THE TREATMENT OF MALARIA

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Hyperinfection in Malignant Tertian Infection

Where there is hyperinfection associated with cerebral features, where algid malaria is found, where the patient cannot swallow or when vomiting and diarrhoea are severe, anti-malaria drugs should be given intravenously. For this purpose, quinine hydrochloride gr. 10 in 10 to 20 ml. of isotonic saline may be slowly injected at the rate of 1 gr. per minute and repeated in six hours if necessary. The injection must be given slowly owing to the severe drop of blood pressure resulting from rapid injection. Never more than three injections should be given in the first 24 hours. If the blood pressure is unduly low or algid symptoms are present, quinine hydrochloride may be given slowly in one pint of saline rather than in concentrated form.

Chloroquine hydrochloride in a dosage of 200 to 300 mg. may be injected intramuscularly and repeated in eight hours, or 400 mg. of base in 500 ml. normal saline may be given slowly by intravenous drip, taking one hour for the injection. The sulphate in a dosage of 200 mg. base may be given intravenously and repeated in eight hours. Parenteral medication is stopped when the patient regains consciousness and when shock and symptoms of collapse improve.

It is often necessary in this condition to combat dehydration and to maintain blood volume by intravenous injections of isotonic saline (0.85 per cent.) or glucose (5 per cent.) given by continuous drip or intermittently.

Mepacrine hydrochloride (0.3 g.) may also be administered intramuscularly if other drugs given by the intravenous route are not available. A total of 1.0 g. mepacrine parenterally should not be exceeded in the first 24 hours of treatment. Lumbar puncture with the withdrawal of 20 ml. of cerebrospinal fluid may be helpful. In addition, should hyperpyrexia be present, the naked patient is placed under a fan on a wire mattress and covered with a sheet sprayed with ice-cold water.

When the rectal temperature reaches 102°F. hydrotherapy should be stopped.

Finally, if haemolytic anaemia be severe the patient should be transfused; in severe cases several pints of blood may be given. Oral medication with iron should follow.

Ordinary M.T. Malarial Attack

Bed rest during the febrile period and for at least three days after the temperature is normal is essential, especially in the first attack of malignant tertian malaria. Should there be anaemia, a pill containing ferrous sulphate (gr. 3) should be given thrice daily and if the anaemia proves severe, blood transfusion will help convalescence.

For M.T. malaria one of the more active schizonticidal drugs should be given orally. Proguanil (paludrine) and pyrimethamine (dara-prim) though effective schizonticides, act too slowly in reducing the temperature and for this reason drugs like chloroquine sulphate or diphosphate and mepacrine hydrochloride are preferable.

Chloroquine sulphate or diphosphate is given orally to non-immunes in the following dosage: six tablets (or 900 mg.) on the first day; two tablets (or 300 mg.) on the second and third days. In partial immunes, four tablets (or 600 mg.) are given on one day only. Chloroquine is probably the best drug to use for the routine treatment of malaria.

Mepacrine hydrochloride is a very effective schizonticidal drug. It is given to non-immunes in a dosage of 300 mg. thrice daily for the first day, twice daily on the second day and then 100 mg. thrice daily for five days. Some 300 to 500 mg. of mepacrine are given to partial immunes in a single dose.

Quinine dihydrochloride or sulphate in a dosage of 10 gr. thrice daily is given for five to seven days to non-immunes. This drug is not used so much now in chronic M.T. malaria owing to the danger of its precipitating blackwater fever.

Lapudrine was discovered by Curd, Davey *et al.* in 1950.² It has one more chlorine atom than proguanil in the benzene ring and is more active than proguanil. It is more effective therapeutically and prevents the development of oocysts in the mosquito stomach.

Radical Cure of Vivax and Quartan Malaria

There is no evidence that in falciparum malaria late exo-erythrocytic forms persist. Once parasites have all been destroyed in the peripheral blood by schizonticidal drugs radical cure has been achieved; the so-called relapses are due either to the persistence of erythrocytic forms in sub-microscopic numbers in the peripheral blood or to reinfection. In vivax and quartan malaria, and possibly in *P. ovale* infections also, this is not the case. With benign tertian and quartan parasites late exo-erythrocytic forms often persist and produce relapses despite the previous total eradication of parasites in the circulating blood by schizonticidal drugs. We are dependent on the 8-amino-quinoline drugs for the radical cure of both these species of parasite. Pamaquine has been successfully used for this purpose for many years and more recently American workers have successfully produced several new 8-amino-quinoline drugs including pentaquine, iso-pentaquine and primaquine which are even more effective.

It was found that primaquine in a dosage of 15 to 30 mg. daily for 14 days completely eradicated *P. vivax* parasites by destroying the persistent exo-erythrocytic forms in the liver. Toxic side-effects include gastro-intestinal disturbances, and haemolytic anaemia to which negroes are prone; the latter may be associated with haemoglobinuria. Concurrent administration of sulphadiazine and mepacrine may increase the toxicity of the 8-amino-quinolines, and for this reason must be avoided.

Reports were published on primaquine by authority of the Council on Pharmacy and Chemistry, U.S.A.¹¹ If fever be present primaquine is given in combination with one of the schizonticidal drugs such as chloroquine or quinine but not mepacrine. Four groups of patients were treated. The first comprised 232 men who received chloroquine 1.5 g. in divided doses over three days; 64 patients (27 per cent.) relapsed. The second group of 246 men received the same dose of chloroquine plus 27 mg. primaquine daily as three divided doses for 14 days; one patient relapsed. The third group of 231 men received the same dosage of chloroquine and primaquine in a single daily dose of 15 mg. for 14 days; none relapsed and there were no significant toxic effects.

Prevention of Transmission

The 8-amino-quinolines in non-toxic dosage also destroy the sexual forms of *P. falciparum* in the peripheral blood and the administration of pamaquine 10 mg. t.d.s. or of primaquine 7 mg. t.d.s. for two or three days are effective from this viewpoint. Proguanil, lapudrine and pyrimethamine do not destroy the gametocytes in the blood stream, but they do prevent their development in the mosquitoes' stomach so that infection of the salivary glands does not occur. In consequence, mosquitoes feeding on patients taking these drugs in appropriate dosage do not transmit the disease to others.

Causal Prophylaxis and Suppression

In experimentally infected volunteers in Cairns it was found with the South West Pacific strains by Fairley *et al.*⁵ that quinine (gr. 10) daily failed to suppress malignant tertian malaria and a proportion of benign tertian infections also. Sulphadiazine proved reasonably satisfactory in a dosage of 1.0 g. daily in M.T. infections, but overt attacks of B.T. malaria very frequently occurred.

When mepacrine (0.1 g.) was given every day invariably, it was found that malignant tertian infections were both suppressed and radically cured and that benign tertian infections were suppressed throughout the period of mepacrine administration. Benign tertian relapses, however, generally occurred from two to seven weeks after the drug was stopped, but malignant tertian malaria never reappeared.

Factors generally regarded as precipitating relapses in latent malaria were also investigated. These included exposure to wet and cold, physical exhaustion, anoxia and chill as in high altitude flying, blood loss, anaesthetics, surgical operations and alcoholic excesses and strong emotions of anger and fear associated with outpouring of adrenalin. No volunteers, however, developed malaria fever while mepacrine was being taken.

Immediately following these experimental results a military conference was held in Queensland and all the measures suggested were adopted. In consequence, malignant tertian malaria and blackwater fever practically disappeared in the South West Pacific and though benign tertian and quartan malaria frequently followed cessation of mepacrine administration, fatalities were almost unknown. Comparable results were obtained amongst British troops in Burma but the incidence of malaria in Japanese troops persisted at a very high level throughout the whole war.

Chloroquine diphosphate was discovered and patented in Germany in 1938 and was synthesized in U.S.A. during the war. Fairley *et al.*⁶ found it prevented symptoms of malaria developing in

volunteers experimentally infected with M.T. malaria while taking 0.1 g. daily. Subinoculations on the eighth day were always positive, but after ceasing the daily dose on the 23rd day, parasites had been destroyed and they never reappeared in blood smears. On the 81st day the volunteers were again successfully reinfected, no evidence of premunity being found. Similar results were recorded in a few volunteers taking 50 mg. of chloroquine daily. As with mepacrine, benign tertian infections were completely suppressed with chloroquine, but relapses generally occurred within two months of cessation of drug prophylaxis. Davey and Robertson⁴ in Nairobi working on Army volunteers confirmed Fairley's findings that chloroquine in a dosage of 50 mg. daily was an effective prophylactic against M.T. malaria, eliminating the infection entirely.

Proguanil was discovered by Curd, Davey and Rose³ to be effective in bird malaria. It was investigated in man by Adams *et al.*¹ and by Fairley *et al.*⁶ In M.T. malaria it was found to be an excellent prophylactic drug destroying the pre-erythrocytic forms in the liver before they reached the blood stream. Subinoculation on the eighth day was always negative in these patients, whereas with mepacrine and chloroquine it was invariably positive, the parasites being destroyed by these drugs in the blood stream later. With B.T. and quartan infected volunteers, fever failed to develop while they were taking proguanil, but generally appeared within two months when drug administration ceased. The dosage of proguanil for non-immune adults is 100 mg. daily; for children under 6 years it is 25 mg. daily and from 6 to 12 years it is 50 mg. daily.

Lapudrine. Robertson⁹ reported that 15 mg. once a week is an effective prophylactic.

Pyrimethamine (daraprim). Rollo¹⁰ described tests of antimalaria activity against the blood forms and exo-erythrocytic forms of *P. gallinaceum* and also against the blood forms of *P. berghei*. Goodwin⁸ stated that good reports on the suppressive action of pyrimethamine had been received from the Belgian Congo, the Gambia, Indo-China and Tunisia but less so from Malaya. Foy and Kondi⁷ investigated the action of pyrimethamine on the gametocytes of *P. falciparum*. They showed it rendered gametocytes uninfected to *A. gambiae*. It is now recognized that the best value of paludrine and daraprim is for prophylactic and suppressive purposes since both these drugs act slowly in the febrile attack. Daraprim in a dosage of 25 mg. per week is given to adults; children under the age of 6 years receive 6.25 mg. per week and those from 6 to 12 years receive 12.5 mg. per week.

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