MALARIA AND ITS TREATMENT.

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MALARIA derives its name from the two Italian words mal (bad) and aria (air), as it was believed that the disease was produced by the inhalation of poisonous emanations which rise from the ground, especially in marshy places. The discovery of the malarial parasite by Laveran in 1880, and its life cycle in the anopheles mosquito by Ross in 1898, made the nature of the disease no longer a mystery and gave indications of how efficient measures of prevention might be instituted. Unfortunately, despite full knowledge of the nature of the disease and its mode of spread, malaria in the tropics still remains responsible for a greater number of deaths and far more disability than any other disease.

Before proceeding to consider the treatment of malaria a few points regarding its symptoms and difficulties in diagnosis might be of interest. The typical attack of malaria comes on every second or third day, and consists of a cold stage followed after half an hour by a more prolonged hot stage, terminating in a sweating stage, during which the fever drops and the patient becomes comfortable again until a further attack comes on. Unfortunately the history of an attack is often not typical and so cannot always be relied on to assist one in arriving at the diagnosis; not infrequently the attack comes on quite irregularly with fever of almost any variety, the correct diagnosis only being made by suspecting its malarial nature and carrying out blood-smear examinations for the detection of the malaria parasite. Even careful blood examination, especially in malignant malaria, may fail to demonstrate the specific parasite owing to the small size of the rings, and more especially to the fact that only the very early stage of the asexual cycle of this type of malarial parasite is found in the peripheral circulation, the amœboid forms disappearing into the deep tissues and thus not being found on blood-smear examination.

I have repeatedly seen cases of subtertian malaria with irregular temperature, or even no temperature at all, suffering from ill-health and anaemia for long periods, the malarial nature of the affection not having been detected owing to the fact that steps had not been taken to procure blood-films at different times during the day, so as to catch the parasite during the short period of its cycle in the peripheral circulation.

A few notes on a series of over 100 cases of malignant malaria cases infected during intravenous heroin administration may be of interest. These malarial cases occurred mostly during the summer of 1929; the

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disease was confined entirely to heroin addicts, the parasites being conveyed from man to man by means of malaria-infected blood gaining access to the syringes used during the intravenous heroin injections and so being passed on to other individuals and setting up an active malarial disease in an ever-increasing number of these heroin addicts.

Fig. 1.—The arm of an intravenous heroin addict, who had become infected with subtertian malaria during the administration of the drug, showing pigmentation along the veins resulting from the repeated injections.

HISTORY OF QUININE AND MALARIA.

In 1638 Contessa del Cinchon, wife of the Spanish viceroy of Peru, is said to have cured an intermittent fever by the bark of an indigenous tree of Peru; the bark was then introduced to Europe, the name cinchona being given to it in honour of the Countess. Much confusion, however, existed as to its value because no accurate differentiation could at that time be made between the many varieties of fevers due to different diseases, many of them resembling malarial fever. This difficulty in diagnosis led Torti in
1753 to divide fevers into those that were cured by cinchona and those that were not, this being at that time the best method of differentiating malaria fever from other types of fever.

In 1820 the alkaloid quinine was isolated from cinchona bark and soon came into general use. It has proved to be as effective against malaria as any of the other alkaloids of cinchona, allowing greater accuracy in dosage than was possible with the bark. Quinine still remains the most effective single drug in the treatment of malaria, but many diverse modes of administration and combinations with other recently discovered drugs are now used.

Unfortunately we have no method of determining when a patient is entirely cured of the disease; he may be afebrile and there may be no parasites in his blood for many days after a course of quinine, and yet suddenly, from exposure to cold or strain of any sort, he may go down with an acute relapse of his old disease. This inability to arrive at a diagnosis of cure leads to great confusion as to the optimum course of quinine treatment, and difficulty in assessing the value of new drugs put on the market as cures of malaria.

Quinine should always be given in a soluble form to enable ready absorption to take place from the intestine; the sulphate of quinine therefore should never be given in tablet form, but should be dissolved by the aid of an acid and taken in solution. Complete absorption of such a preparation takes place within six hours of administration and its presence can usually be detected in an unchanged form in the urine within half an hour of administration; this latter fact can be made use of to test whether the quinine given is being absorbed or not. After reaching the blood-stream it is quickly deposited in the liver, spleen, kidneys, etc., and being broken up in these organs is believed to become inert.

The mode of action of quinine is not definitely known, but during or after absorption some change in its composition apparently takes place enabling it to act on the parasites in the blood-stream and destroy them, the resultant product of this destruction perhaps stimulating the defensive mechanism of the body and so enabling it to deal with the remaining parasites.

The usual dose recommended for a fresh infection is ten grains of a soluble salt of quinine or of the sulphate of quinine in solution three times a day for one week, followed by a further week's course of ten grains twice a day; this course can be repeated or modified if relapse occurs. Absorption of the drug is assisted by keeping the bowels well open, so treatment is usually commenced by giving three grains of calomel followed by two to four drams of magnesium sulphate in a small amount of water, and repeating the saline aperient daily if required. Sugar-coated tablets should never be used owing to difficulty in their absorption; but fresh tablets of a soluble salt of quinine, such as the hydrochloride of bihydrochloride, are quite suitable, though more expensive than the quinine sulphate solution.
Sinton discovered that quinine acts better when associated with massive alkaline treatment, and in certain resistant cases very good results have been obtained by this method, large doses of alkalies being given along with the quinine course.

In benign tertian and quartan infection, if the patient is actually in an attack of "ague," the commencement of quinine treatment may, with advantage, be delayed till the termination of the attack, aspirin, the application of heat and hot drinks being employed to hasten the onset of the sweating stage. In subtertian malaria, however, quinine should always be given without delay, as an apparently mild attack may suddenly develop severe complications with coma, convulsions, or acute intestinal symptoms. In fact, malignant malaria cases are as urgent as cases of acute appendicitis and should be treated by the specific drug at the earliest possible moment after diagnosis. One has not infrequently seen a case of malignant malaria, apparently quite well, suddenly fall down unconscious from blockage of the cerebral vessels, and then even the most energetic treatment may be of no avail to save the life of the patient. Cases of malignant malaria, however, once they have been got under the influence of quinine, do not tend to have the troublesome relapses which are sometimes found with the benign tertian and quartan types of infection.

Cases of pregnancy with malarial infection are often given insufficient quinine owing to the fear of inducing abortion, but this is much more likely to occur as a result of withholding quinine than from the administration of adequate doses of the drug, and threatened abortion should be looked upon as a definite indication for quinine treatment, half the usual dose being given twice as often, so that the total administered may be the same as if the patient were not pregnant. Nowadays, plasmoquine may be employed with quinine in the treatment of these cases.

The oral method of administration of quinine is the method of choice, but in certain emergencies other routes may have to be employed; where the infection is due to malignant malaria and complications, cerebral or otherwise, set in, then the patient should be rapidly brought under the influence of the drug by using the intravenous method. As quinine is a cardiac depressant the individual dose should be reduced to 0.5 gramme, diluted in ten cubic centimetres of water, which should be injected slowly. As soon as the emergency is over, the oral route should be again employed. I have known a case where sudden death of the patient occurred almost immediately after intravenous injection of one gramme of quinine, given rapidly, the doctor being under the misapprehension that he was giving only one grain.

Intramuscular administration is occasionally used, but here the rate of absorption is as slow as by the oral route; it is also very irritating locally, and is not devoid of risk owing to the local necrosis so produced being a suitable nidus for the development of tetanus and other bacilli. I have seen more than one case showing resultant nerve lesions due to the injection
having been made close to important nerves, such as the sciatic and musculo-spiral, the paralysis produced by damage to these nerves persisting for very long periods. On investigating the history of two such cases seen in Egypt, there did not appear to have been sufficient reason for the intramuscular route being employed instead of the oral one, no urgent symptoms being present when the quinine was given. If the intramuscular route is selected, one of the safest sites of administration is in the buttocks with the patient seated, so that the area with important nerves, etc., shall be protected from injury.

The subcutaneous route should never be employed, owing to danger of causing sloughing of the superficial tissues in the vicinity.

Real cases of quinine intolerance are very occasionally met with where even such small doses as one grain may cause marked cardiac and other symptoms. I have only met one such case amongst many thousands of cases treated with quinine. Where the patient states that he is intolerant, this statement can be readily verified by the application of a ten per cent. solution of quinine to a scratch on the arm, using normal saline as a control. If he is sensitive the scratch becomes red and swollen within a few minutes of applying the test. If the patient is sensitive, treatment can be commenced by giving \( \frac{1}{3} \) of a grain as an initial dose, and doubling the dose every two hours until two grains are being given. Sodium bicarbonate in ten-grain doses should be given along with each dose of quinine.

Ringing in the ears and deafness almost inevitably result from the taking of quinine, and indicate that absorption is taking place. Permanent deafness and blindness, however, have resulted from over-dosage, so excessive doses should be avoided. Quinine amaurosis may occur from a single excessive dose, or, more often, from such doses repeated over a long period, permanent damage to the optic nerve with resultant blindness occurring. I have seen one such case follow soon after the taking of a large quantity of quinine sulphate solution at one draught, the patient having done so to show that he did not mind the taste of the drug.

Euquinine has the advantage with children of being almost tasteless; it is quite an efficient preparation.

Quinine tannate, on the other hand, is insoluble, and therefore not so useful, as it is only slowly absorbed.

Cinchona febrifuge varies markedly in its composition, and many consist of (a) all the alkaloids derived from the cinchona bark, or (b) residual alkaloids left after quinine has been separated in its manufacture. Its great advantage is its cheapness, but the disadvantage is the uncertainty of its composition and dosage.

Arsenic has been employed for many years in the treatment of malaria, Fowler's solution being the preparation originally used for this purpose. The results obtained are satisfactory in both fresh infections with malaria and in chronic relapsing cases of this disease; in the latter type of case, cures have frequently been brought about by beginning with one drop of
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Fowler's solution three times a day, and increasing the amount given by one drop at each dose till ten drops three times a day are being administered; if symptoms of intolerance have appeared, the drug should be discontinued for a fortnight before repeating the course of treatment. During this arsenical treatment of chronic malarial cases ten grains of quinine may be given twice daily with advantage on two consecutive days during each week.

Recently new organic compounds of arsenic have been employed. One of these, stovarsol, has a marked effect in producing a clinical cure in benign tertian malaria, causing the parasites, both sexual and asexual, to disappear from the peripheral circulation. Its action is very much enhanced when given with quinine, and their combined use seems to lessen the tendency to relapse in cases of chronic benign tertian infection. The general condition of the patient under stovarsol treatment usually markedly improves; precautions must, however, be taken to prevent the toxic manifestations which occasionally occur during its administration. Stovarsol seems to have little or no action on the parasites of malignant tertian malaria.

About 1925 plasmoquine, a synthetic derivative of quinoline having a formula resembling quinine was introduced and its effect on malarial parasites investigated. It was found to have a markedly lethal action on the parasites, both sexual and asexual, of benign tertian and quartan infections, but, whilst having a destructive effect on the gametocytes of *Plasmodium falciparum*, it has little or no action on the asexual forms of this parasite, and so does not influence the course of the malignant tertian disease. Another great drawback to plasmoquine is its toxic effect, several deaths having been recorded from its use. The chief toxic symptoms observed were cyanosis, pallor, nausea, gastric pain and haemoglobinuria. These toxic effects led to the diminution of the dosage of plasmoquine and its use combined with quinine. Since this modification has been carried out, toxic effects have been much less evident. In a recent series of over fifty cases of malignant tertian malaria treated by us in Kasr-el-Aini Hospital with plasmoquine and quinine, careful watch was kept for the appearance of symptoms of toxicity, but in no case were any serious symptoms observed; very occasionally slight discomfort was complained of in the mid-epigastric and splenic region, usually towards the end of the first week's course, but in no case had the course to be modified in any way owing to the appearance of these toxic symptoms. No cyanosis was observed in any of these cases.

Plasmoquine and quinine together are now used extensively in the treatment of malaria, very good results being obtained by this combined treatment, the best route of administration being the oral one. We have employed the intravenous method in a series of cases of malignant malaria, but the results were no better than those obtained by using the oral method. We have found the combined treatment with plasmoquine and quinine, in
doses of plasmoquine 0.04 gramme and quinine 1.2 grammes daily, to be a safe and effective dosage for the treatment of adult patients suffering from malaria; such doses have proved of great value in bringing about a cure in chronic benign tertian malaria and in rapidly clearing the peripheral circulation of both asexual forms and crescents in malignant tertian malaria. In a series of malignant tertian cases observed by us under this course of treatment the average time taken for the crescents to disappear was four and a half days and for rings 3.25 days. The rapid disappearance of crescents compares very favourably with the results previously obtained by quinine alone, when crescents were frequently observed to persist for very long periods, even when the dose of quinine administered had been an adequate one. The persistence of crescents in the peripheral circulation may result in anopheles mosquitoes becoming infected and the disease being carried to other individuals in the vicinity.

A most important observation was made by Barber, Komp and Newman in 1923; they found that mosquitoes fed on human crescent carriers who had received small doses of plasmoquine for short periods of twenty-four to forty-eight hours never became infected, even though crescents were still present in the blood. If these observations are confirmed, this action of plasmoquine in inhibiting the further development of the gametocytes in the mosquitoes may be utilized in areas where human carriers are prevalent, small doses being given to prevent infection of the mosquitoes.

Using daily doses of plasmoquine 0.04 gramme, and quinine 1.2 grammes, given in three divided doses, the best course of treatment is to begin with one week’s continuous treatment, this to be followed by four days’ rest and three consecutive days’ treatment. The interrupted treatment is then repeated till one month’s treatment in all has been completed.

We consider the interval at the end of the first week advisable, for it
is at this stage of the treatment that toxic symptoms are most likely to appear, and this break in the treatment allows of recovery from any toxic effects of the drug before the treatment is continued, so as to complete the month's course.

Some observers, however, prefer to carry out continuous treatment with similar doses over a period of twenty days, and state that they have obtained good results from this method of administration.

If only one drug is to be used in the treatment of malaria, quinine is the one of greatest value, and its use will bring about a cure in the great majority of cases of fresh malarial infections.

The oral method of administration is the method of choice, and care should be exercised to ensure that the bowels are kept well prepared for the absorption of quinine by the administration of saline aperients.

Arsenic is of considerable value, employed either at the same time as the quinine treatment or given during convalescence, using Fowler's solution in gradually increasing doses with intervals, or one of the newer organic compounds such as stovarsol.

The employment of plasmoquine with quinine has proved of the greatest value in bringing about a cure, especially in chronic relapsing cases of benign tertian and quartan malaria. This combined treatment has also been of great assistance in malignant tertian cases, owing to its effect in rapidly clearing the peripheral circulation of crescents and inhibiting the further development of these parasites in the anopheles mosquitoes. When given in the smaller doses now recommended and combined with quinine, toxic symptoms are either slight or entirely absent, and we need have no fear in prescribing the drug.