a solution of one part of Quinine urea bi-hydrochloride in ten of water is particularly suited for subcutaneous use. Table II shows that in this dilution Quinine urea forms a curdy mass only when mixed with serum, and that, in the same dilution, quinine bi-hydrochloride produces a gelatinous mass. The latter salt, however, contains considerably more Quinine base than the former; and, when solutions of both salts each containing 1 in 80 of Quinine base were tested with serum, no difference in the behaviour of the two salts could be detected.

From the small amount of Quinine eliminated in the urine after hypodermic injections and from his findings at the point of injection Kleine<sup>22</sup> came to the conclusion that Quinine was precipitated largely at the seat of injection, and that Quinine was very slowly absorbed from this depôt by the lymph stream. He was of opinion that absorption lasted for weeks, and that such a prolonged action would be useful in the treatment and prophylaxis of malaria. Mariani,<sup>13</sup> however, showed that this Quinine depôt at the point of injection did not persist beyond five or six days, and so rejected the idea that subcutaneous administration was particularly useful for the prophylaxis of malaria. That Quinine was precipitated at the point of injection he settled by experiment. He injected Quinine bi-hydrochloride (about 1 in 5) intramuscularly in the leg of a rabbit and 17 hours thereafter killed the rabbit and recovered from the muscles 66.5 per cent. of the amount injected. Kleine,<sup>22</sup> on finding that elimination in the urine was so small in amount and that elimination did not continue so long as he had formerly supposed, concluded that the subcutaneous administration of Quinine was of less therapeutic value than the oral.

There is very little harmony in the results of experimenters who have investigated the proportion of Quinine eliminated in the urine after hypodermic injection. There is one point, however, on which they are all in agreement, namely, that the proportion of Quinine eliminated, when administered subcutaneously, is much less than when given by the mouth. The following gives the proportions eliminated in the first twenty-four hours after administration (1) by mouth and (2) subcutaneously:—

By mouth (fasting)	=	$\frac{21.91\%}{12.13\%}$	(Kleine). <sup>22</sup>
Subcutaneously			
Do.	=	$\frac{24.7\%}{14.74\%}$	(Mariani). <sup>13</sup>
Do.	=	$\frac{19.50\%}{17.9\%}$	(Schmitz). <sup>21</sup>
Do.	=	$\frac{25.8\%}{21.6\%}$	(using dilute solution) (Giemsa and Schaumann). <sup>5</sup>

Kleine<sup>22</sup> gave .5 gramme Quinine bi-hydrochloride subcutaneously to each of two patients and found the amount eliminated in the first 24 hours in one case was 11.37 *per cent.* and in the other 9.70 *per cent.* To another patient he gave .5 gramme Quinine hydrochloride, and the amount eliminated in the first 24 hours was 15.32 *per cent.* The greater excretion in the last case probably accompanied a greater absorption due to the greater dilution in which the hydrochloride was probably given owing to its less solubility. Mariani<sup>13</sup> tested the effect of concentration of the Quinine injection on the elimination. In the one case he injected one gramme of Quinine bi-hydrochloride in ten cubic centimetres of water and in the other case the same salt and dose in two cubic centimetres of water; in the former, 13.7 *per cent.* was eliminated in the first 24 hours; in the latter, 15.791: in the former, elimination was at its height between the sixth and twelfth hours after injection; in the latter, between the ninth and eighteenth hours after injection. It is worthy of note that differences in dilution of 1 in 2 and 1 in 10 had no great influence on the amount of Quinine excreted and probably absorbed. This agrees with the results obtained by me in the minimum-lethal-dose experiments. Giemsa and Schaumann,<sup>6</sup> however, using Quinine urea have obtained very different results. They carried out two sets of experiments: in one set they administered one gramme of Quinine urea in ten cubic centimetres of water to each patient daily, and in the other set one gramme of Quinine urea in one cubic centimetre of water daily, with the following tabulated results:—

Table VI.

*A.—Daily subcutaneous injection of 1 gm.  
Quinine urea in 10 c.c. of water.*

*B.—Daily subcutaneous injection of 1 gm.  
Quinine urea in 1 c.c. of water.*

	No. 1.	No. 2.	No. 3.		No. 1.	No. 2.
	per cent.	per cent.	per cent.		per cent.	per cent.
1st day . . .	21.0	24.1	19.8	1st day . . .	10.3	12.1
2nd day . . .	26.2	24.9	22.0	2nd day . . .	16.3	15.1
3rd day . . .	...	26.9	...	3rd day . . .	18.2	19.3
AVERAGE . . .	23.6	25.3	20.9	AVERAGE . . .	14.9	15.5

They report that, in the case of those who received the Quinine in a dilution of 1 in 10, elimination ended within 48 hours after the last injection ; and that in the other case elimination was pronounced for four or five days after the last injection. It is difficult to explain the differences in elimination shown in Tables A and B. Judging from the *in vitro* experiments, there is no reason why Quinine urea should be better absorbed than Quinine bi-hydrochloride. It would appear, moreover, that Quinine urea has not fulfilled the hopes entertained of it ; for Giemsa<sup>34</sup> has recently recommended the combination of Quinine hydrochloride with urethane for hypodermic injection. Urethane and antipyrine increase the solubility of Quinine hydrochloride, new chemical products being formed from which, it is thought, Quinine is liberated in the body. Gaglio<sup>35</sup> recommended the urethane solution as being neutral, non-irritating and stable : after its hypodermic injection he recovered from 30 to 50 *per cent.* in the urine and concluded that it was rapidly and completely absorbed. Schmitz,<sup>21</sup> however, has been unable to confirm these results ; giving the urethane solution hypodermically to a patient daily for seven days, he found the daily amount eliminated was only 16.1 *per cent.* on an average. Recently Giemsa<sup>34</sup> seems to have given up the use of Quinine-urea in favour of this urethane solution of Quinine hydrochloride, the advantages he puts forward for the latter being : that it will stand boiling for an hour and is not decomposed by heat like Quinine urea while being sterilized, that it is well absorbed, that it has a similar re-action to that of the tissue fluids and that its intramuscular injection is almost painless. In the antipyrine solution of Quinine hydrochloride, quinopyrin is formed, which according to Santesson is less toxic than Quinine, but according to Stofella is useless.<sup>36</sup> Regarding these solutions resulting in the formation of new compounds Marshall<sup>36</sup> states that they should be looked upon with suspicion. Moreover, it should be noted that their miscibility with ox blood-serum is no greater than that of solutions of simple Quinine hydrochloride itself. Solubility in water is merely of advantage during the process of injecting ; it is solubility or miscibility in serum that favours absorption.

Clinically, one striking point about the hypodermic administration of Quinine is the sudden great increase recently in dosage by this method. A few years ago the hypodermic dose of Quinine was usually given as from four to six grains ; at present the dose is generally from ten to fifteen grains—the same as when given by the mouth. This indicates that absorption after oral administration is at least as complete as after hypodermic. In comparing the two methods of administration there remains therefore only the question of promptness of action. Smythe's<sup>14</sup> experience is that after hypodermic injection Quinine is slowly absorbed and that its elimination takes weeks ; that 20 grains injected

in the flanks give protection from malaria for at least a month. According to Megaw,<sup>15</sup> the temperature of malarial patients takes about twelve hours longer in coming to normal when treated by the hypodermic method than when Quinine is given by the mouth; from this it is assumed absorption is slower from the subcutaneous tissues than from the mucous membrane of the gastro-intestinal tract. Scott<sup>16</sup> has come to the conclusion that the hypodermic (intramuscular) mode of administration of Quinine has no special value in the treatment of acute cases of malarial fever owing to slowness of absorption. The results obtained by Cohen<sup>37</sup> are interesting from two points of view: they show the conclusions arrived at by an advocate of Quinine injections, and they were obtained by the use of Quinine urea which was so strongly recommended by Giemsa and Schaumann. Cohen states that 15 grains of Quinine urea, if injected during or within four hours after a paroxysm of malarial fever, were readily absorbed and procured freedom from fever for a period of from six to thirteen days: he, however, admits that Quinine by the mouth is "equally efficacious". His statements that the Quinine urea was readily absorbed from the point of injection and that freedom from fever was obtained for from six to thirteen days are hardly consistent.

The evidence, so far, casting doubt upon the alleged therapeutic value of the subcutaneous administration of Quinine can be summarised as follows:—

#### I.—ABSORPTION.

(1) *Experimental*.—The behaviour of Quinine solutions when mixed with ox blood-serum suggest the possibility of very dilute solutions of Quinine (1—150) but the unlikelihood of concentrated solutions, such as ordinary Quinine hypodermic injections, being readily absorbed: it suggests the probability that most of the Quinine in hypodermic injections is thrown out of solution at the point of injection, is combined with albumen in an oxidised but unstable form and is gradually liberated from this combination.

Mariani's<sup>13</sup> experiment, in which he recovered from rabbit's muscle 66·5 per cent. of the dose of Quinine (Quinine bi-hydrochloride 1 in 5) injected 17 hours before the rabbit was killed, is positive proof that Quinine was deposited at the point of injection, and that most of the Quinine was still lying at the point of injection 17 hours after the injection was made.

The experiments on Quinine elimination in the urine give very little information regarding Quinine absorption. One point which seems to be definitely settled is that the amount of Quinine eliminated in the urine after hypodermic injection is invariably less than that after oral administration. By

the advocates of hypodermic injection, the diminution in Quinine excretion is attributed to greater cleavage of Quinine in the body after absorption from the seat of injection. The results of different experimenters vary considerably,—as one would expect seeing that the degree of dilution of the Quinine solution both before and after injection (and consequently the amount of Quinine thrown out of solution at the point of injection) is subject to considerable variation.

(2) *Clinical*.—There is a considerable amount of evidence that absorption is no better after hypodermic than after oral administration; and that, however useful hypodermic injections may be for prophylaxis, hypodermic medication is not so good in the treatment of malaria as oral. Reference has already been made to the recent great increase in the dose of Quinine when given hypodermically and to the observations of Smythe and Scott.

## II.—PROMPTNESS OF EFFECT.

(1) *Experimental*.—Mariani<sup>13</sup> after injecting one gramme of Quinine bi-hydrochloride dissolved in ten cubic centimetres of water found that the maximum elimination of Quinine in the urine occurred between the sixth and twelfth hours after injection; and that, after injecting one gramme of the same salt dissolved in two cubic centimetres of water, the maximum elimination occurred between the ninth and eighteenth hours. It has already been stated that after oral administration during fasting the maximum elimination of Quinine occurs between the third and sixth hours; and during or soon after meals, between the sixth and twelfth hours. It is evident therefore, if permissible to draw conclusions regarding absorption from Quinine elimination in the urine, that maximum absorption and consequently maximum therapeutic effect is obtained later after hypodermic injection (in dilutions at least up to 1 in 10 which include all Quinine hypodermic injections as ordinarily given) than after oral administration.

(2) *Clinical*.—The results obtained by Megaw<sup>15</sup> point to absorption being slower from the subcutaneous tissues than from the gastro-intestinal mucous membrane.

### Minimum-Lethal Dose experiments on Guinea-pigs with Quinine bi-hydrochloride by oral and subcutaneous administration.

Reid Hunt<sup>33</sup> has shown that temperature may have a great influence on the results of such experiments on small animals. Experimenting by subcutaneous injections on mice, he found that doses otherwise non-lethal were fatal on cold days. All the following experiments were carried out at a temperature within the limits of 71°—76° F., so that they should be strictly comparable so far as temperature is concerned.

Table VII.

## A.—MINIMUM-LETHAL DOSE BY ORAL ADMINISTRATION.

*(After fasting 24 hours.)*

Weight of animal in grammes.	Actual dose in grammes.	Dose per kilogramme of animal in grammes.	Result.
550	0.165	0.3	Recovery. Distinct effects.
620	0.217	0.35	Recovery. Distinct effects.
510	0.204	0.4	Recovery. Very severe effects.
610	0.244	0.4	Recovery. Very severe effects.
600	0.240	0.4	Died in 6—7½ hours.
470	0.2115	0.45	Died in 8 hours.
520	0.234	0.45	Died in 6 hours.
500	0.25	0.5	Died in 21 hours.

## B.—MINIMUM-LETHAL DOSE BY ORAL ADMINISTRATION.

*(Immediately after food.)*

Weight of animal in grammes.	Actual dose in grammes.	Dose per kilogramme of animal in grammes.	Result.
630	0.252	0.4	Recovery. Slight effects.
630	0.2835	0.45	Recovery. Slight effects.
660	0.295	0.45	Died in 11 hours.
500	0.25	0.5	Died in 6½ hours.
500	0.25	0.5	Died in 6—7 hours.

## C.—MINIMUM-LETHAL DOSE BY SUBCUTANEOUS INJECTION.

*(Dilution 1 in 150.)*

Weight of animal in grammes.	Actual dose in grammes.	Dose per kilogramme of animal in grammes.	Result.
730	0·073	0·1	Recovery. Very slight effects.
590	0·118	0·2	Recovery. Marked effects.
710	0·1775	0·25	Recovery. Very severe effects.
570	0·1596	0·28	Recovery. Very severe effects.
490	0·147	0·3	Died in 7½ hours.
620	0·186	0·3	Died in 7 hours.

## D.—MINIMUM-LETHAL DOSE BY SUBCUTANEOUS INJECTION.

*(Dilution 1 in 2.)*

Weight of animal in grammes.	Actual dose in grammes.	Dose per kilogramme of animal in grammes.	Result.
475	0·1425	0·3	Recovery. * Marked effects.
610	0·244	0·4	Recovery. Slight effects.
550	0·275	0·5	Recovery. Distinct effects.
510	0·306	0·6	Died in 23½ hours.
660	0·396	0·6	Died † in 4 hours.
650	0·455	0·7	Died in 19½ hours.
580	0·522	0·9	Died in 9—11 hours.

\* This animal was a weakling and was accidentally chosen for experiment.

† At the *post-mortem* examination, much exudate was found in the loose tissue at the point of injection.

## E.—MINIMUM-LETHAL DOSE BY SUBCUTANEOUS INJECTION.

(Dilution 1 in 8.)

Weight of animal in grammes.	Actual dose in grammes.	Dose per kilogramme of animal in grammes.	Result.
570	0·171	0·3	Recovery. Slight effects.
590	0·236	0·4	Recovery. Slight effects.
580	0·29	0·5	Recovery. Distinct effects.
560	0·246	0·6	Recovery. Marked effects.
410	0·336	0·6	Died in 8½ hours.

The minimum-lethal doses, therefore, sufficiently accurate for comparative purposes are as follows:—

By oral administration (fasting)	.	.	=	·45 gm. per kilo.
"          "          (after food)	.	.	=	·5 " "
By subcutaneous injection 1—150	.	.	=	·3 " "
"          "          1—2	.	.	=	·6 " "
"          "          1—8	.	.	=	over ·6 " "

The higher minimum-lethal dose shown by these results for injections of 1 in 8 dilution, as compared with 1 in 2, is probably explained by my having carried out the experiments with 1 in 8 dilution last of all; for, having observed that diffusion of the injected fluid by massage or movement on the part of the animal had some effect—although slight—on the results, the animals that received injections of 1 in 8 dilution were kept quiet in the hands for five or ten minutes after injection. The lethality, and therefore the absorbability, of Quinine are in the following order, beginning with the most lethal mode of administration:—

- (1) Subcutaneous injection in extreme dilution (1—150);
- (2) Oral administration during fasting;
- (3) Oral administration with or soon after food;
- (4) Subcutaneous injection in the strengths generally used for hypodermic injection (1 in 2 and 1 in 8).

And as that mode of administration which is most lethal to the animal would almost certainly be the most lethal to any parasite in the animal's blood or tissues, it follows that the therapeutic value of the different modes of administration is also in the order given for lethality. As will be evident later, the subcutaneous injection of Quinine in extreme dilution (or rather, as it should be called, subcutaneous *infusion*) is not feasible for clinical reasons; so for all practical purposes, if it is permissible to generalise from those experiments on guinea-pigs, Quinine by the mouth is of greater therapeutic value in respect of *amount of absorption* than subcutaneous Quinine injections.

With the object of getting some idea as to the relative *promptness of action* attained by the different methods of administration, the time of appearance of the various toxic symptoms in each experiment was carefully noted,—with the following results.

**Table VIII.**  
**Minimum-Lethal Dose Experiments on Guinea-pigs.**  
*Order in which Toxic Symptoms Appeared.*  
(Quinine Bi-Hydrochloride.)

Time after administration.	ORAL ADMINISTRATION.		SUBCUTANEOUS INJECTION.		
	Fasting. Dose=about .45 gm. per kilo.	With food. Dose=about .5 gm. per kilo.	1-150. Dose=about .3 gm. per kilo.	1-2. Dose=about .6 gm. kilo.	1-8. Dose=about .6 gm. per kilo.
$\frac{3}{4}$ hour.	...	...	Unsteadiness	...	...
1 "	...	...	Convulsions	...	...
2 hours.	...	...	Inability to stand.	...	...
$2\frac{1}{2}$ "	Unsteadiness	...	...	...	...
3 "	...	Unsteadiness	...	...	...
$3\frac{1}{2}$ "	Twitchings and "starts"	...	...	...	...
4 "	...	Twitchings and "starts"	...	...	...
$4\frac{1}{2}$ "	Convulsions	...	...	...	Unsteadiness
5 "	...	...	...	...	Twitchings and starts.
6 "	...	...	...	Unsteadiness	...
$6\frac{1}{2}$ "	...	Convulsions	...	...	...
8 "	...	...	...	Convulsions	Convulsions
	Recovery under 24 hours if dose sub-lethal.	Recovery under 24 hours if dose sub-lethal.	Recovery under 24 hours if dose sub-lethal.	Recovery took at least 30 hours if dose sub-lethal.	...

From this table it is evident that, as regards promptness of effect, the various modes of administration stand in exactly the same order as that given for lethality or absorbability. The time at which the various toxic symptoms appeared in the case of suicide (already described) by swallowing four drachms of Quinine, which is about the minimum lethal dose for man, corresponded so

closely with that given in this table that probably all the results tabulated here hold good approximately for man. Other reasons that justify the application of this table to man are the following:—

The maximum elimination of Quinine in man's urine after Quinine by the mouth during fasting occurs between the third and sixth hours (Mariani<sup>13</sup>).

The maximum elimination of Quinine in man's urine after Quinine by the mouth after food occurs between the sixth and twelfth hours (Mariani<sup>13</sup>).

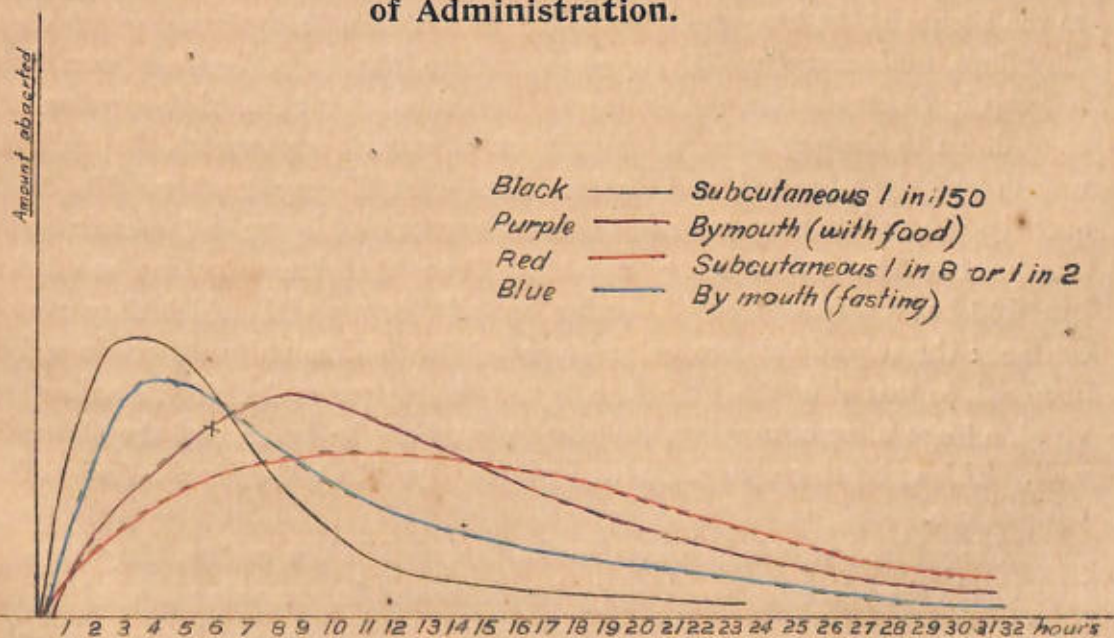
The maximum elimination of Quinine in man's urine after a subcutaneous injection of one gramme of Quinine bi-hydrochloride (1) dissolved in ten cubic centimetres of water occurs between the sixth and twelfth hours, and (2) dissolved in two cubic centimetres of water occurs between the ninth and eighteenth hours (Mariani<sup>13</sup>).

These results obtained by Mariani correspond in a very striking manner with the appearance of convulsions in the guinea-pigs in the minimum-lethal dose experiments.

The results tabulated above may therefore be taken as practically conclusive; and they show that the oral administration of Quinine affords more prompt action of the alkaloid than does the subcutaneous.

The following curves give a graphic representation of the absorption of Quinine after administration in the various methods already referred to, the dose of Quinine being taken to be the same in each case:—

#### Curves of Quinine Absorption after various Methods of Administration.



Subcutaneous Quinine *infusions* being debarred, Quinine by the mouth with or soon after meals suggests itself as particularly suited for the treatment of malaria in which sporulation is irregular, and also for prophylaxis. Quinine by the mouth while fasting would be serviceable two or three hours before a paroxysm where sporulation recurred regularly.

In the curve representing absorption when Quinine is given with meals (absorption in such a case according to Mariani<sup>13</sup> is at its height between the sixth and twelfth hours) it will be noticed that absorption from the fifth to the thirteenth hour, *i.e.*, for eight hours, is higher than it ever reaches when an ordinary Quinine hypodermic injection containing the *same dose* of Quinine is given. It follows therefore that Quinine given with (or soon after) meals three times a day every eight hours, will keep the amount of Quinine in the body at a higher level than one could ever hope to do by giving similar doses of Quinine hypodermically in the usual concentrated solutions.

#### **Local and Post-mortem Changes found in the Guinea-pigs used for the Minimum-Lethal Dose Experiments.**

A few minutes after injection into the subcutaneous connective tissue, the skin overlying the injection became discoloured and yellow, and soon an area of skin corresponding to the size of the injection had undergone necrosis—killed directly by the action of the Quinine. The epidermis and hairs over this area could be peeled off by rubbing it with the blunt edge of a knife. If the animal survived, a red raw ulcer resulted; no pus was seen, possibly owing to the tissues at the base and edge being saturated with Quinine which checks diapedesis of leucocytes. In one case, where the injection had been large, necrosis had extended on the deeper surface through all the abdominal muscles right down to the peritoneum. The layer of muscle underneath the injection was invariably necrosed and looked like washed gray leather. Not infrequently the yellow necrosed mass became surrounded by an inflamed indurated area prior to the eschar being cast off. Even Quinine solutions so dilute as 1 in 150 had a severe necrotic action on all tissues with which they came in contact: the superficial muscular layer of the abdominal wall was invariably necrosed, as was also the skin, the result being generally, if the animal survived, a huge ulcer occupying the greater part of the surface of the abdominal wall. This extensive ulceration and necrosis preclude Quinine *infusions* from clinical use.

If any blood vessels happened to be included in the eschar, they appeared like black threads and could easily be picked out in the pale necrosed tissues: the blood they contained was invariably clotted. In several instances, includ-

ing cases both of oral and subcutaneous administration, hæmorrhagic erosions were found in the stomach,—particularly in guinea-pigs that had survived some twenty hours or so after injection. One guinea-pig which had received Quinine by the mouth was found to have had an extensive hæmorrhage in the lower part of the large intestine. These hæmorrhages are most probably due to engorged capillaries giving way. In typical cases, the ventricles of the heart were found empty and pink in colour (therefore not contracted or in *rigor*); both auricles were enormously distended with dark venous blood; and all large veins were engorged with blood.

### Hypodermic Injections in General and those of Quinine in Particular.

A substance, to be suited for hypodermic injection, should satisfy the following requirements:—

- (1) It should be capable of being easily sterilized, *e.g.*, stand boiling.
- (2) Its solution ready for injection should be in small bulk, *i.e.*, the substance should be very active pharmacologically and be very soluble in water, saline or other menstruum.
- (3) It should be capable of rapid and thorough absorption, *i.e.*, its solution in the concentration in which it is injected should be compatible with serum and lymph.
- (4) It should be non-injurious to the tissues locally.
- (5) It should be non-irritating.

Now, examining Quinine according to this standard, it is evident that one only of these five requirements is satisfied. Quinine can be got into sufficiently small bulk for injection, but in this concentration it cannot be absorbed rapidly or thoroughly, and it is irritating and very injurious to the tissues at the point of injection. Regarding sterilization, none of the salts of Quinine stands heating well. Quinine is therefore fundamentally unsuited for hypodermic use.

Further, Quinine injections, although devoid of any therapeutic advantage over administration by the mouth, are not infrequently attended by serious complications, mutilation and dangers.

(1) *Necrosis*.—From the rapidity with which this occurred in the guinea-pig experiments and from the rapid yellow discolouration of the skin, it is practically certain that this necrosis is due to the direct action of the Quinine, which even in a dilution of 1 in 150 kills outright all tissues which by diffusion it reaches. Thrombosis could not possibly produce necrosis so rapidly.

(2) *Thrombosis*.—If by accident some solution is injected into a blood vessel, rapid thrombosis and possibly embolism results. Thrombosis, however, occurs in vessels which have not been directly injured by the hypodermic needle; for, all vessels in the necrosed area contain clotted blood. If, therefore, the injection is made *near* a large blood vessel, thrombosis in that vessel may cause ischæmic paralysis.

(3) *Paralysis*.—Besides ischæmic paralysis from thrombosis of a large artery, paralysis may also occur from direct destruction of a nerve near which the Quinine may have been injected. Quinine has no specific affinity for any special tissue, such as strychnine and nerve cells: if in sufficient concentration it is a poison to all forms of living matter. According to Sollmann,<sup>4</sup> Quinine will kill a nerve if applied directly to it; according to Kobert,<sup>26</sup> it kills whatever it reaches—nerve, skin, *etc.*

(4) *Ulceration*.—If the necrosed area reaches skin the eschar must necessarily be thrown off, and leave an ulcer. In intramuscular injections, the necrosed area does not reach skin, so no ulceration results; the necrosed area is ultimately converted into a fibrous nodule in the muscle. If the needle during injection is kept parallel to the skin-surface, ulceration will infallibly occur; for the Quinine by diffusion reaches the surface and includes the skin in the necrosed area.

(5) *Tetanus*.—The occurrence of tetanus as a not infrequent sequel to Quinine injections has long been recognised; but a definite explanation of this phenomenon has not yet been given. The convulsions which occur in Quinine poisoning are recognised as distinctly epileptiform, and not tetanic;<sup>39</sup> so the opinion of some that the tetanic symptoms are simply a manifestation of Quinine poisoning may be dismissed at once as untenable. But even with reference to true tetanus there are two ideas regarding the mode of infection. The more generally accepted one is that tetanus spores are introduced during or after the injection of Quinine; the other is that tetanus spores are already existent in a latent condition in the body and that they are stirred into activity by the trauma or the Quinine at the time of injection. In support of the latter idea, Tarozzi<sup>40</sup> has shown that tetanus spores can live for over three months in the liver or kidney in a latent condition, but are gradually destroyed; and by an artificial trauma he was able to induce these spores to germinate and produce "spontaneous tetanus." Regarding infection during or after injection several points have to be considered. If pure tetanus cultures are introduced into the blood or organs of the body, the spores are soon destroyed unless conditions favouring their multiplication are present:<sup>41</sup> the bacilli and spores by themselves in the tissues form relatively bland foreign bodies, and are slowly taken up by the

leucocytes, possibly hours or, as stated by Tarozzi, months after injection. Factors which favour multiplication of tetanus bacilli in the body, according to Vaillard,<sup>42</sup> are—(1) much dirt introduced into the wound, (2) all means that keep leucocytes away from the inoculated spot, (3) means which afford mechanical protection to the bacilli, (4) the addition of certain chemicals, *e.g.*, lactic acid, (5) severe mechanical lesions, *e.g.*, fracture and contusion, and (6) the introduction of certain saprophytes. As regards tetanus following Quinine injections, the first and fifth of these factors may be dismissed at once, and probably also the sixth, as tetanus has occurred even after scrupulous care in sterilising the injection—quite sufficient to destroy all saprophytes—had been taken. That Quinine can keep leucocytes away from the inoculated spot is well recognised (Binz):<sup>41</sup> and this action of Quinine is accentuated in two other ways—(1) Quinine causes impairment of phagocytosis (Gölggi),<sup>43</sup> and (2) diminishes the number of leucocytes in the body, 3 grammes of Quinine sulphate being capable of reducing the number of leucocytes by 7 *per cent.* in six hours (Marshall,<sup>3</sup> Sollmann<sup>4</sup>). The coagulum at the seat of injection may possibly afford some mechanical protection to tetanus spores, but it can also favour their development in another way—phagocytes may be diverted from the relatively bland spores to the more irritating coagulum. Heddæus<sup>44</sup> has reported the occurrence of tetanus after the subcutaneous injection of gelatine, where probably the same causes, mechanical protection and diversion of leucocytes, were at work. Quinine is generally included with lactic acid among the chemical agents that favour tetanus. A probable explanation of its action is suggested by my serum compatibility experiments. In the coagulum formed by adding Quinine solutions to ox blood-serum, Quinine was precipitated in an apparently oxidised form in combination with proteids (*cf.* Rossbach's<sup>38</sup> experiments on the compound formed by the combination of Quinine and albumen, and Kerner's<sup>37</sup> experiments with dihydroxyl-quinine formed by acting on Quinine with permanganate of potassium). It is possible therefore that tetanus spores introduced at the time of injection may be included in interstices of the coagulum produced by the Quinine and in a favourable fluid medium deprived of its oxygen. The action of Quinine in inhibiting the oxidation of guaiacum<sup>45</sup> in the ordinary blood test, in inhibiting the so-called "acid fermentation of the blood"<sup>46</sup> and in diminishing the synthesis of hippuric acid in the kidney perfusion<sup>47</sup> experiments may be similarly explained: oxygen is used up in the Quinine albumen compound, and none is available for guaiacum, for the blood or for the nourishment of the renal cells, respectively. Regarding sterilisation of Quinine injections, it should be noted that all bacilli are not equally susceptible to the action of Quinine: anthrax spores for instance are fairly refractory (Koch)<sup>48</sup>; tetanus spores may be likewise.

### Intramuscular Injections.

Intramuscular injections in no way differ essentially from subcutaneous. Possibly absorption is slightly more energetic owing to a more active blood and lymph circulation and less pain is occasioned, but the same destructive and necrotic changes occur as in the subcutaneous proper. Kleine<sup>22</sup> reports that the tissues after subcutaneous injection, especially if intramuscular, look severely damaged for a long time after injection; and Mariani<sup>13</sup> made the same observations in his rabbit experiments (intramuscular injections). These injurious effects are hidden from view: necrosis does not reach the skin, so no ulceration follows. Paralysis, however, whether from thrombosis of blood vessels or from direct destruction of nerve fibres, is more liable to occur after intramuscular injections.

Quinine solutions so dilute as 1 in 150 and containing sufficient Quinine to be of any therapeutic value could not possibly be injected intramuscularly. Such solutions would therefore have to be injected into the subcutaneous connective tissue, as a Quinine *infusion*. The rapid and thorough absorption that would follow such a Quinine *infusion* is more than counterbalanced by the large ulcer that would infallibly result. Further, we have in the intravenous injection of Quinine a method which will give still greater Quinine concentration in the blood without any of the special dangers of Quinine *infusions*.

### Intravenous Injections of Quinine.

The intravenous method of administering Quinine was introduced by Bacelli,<sup>40</sup> who used a solution containing Quinine hydrochloride, 1; sodium chloride, .075; distilled water, 10 parts. This solution, however, the strength of which is about 1 in 10, did not find favour, and certainly the serum compatibility experiments would lead one to expect the introduction of this concentrated solution intravenously to be attended with grave danger. The addition of sodium chloride does not increase the compatibility of Quinine hydrochloride with ox blood-serum.

If a Quinine salt is to be safely introduced intravenously, it must be in a dilution of 1 in 150 at least. Preferably the Quinine salt (*e.g.* about seven grains of Quinine bi-hydrochloride) should be dissolved in two or three pints of normal saline. In this dilution there is no danger of thrombosis or precipitation: the toxins in the blood are also diluted and their elimination favoured—this mode of administration being specially indicated in malignant types of malaria. Such solutions have been infused intravenously with good effect in cases of pernicious malaria. If there is any tendency to hæmoglobinuria, I

should recommend the substitution of Quinine alkaloid for Quinine bi-hydrochloride; as the alkaloid delays hæmolysis, while the acid salts of Quinine are strong hæmolytic agents.<sup>60</sup>

By this method of administration the special dangers of the subcutaneous injection of Quinine are avoided. There is no danger of necrosis, paralysis, ulceration or thrombosis. It is also very doubtful if the introduction of tetanus spores with the intravenous Quinine infusion, in a bulk of two or three pints, would produce any harm. Pure tetanus cultures introduced into the blood are soon destroyed unless conditions favouring their multiplication are present.<sup>41</sup> Of the five factors already mentioned which would favour their multiplication, only one—the presence of the chemical agent Quinine itself—would be operative in intravenous infusion; and the Quinine would probably be in too great dilution to favour the development of tetanus bacilli.

The average amounts of Quinine eliminated in the urine after intravenous injection are, according to Mariani,<sup>13</sup> 20.54 *per cent.* on the first day, 6.33 *per cent.* on the second and 1.07 on the third. These results lead one to suppose that the therapeutic action of the intravenous administration of Quinine is not so fleeting as one might expect.

While investigating the hæmolytic action of Quinine and its salts I devised a method of injecting Quinine alkaloid intravenously by dissolving it in 33 *per cent.* alcohol (in saline), the strength of the injection fluid being about 1 in 135.<sup>60</sup> As one grain of Quinine alkaloid thus requires a bulk of about eight cubic centimetres, this mode of injecting Quinine is not likely to be of use clinically; so only a short description is required.

First of all, the strength of alcohol which can safely be added to blood serum was determined: it was found that 33 *per cent.* alcohol is miscible with ox blood-serum provided that in the final mixture not more than 10 *per cent.* alcohol is present. In the next place the solubility of Quinine alkaloid in 33 *per cent.* alcohol was estimated: it was found that .2 gramme Quinine alkaloid is soluble in 2.7 cubic centimetres of 33 *per cent.* alcohol, *i.e.*, about 1 in 135. It will be noted that this solution is more concentrated than solutions of soluble Quinine salts which can be used with safety for intravenous injection. Lastly the miscibility of this Quinine alcoholic solution with ox blood-serum was studied: it was found that half a cubic centimetre of Quinine alcoholic solution is miscible with two cubic centimetres of ox serum. It seemed probable therefore that this Quinine alcoholic solution could be injected intravenously without any change occurring in the blood, provided the quantity injected met with four times its own bulk of blood. These limits of safety were based on the changes which occurred *in vitro* after standing twenty-four hours, and not on any changes that occurred immediately on mixing the proposed injection

with serum; so that the figures given are well within the actual limits of safety.

Quinine alkaloid in doses up to .03 gramme per kilogramme of animal weight, dissolved in 33 *per cent.* alcohol (in normal saline) was injected intravenously in rabbits without any ill-effects being observed to follow. A dose of .03 gramme per kilogramme of animal weight would correspond to a dose of 2.1 grammes ( $32\frac{1}{2}$  grains) of Quinine alkaloid to man. The injections, moreover, were not made slowly but as quickly as with any other solution. Quinine alkaloid is no doubt precipitated as it enters the vein, but it is in such a fine state of sub-division that, even if it could reach capillaries before being re-dissolved in the blood-serum, it could cause no obstruction.

In passing, it may be noted that, by first dissolving Quinine alkaloid in a minute amount of absolute alcohol and then adding normal saline to make a dilution of 1 of Quinine alkaloid in 2,000 or 5,000, a rapid and easy solution of the alkaloid is obtained for intravenous infusion. To dissolve Quinine alkaloid directly in water or saline is a very slow and laborious process.

#### Rectal Administration of Quinine.

*Quinine enemata.*—Quinine enemata are probably used as often for amoebic dysentery as for malaria. In the former case, absorption is not desired; in the latter, absorption is our object. The chief drawback to Quinine rectal injections is that Quinine salts, and particularly the more saluble salts, are so irritating to the mucous membrane that they are generally quickly returned. Prolonged retention is necessary for the efficient action of these injections whether they be given for amoebic dysentery or for malaria. In order to get sufficiently long retention, it is always necessary to add opium, belladonna or cocaine to the injections. Yet these substances, although they prolong retention, are apt to retard absorption. It is necessary, of course, before giving a Quinine enema to clear out the bowels with a simple enema. According to the National Dispensatory,<sup>10</sup> an enema of Quinine hydrochloride in the same dose as by the mouth has nearly the same therapeutic effect as when given by the mouth, provided the Quinine salt in the enema is given in watery solution. This view of Quinine enemata appears to be too optimistic. Kleine<sup>12, 23</sup> after giving an enema consisting of two grammes of Quinine hydrochloride in 100 cubic centimetres of water found the average Quinine elimination in the urine to be 17.5 *per cent.*, maximum elimination occurring between the fourth and tenth hours. He concluded that elimination and probably absorption from an enema containing a *soluble* Quinine salt are considerably smaller than those which take place when Quinine is given by the mouth; and that with a Quinine preparation which is *not easily soluble* absorption must be

much smaller still, for peristalsis is poor and the Quinine is merely in suspension. These results have been confirmed by Flamini<sup>23</sup> who, after an enema containing two grammes of Quinine tannate, found 2.65 *per cent.* only eliminated in the first 24 hours; and also by Giemsa and Schaumann<sup>5</sup> who after giving an enema containing one gramme of Quinine alkaloid with mucilage of acacia and tincture of opium found only 5.177 *per cent.* eliminated in the urine in the first 24 hours. From these results Giemsa and Schaumann infer that Quinine enemata are little suited for the treatment of malaria, because—even if sufficiently long retained—Quinine absorption is quite insufficient, and particularly so if Quinine salts which are not easily soluble are employed.

As carbonic acid and bile appear to play such a prominent part in the absorption of Quinine from the small intestine, it is possible that the addition of these to enemata would help absorption. Kerner<sup>51</sup> seems to have obtained quite good results with carbonic acid, the salt used being Quinine hydrochloride. The amount of Quinine he found eliminated in the urine is given in the accompanying table, which is self-explanatory.

Table IX.

## Elimination of Quinine in Urine after Quinine Enemata.

Quinine hydrochloride.	Hours.									
	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{3}{4}$	1	3	6	12	24	36	48
1 <i>per cent.</i> solution in 150 c.c. of water.	...	1	4	9	16	16	14	9	2	...
1 <i>per cent.</i> solution in 150 c.c. carbonated water; and 100 c.c. more carbonated water injected one hour later.	1	5	5	10	19	28	15	5	4	...

Further investigations regarding Quinine enemata are necessary. So far as our present knowledge takes us, the best results are obtained by using Quinine hydrochloride in a dilution of about 1 in 50 of water with tincture of opium or belladonna or cocaine added, and injected as high as possible. Even under the most favourable circumstances, when retention has been sufficiently long, we cannot expect as much from Quinine enemata as from Quinine by the mouth.

*Quinine suppositories.*—These are very irritating and useless in the treatment of malaria. Binz<sup>11</sup> states that, with the rectum previously washed out and the suppository passed high up with the finger, retention beyond one hour is very exceptional.

## SUMMARY OF CHIEF RESULTS AND CONCLUSIONS.

### Solutions of Quinine Salts and Moulds.

The sulphate is not the only salt of Quinine that is liable to infection with moulds, and the moulds which infect solutions of Quinine salts are not limited to the genus *Penicillium*. Quinine is not so inimical to the higher fungi as to the lower yeast forms.

### Miscibility of Quinine Salts with Ox Blood-serum.

The salts of Quinine most soluble in water, even in a dilution of 1 in 100 are not miscible with ox blood-serum. The three salts, Quinine bi-hydrochloride, Quinine bi-hydrobromide and Quinine urea, most frequently used for subcutaneous injection and in the dilution most frequently employed, mixed with an equal volume of ox blood-serum, in a few minutes at 17°C. result in the formation of a solid gelatinous mass. Quinine bi-hydrobromide even in a dilution of 1 in 20 produces a mass of curdy consistence. Quinine salts in the dilutions usually employed are quite unsuited for hypodermic use. The deposit which forms *in vitro* on adding a concentrated solution of Quinine salt to blood-serum seems to contain Quinine in altered form, oxidised and combined with proteid. Mixing equal volumes of blood-serum and Quinine hydrochloride 1 in 20, it is found that slightly over half the Quinine is in solution and slightly under half is contained in the deposit. The greater the dilution of Quinine salt, the less the deposit that forms on mixing with blood-serum; and therefore presumably the greater the amount of Quinine that remains in solution.

### Solubility of Quinine Alkaloid in Ox Blood-serum and in Ox Bile.

Quinine alkaloid is soluble 1 in 625 of ox blood-serum, *i.e.*, nearly three times as soluble in ox blood-serum as in ordinary water.

Quinine alkaloid is soluble 1 in 183 of ox bile, *i.e.*, about nine times as soluble in ox bile as in ordinary water.

### Absorption of Quinine.

Too much reliance must not be placed on the amount of Quinine elimination in the urine as a gauge of the amount of Quinine absorbed, especially when different modes of Quinine administration are being compared. *Lethality* varies directly with thoroughness of absorption and is a reliable measure of the amount of absorption when comparing different modes of Quinine administration.

*Oral Administration.*—Under ordinary circumstances, most of the Quinine administered by the mouth is absorbed from the small intestine; a small amount possibly from the stomach, especially if administered while fasting and in the form of a salt easily soluble in water; and also a relatively small amount from the large intestine.

Affections of the gastro-intestinal tract and liver have a marked influence on the amount of Quinine absorbed, as have also the food contents of the gastro-intestinal tract and the degree of solubility of the Quinine salt employed. Absorption is retarded if Quinine is given with or soon after food and also if the less soluble preparations of Quinine are administered. Rapid and energetic absorption is best obtained by giving a soluble Quinine salt during fasting: gradual and prolonged absorption is attained by giving one of the less soluble salts of Quinine with or soon after meals, absorption under such conditions being maintained at a considerable level for some eight hours. Hence, where sporulation is regular, a soluble Quinine salt should be given, during fasting, two or three hours before a paroxysm; in other cases, one of the less soluble preparations of Quinine, with or soon after meals, every eight hours. Carbonic acid, like bile, probably plays an important part in the process of Quinine absorption.

The administration of soluble Quinine salts in capsules is bad: gastric irritation and trouble may follow. Where Quinine causes gastric irritation, the least soluble salts of Quinine, *e.g.*, tannate, should be given.

Large doses, *e.g.*, 15 grains three times daily, give better therapeutic results than fractional doses, *e.g.*, four grains every two hours day and night. In cases where Quinine by the mouth does not produce the desired effect, attention should be directed to the condition of the gastro-intestinal tract and liver.

*Subcutaneous (including intramuscular) administration.*—Quinine salt solutions in the concentration usually employed for hypodermic injection, when mixed with blood-serum produce a coagulum which contains Quinine in altered form.

Quinine is precipitated at the seat of injection and over 66 *per cent.* of the amount injected intramuscularly has been recovered 17 hours afterwards from the muscles at the site of injection.

The amount of Quinine eliminated in the urine after this mode of administration varies between wide limits.

Urethane, antipyrine and sodium chloride, although they increase the solubility of Quinine hydrochloride in water, do not increase the miscibility of that Quinine salt with ox blood-serum; and the new compounds formed in such solutions are of doubtful therapeutic value.

As regards guinea-pigs, the *lethality* (and therefore *absorbability*) of Quinine by the several modes of administration is in the following order, beginning with the most lethal mode of administration: (1) subcutaneous injection in extreme dilution (1 in 150), (2) oral administration during fasting, (3) oral administration with or immediately after food, and (4) subcutaneous injection in the strengths generally used for hypodermic injection (1 in 2 and 1 in 8). The oral administration of Quinine also affords *more prompt* therapeutic action of the alkaloid than does the subcutaneous, the subcutaneous injection of Quinine in extreme dilution (1 in 150) being excluded for clinical reasons. Further, subcutaneous injections are followed by various complications and mutilation. Intramuscular injections are attended by the same drawbacks as subcutaneous proper; and although ulceration rarely occurs, they are more liable than the latter to be followed by thrombosis and paralysis.

The harmony between the results of various observations on man and those of my experiments on guinea-pigs justify the inference of general applicability—that subcutaneous and intramuscular Quinine injections, in solutions of the usual strength (1 in 1 to 1 in 10) are inferior to Quinine by the mouth in *rapidity of action* and *thoroughness of absorption*, and that they are liable to be attended by grave complications, mutilation and dangers. Quinine and its salts are, moreover, fundamentally unsuited for hypodermic use. *This mode of Quinine administration should therefore be abandoned.*

*Intravenous injections of Quinine.*—Great dilution (at least 1 in 150) is necessary in order to avoid the dangers special to Quinine. The Quinine, *e.g.*, seven grains of Quinine bi-hydrochloride, should be dissolved in two or three pints of saline. This mode of administration is called for in cases of emergency, *e.g.*, pernicious malaria with coma or other cerebral symptoms; and in such cases this extreme dilution affords the additional advantage of attenuating the toxins and favouring their elimination. In this dilution intravenous injections of Quinine are quick and sure; and, judging from the subsequent Quinine elimination in the urine, their action is not fleeting: they are attended by no risks peculiar to Quinine, but merely by those attendant on intravenous infusions generally.

Quinine alkaloid itself, instead of one of its salts, should be used where there is any tendency to or fear of hæmoglobinuria: the alkaloid delays hæmolysis, its acid salts are powerful hæmolytic agents. A solution of the alkaloid can be obtained rapidly and easily for intravenous infusion by first dissolving the alkaloid in a minute amount of absolute alcohol and then adding normal saline to make a solution of 1 in 2,000 or 5,000.

Intravenous injections of Quinine alkaloid dissolved in 33 *per cent.* alcohol (in saline) in a strength of about 1 in 135, have been made quickly

and safely in rabbits, and without any subsequent ill-effects—the amount of Quinine in the injections being equivalent to doses of  $32\frac{1}{2}$  grains Quinine alkaloid to man.

*Rectal administration.*—Quinine enemata are very irritating and are generally quickly returned; they are of little therapeutic value in malaria, as comparatively little Quinine is absorbed even when retained sufficiently long. The addition of bile or carbonic acid might increase their therapeutic action. Salts of Quinine which are not easily soluble in water should be avoided. Hitherto, the best results have been obtained from Quinine hydrochloride in water (1 in 50) with tincture of opium or belladonna or cocaine, injected high up in the bowel, which has been previously washed out with a simple enema. Even under the most favourable circumstances, with sufficiently long retention, we cannot expect as much from Quinine enemata as from Quinine by the mouth.

Quinine suppositories are irritating and useless in the treatment of malaria.

The experimental work included in this article was carried out partly in the Pharmacological Laboratory of the University of Edinburgh and partly in the Pasteur Institute of India at Kasauli; and to Professor Sir Thomas R. Fraser and Captain W. F. Harvey, I.M.S., respectively, I tender my thanks for permission so freely granted to work in their laboratories.

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