Quinine Therapy in Malaria.

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THE salt of quinine which is most commonly in use is the sulphate which is the cheapest, and in many ways, the most popular, but as it is only soluble in 800 parts of water the addition of some acid is necessary in order to keep it in solution. The hydrochloride is more expensive and at the same time more soluble—in 40 parts of water. The so-called tasteless salts of quinine, euquinine (the ethyl carbonate) the tannate and the carbonate are practically insoluble, and, therefore, should not be used except in extremities in dealing with nervous ladies and some children who will not, or cannot, swallow the liquid preparation. The hydrochloride is regarded usually as the most useful preparation for general routine use, whilst the more soluble bihydrochloride is reserved for injection either by the intramuscular or by the intravenous route.

The most propitious moment to administer quinine during the actual attack of malaria has been the subject of speculation. It is no longer regarded as dangerous to exhibit quinine when there is a degree of pyrexia, but it is, I think, generally agreed that the drug exerts its maximum effect if given when the acute paroxysm is declining and when the patient is beginning to perspire, for at that moment the parasites have sporulated and the merozoites are free in the blood plasma, and in a condition in which they are most susceptible to the action of quinine.

Many methods have been advocated in order to mask or remove the bitter taste of quinine. An agreeable and efficacious method is to prescribe it in an effervescing mixture with citric acid gr. X to which are added four grains of ammonium carbonate and gr. XX of potassium bicarbonate. Quinine is rendered less bitter if dissolved in milk, whilst syrup of orange and glycerine disguise the

taste, and a practical method of cleansing the mouth is to chew a piece of bread.

Something must be said about the toxic effects—occasionally when given in large doses it may produce deafness and amblyopia, which may prove very persistent and occasionally permanent. The amblyopia is due to spasm of the arterioles of the retina and the deafness to the direct action of quinine upon the auditory nerve.

Quinine idiosyncrasy or quinine intolerance is occasionally met with and may be a most disturbing factor. In some people even minute doses of quinine may produce a profuse and most irritating urticaria, in others intractable dyspepsia, whilst in others again a rare, but genuine, quinine hæmoglobinuria has been noted. A useful method of determining quinine idiosyncrasy when present has been described by Dawson and Garbale, who have shown that if a solution of 1 : 10 quinine is applied to a scratch on the forearm a zone of ædema and erythema immediately appears in a susceptible person.

Quinine in Benign Tertian Malaria.

The most dramatic results of quinine therapy are seen in this form of malaria, so striking is the cutting short of the fever and the disappearance of the parasites from the bloodstream that the effect of quinine upon the temperature curve is often used as a method of differential diagnosis from other fevers, in the absence of a microscopical examination. Whatever the exact explanation may be, it has been established as a scientific fact that quinine has a selective action for the trophozoites of this infection and a much less marked action upon the sexual forms. This phenomenon is much more striking in subtertian infections as will be noted later. A benign tertian malaria attack is usually ushered in with a rigor and a high temperature.

Vomiting is not usually a special feature, so that quinine may be readily exhibited by the mouth. Directly the patient commences to perspire the first dose should be administered and, to promote sweating, it is advantageous to combine it with 10 grains of aspirin. For an adult male European the optimum dosage, as laid down originally by Manson (a rule which followed at the present day) is 30 grains a day, divided into three doses of 10 grains each. There appears to be no special advantage in giving larger doses than this; but I have frequently observed that smaller doses, such as 15 grains daily, do not control the fever, nor cause the parasites to disappear from the circulation. This,

the maximum dosage, should be kept up for the next four days and then subsequently dropped to 20 grains daily for the next week. I am convinced that the generally held belief that it is only necessary to exhibit quinine for a short period subsequent to the fever attack is a great mistake and actually predisposes towards further relapse, so that it is necessary to institute an anti-relapse treatment. Personally, I favour the method of giving 10 grains of quinine daily for six weeks following the more massive treatment described. Others, I know, favour the week-end treatment, which consists of 15 grains daily for three days in the week. The underlying principle is by daily bombardments with quinine to extirpate the last remaining malaria germ in the system. Unfortunately, this *desideratum* is by no means always obtained.

Smaller doses of quinine are given to women, the maximum being 20 grains a day, whilst children tolerate the drug well—one-twentieth of the adult dose should be given for each year of age, so that a child of five years would receive one quarter of the adult dose.

It is to be regretted that even by continuous therapy the occurrence of subsequent relapses cannot be absolutely guaranteed; as James has shown, they may occur from nine months to one year after the apparent cure of the infection. In order to avoid this disagreeable possibility, one should endeavour to build up the resistance of the body by good food, fresh air and moderate exercise. There is some reason to suppose in the quiescent stage that salvarsan has some action on the parasite, or at least, exerts a definite tonic action on the body, so that I am in the habit of combining one or more injections of neosalvarsan 0.3 grains as an adjuvant to quinine therapy. Then there are iron and arsenic tonics which are frequently given with the quinine. Of one thing I am certain, and that is that quinine does not exert its maximum effect unless the intestinal tract is in a receptive state for its absorption. Therefore, it is necessary to combine quinine therapy together with a saline aperient such as Epsom salts, which should be given at the commencement of quinine, and subsequently once or twice weekly.

Although intravenous and intramuscular quinine injections may on occasions be useful in combating specially virulent benign tertian infections, yet there is no evidence to show that the course of the disease is necessarily shortened thereby. In malarial cachexia I am convinced that only small doses of quinine are indicated; it is much more

advisable to give suitable arsenical tonics and iron injections than to resort to continuous drenching with quinine.

Subtertian malaria infections may run a very mild course or be extremely severe. The parasite differs from the foregoing, mainly by the rapidity with which it multiplies and by its mode of reproduction by sporulation in the smaller capillaries, which by these means may be completely blocked with masses of parasites and blood-stasis may be produced. It is a curious fact that the trophozoites are extremely susceptible to the action of quinine even in small doses, while the sexual forms, or crescents, are extremely resistant. Thus it comes about that it is comparatively easy to control the more urgent signs and symptoms with relatively small doses of quinine, yet when the patient is recovering and the fever is quiescent, crescents may be found in numbers in the bloodstream and they may persist for several weeks. In fact, it is extremely difficult to extirpate the crescents with quinine. I have records of cases in which crescents persisted in the blood for 28 days after 840 grains of quinine had been absorbed. When there is no persistent vomiting or other contra-indication, quinine should be given by the mouth in subtertian malaria. It is not necessary to give such large doses as in benign tertian. One should commence with grs. XV of the alkaloid in solution and gradually increase to the maximum of gr. XXX daily. But in very severe toxic cases, in which there has been a considerable degree of blood destruction with consequent anæmia great caution has to be observed in "pushing" quinine on account of the liability to *blackwater fever*, a danger to which further allusion will be made. One should, therefore, commence with grs. V daily and gradually increase. In the more severe clinical forms with bilious vomiting, and it may be with delirium, quinine given by the mouth does not suffice to control symptoms, then resort must be had to intramuscular injections. In such circumstances intramuscular injections appear to act like a charm and are certainly indicated. The bihydrochloride salt should be used. The whole rationale of intramuscular quinine has been much discussed. It is unquestionable that whenever or wherever quinine comes into contact with muscle fibre it causes a degree of necrosis, so that the dosage of quinine must be carefully gauged and the site of injection selected. The proper dosage for quinine injection is about 10 grains, and the site the gluteus maximus muscle. I am very averse to multiple quinine injections and I cannot see that they are therapeutically indicated, even when given daily I am very

much opposed and I consider three or four weekly ample. It is hardly necessary to state that quinine injections, especially if given into a limited area and at frequent intervals, are not without danger. They may produce profuse necrosis and even (in the absence of any specific microbic injection) profuse suppuration and tetanus. I have seen cases uncontrolled by blood examination (which they should be) treated by continued injections in the belief that they were controlling fever, when all the time the rigors were brought about, not as had been supposed by a particularly resistant parasite, but by the continued absorption of pus from minute intramuscular abscesses.

Intravenous injections of quinine are indicated in the so-called pernicious forms of subtertian malaria, especially when the sporulating parasites are congregated in the capillaries of the brain, producing coma, or in the coats of the intestines producing choleraic diarrhoea or other forms of abdominal disease. The rapidity with which intravenous quinine acts in these dramatic states is remarkable. The hydrochloride salt should be used, in a dosage of 10 grains in 10 c.c. of distilled water and given into the median basilic vein. There is no indication for more heroic doses than this as larger quantities of quinine are very apt to bring about too great a dissolution of the parasites and dangerous symptoms may ensue. Much safer is it to give smaller injections of quinine—grs. III—each at frequent intervals, so as to avoid this contingency. As it has been shown that intravenous injections of quinine are apt to be followed by a fall of blood pressure it is advisable to combine it with the injection of 5 min. of a 1 : 1,000 solution of adrenalin.

Subtertian infections are more easily cured by quinine than are benign tertian, so that it is not necessary to give such a prolonged course of anti-relapse treatment, and I am convinced that often in this disease the desideratum of *Therapia magna sterilisans* is attained. However, in general the main scheme of quinine therapy should be adhered to.

Now we come to the difficult question of blackwater fever. Does quinine produce this catastrophe, or does it pre-dispose towards it, or does it not? I confess I find it more difficult than ever to answer this question. To my mind it is unquestionable that blackwater fever is an accident which occurs only in subtertian infections, not in the other two forms of malaria. In many cases I have noted that the exhibition of massive doses of quinine (by this I mean 20-50 grains) does certainly seem to precipitate the attack, and I have learned to be specially suspicious of those cases of subter-

tian malaria who are obviously ill, whose spleens are greatly enlarged, but in whose blood relatively few parasites are to be found. It may be that quinine is but one of the factors that predispose towards the blackwater state—there may be others, such as cold, alcohol or the toxins of some other disease—or it may be that quinine in certain individuals brings about a state in the red corpuscles of greater susceptibility to lœmolytic. At any rate it must be borne in mind that the rôle of quinine in the production of blackwater fever is very widely held. The outcome of this is that one should treat suspicious cases of subtertian infection with great circumspection, combining graduated quinine dosage with alkalies and with a liberal supply of glucose.

There is not very much to be said about the use of quinine in quartan malaria. Large doses should be used and the maximum dose of 30 grains should be persisted in longer than in benign tertian, as quartan parasites are much more resistant to the action of quinine than the other two, so that parasites can be demonstrated in the blood for ten or more days after the initiation of quinine therapy. The question of anti-relapse treatment is also important as quartan is by far the most persistent infection and relapses may occur over as long a period as five years. The tendency of quartan infections to be associated with nephritis should also be noted, and it has been shown that the appearance of albumin in the urine in this infection is an indication for pushing the quinine dosage, not the reverse.

It is necessary now to give a short account of recent attempts to improve the standard treatment of malaria by newer compounds. In attempting to synthesize quinine in the laboratory Schulemann, Schönhofer and Wingler produced some seven years ago a derivative of quinoline—(alkyl-amino-6-methoxy-quinoline) which is now known as *plasmoquine*. The probable action of this compound on malaria in man was gauged by its comparative action upon the *plasmodium* of birds (canaries artificially infected). Roehl and Horlein were better enabled to do so as it had already been shown by Sargent and Giemsa that quinine acted similarly upon the plasmodium in the birds' blood as it did upon the human malaria parasites. Plasmoquine in doses of 0.06 g. (gr. I) daily caused a rapid disappearance of benign tertian parasites from the blood of man, but had a less effect upon the ring forms of the subtertian parasite. Most remarkable, however, is its marked selective action upon the sexual forms of these parasites. The benign sporonts disappear almost immediately, whilst the

otherwise refractory crescents disappear in about four days after a total of 0.24 g. of the drug, so that in plasmoquine undoubtedly a new malaria specific has been discovered. But there are cogent defects in the drug. The large doses originally advocated, 0.25 g. and 0.12 g., daily were obviously far too large and were often accompanied by alarming toxic symptoms, such as a livid blue cyanosis of the lips and nails, which is due to the conversion of hæmoglobin into methemoglobin by plasmoquine. Moreover, its inability to control subtertian fever and to extirpate the ring forms of the parasite associated with this fever were disappointing. It was then demonstrated by Schulemann and Memmi that, not only was the therapeutic action of plasmoquine greatly enhanced, but its toxic manifestations were greatly diminished, or rather neutralised, by the addition of a small amount of quinine. Hence the composition of *plasmoquine compound*. Each modern tablet of plasmoquine compound contains 0.01 g. (one-sixth grain) plasmoquine with 0.125 g. (2 grains) quinine sulphate. The scheme of dosage is to give the drug in full doses of six tablets daily for one week (*i.e.*, plasmoquine gr. I and quinine 12 grains daily) with three days' interval between each weekly course for five separate weeks, and as anti-relapse treatment.

The question next arises—can one estimate the present position of plasmoquine in malaria therapy? Personally, I believe that plasmoquine compound is a useful adjuvant to quinine treatment and in many circumstances is an efficient substitute. Firstly it is easy to take, and it is comparatively tasteless. Many people can tolerate it who are intolerant of quinine in ordinary therapeutic doses. It is, in my opinion, more efficacious in controlling benign tertian malaria than is pure quinine; it frequently cures an infection which appears resistant to pure quinine. It banishes the crescents from the blood in subtertian malaria; it is readily taken and readily absorbed by children in smaller doses and it is readily borne by pregnant women in whom it controls the fever and does not predispose to absorption, as does pure quinine. I have had several cases of intractable malaria in pregnant women who have gone to full term on plasmoquine therapy without any further attacks.

Manifestly the plasmoquine has attained a distinct place in our armamentarium against malaria.

Whatever may prove to be the limitations of plasmoquine in its present form, it has opened up new avenues for exploration, so that it is quite possible that less toxic and more highly specific antimalarial compounds may be obtained.