BRITISH MEDICAL JOURNAL

LONDON SATURDAY JULY 18 1942

THE DIAGNOSIS AND TREATMENT OF MALARIA IN ENGLAND

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One of the consequences of the war is the arrival in this country of a considerable number of cases of malaria, especially among members of His Majesty's Forces and the Mercantile Marine. As malaria is very amenable to treatment if recognized in time, and as it is highly dangerous and often fatal if not recognized and adequately treated, it is obvious that its diagnosis and treatment are matters of great importance. The object of this article, which has been written at the request of the War Office and Ministry of Health, is to set out briefly and simply the main points in the diagnosis and treatment of the disease.

Diagnosis

There are three common forms of malaria, caused by three different but closely related malaria parasites—viz., simple or benign tertian malaria, due to *Plasmodium vivax*; quartan malaria, due to *Plasmodium malariae*; and malignant or sub-

from the blood as the result of treatment it is important that blood films should be made before any antimalarial drug is given.

Simple Tertian Malaria

Broadly speaking, acute malaria consists of a series of malarial paroxysms associated with progressive blood destruction, debility, and enlargement of the spleen. The paroxysms of simple tertian malaria are very characteristic. They consist of three stages:

Cold Stage or Rigor.—During this stage the patient complains of a sensation of intense cold, his teeth chatter, and he shivers violently; the feeling of cold is, however, entirely subjective, and if the temperature is taken it will be found to be raised. The cold stage lasts about an hour.

Hot Stage.—The feeling of cold gives place to a sensation of intense heat; the skin is hot and dry, the face flushed, the pulse full and bounding; headache and vomiting are often severe, and the temperature is raised to from 103° to 106° F. or even higher. This stage lasts 3 to 4 hours.

Sweating Stage.—The patient breaks out into a profuse perspiration, his temperature falls rapidly, the headache disappears, the vomiting ceases, and the paroxysm is over, leaving the patient somewhat exhausted but otherwise little the worse for his experience. This stage lasts 2 to 4 hours.

The duration of the complete simple tertian paroxysm varies, therefore, from about 6 to 10 hours. Typically in this type of malaria a paroxysm recurs with almost clocklike regularity every 48 hours, and the temperature chart can hardly be confounded with that of any other complaint (Fig. 3). Unfortunately, however, all the parasites in the blood of a case of simple tertian malaria may not complete the cycle of multiplication on the same day, some of them reaching maturity on Monday, Wednesday, Friday, and Sunday, and the remainder on Tuesday, Thursday, and Saturday. In such cases of so-called double infection there is a malarial paroxysm every day, and the temperature chart is of the quotidian instead of the tertian type (Fig. 4). But even here the chart exhibits certain striking characteristics—viz., the regularity of

FIG. 1

FIG. 2

FIG. 1.—Diagrams illustrating method of making thin film. 1. Place a small drop of blood near end of slide. 2. Apply spreader slide at an angle of about 30° and allow blood to flow across angle formed by the two slides. 3. Push spreader forward at uniform rate, drawing the blood after it; a thin evenly distributed film will result.

FIG. 2.—Diagram illustrating method of making thick film. Place a small drop of blood on centre of slide and spread with needle until it occupies about the area of a sixpence. N.B.—The film should not be so dense that the hands of a watch cannot be seen through it.

tertian malaria, due to *Plasmodium falciparum*. These parasites inhabit the red blood cells. They have a regular cycle of multiplication, which in the case of simple tertian malaria is complete in 48 hours, in quartan malaria in 72 hours, and in malignant or subtertian malaria in about 36 hours. When multiplication is complete the young parasites escape from the infected red cells into the plasma and invade new red cells, and the patient experiences a malarial paroxysm.

A definite diagnosis of malaria can be made only by microscopical examination of the blood and recognition of the parasite. While this may be beyond the scope of the general practitioner, it should at least be possible to make suitable blood films and send them to a pathological laboratory for a report. A method of preparing thin and thick blood films is shown in Figs. 1 and 2. Since the parasites disappear quickly

FIG. 3

FIG. 3.—Typical simple tertian temperature chart.

FIG. 4

FIG. 4.—Quotidian simple tertian temperature chart.

the daily febrile paroxysms, their short duration (6 to 10 hours), and the fact that the febrile disturbances are separated by a definite afebrile period lasting at least 12 hours. Except at the beginning of the attack before the paroxysms have become fully developed, when the temperature tends to be irregular, the simple tertian temperature chart is characteristic enough to suggest to the physician the true nature of the complaint.

If treatment is withheld and the disease is allowed to run its course, successive paroxysms result in progressive anaemia and debility; the spleen enlarges, the patient becomes icteric (haematogenous jaundice), and he often develops herpes, especially of the lips. If still untreated he may die of exhaustion, or the paroxysms may become less severe and finally cease and the disease become chronic. In this condition the patient remains in poor health; he is anaemic, the spleen is palpable, he often suffers from slight febrile disturbances, and is liable to relapse into the acute stage.

Quartan Malaria

Quartan malaria shows no essential differences from simple tertian malaria except that the cycle of multiplication of the parasite occupies 72 hours, and consequently the patient has a paroxysm, which is in all respects similar to that of the simple tertian paroxysm, every 72 hours—i.e., on the 1st, 4th, 7th, 10th days, and so on. Here again so-called double infections are not uncommon, so that not infrequently patients suffering from quartan malaria may have paroxysms on the 1st and 2nd, 4th and 5th, 7th and 8th days, and so on.

Malignant Tertian

Malignant tertian malaria is, however, a widely different and highly dangerous infection. The paroxysms are atypical; the cold stage is of short duration and ill defined or even absent, whilst the hot stage is greatly prolonged and is associated with intense headache, frequent vomiting, and severe constitutional disturbance. The ill-defined nature of the cold stage or rigor in malignant tertian malaria is a common cause of failure to suspect the true nature of the condition by medical men who have no special knowledge of the disease, and by the patients themselves, in whose mind the rigor is so firmly associated with malaria that a rigor and a malarial paroxysm have come to be synonymous.

The temperature chart of malignant tertian malaria bears little resemblance to that of simple tertian and is consequently a common cause of failure to diagnose the condition correctly. Owing to the prolongation of the hot stage the length of the

FIG. 5

FIG. 6

FIG. 5.—Malignant tertian temperature chart.

FIG. 6.—Malignant tertian temperature chart, showing continuous fever.

febrile disturbance sometimes exceeds 24 hours. Moreover, as the interval between successive paroxysms is nearer 36 than 48 hours, the afebrile period between successive febrile disturbances is relatively short (Fig. 5). The greatest difficulty, however, is met with in cases of so-called double malignant tertian infection, in which the various paroxysms tend to run one into another, so that the temperature merely remits or is actually continuous (Fig. 6). It cannot be too strongly emphasized that a continuous temperature in malaria is a grave sign, and indicates that unless adequate treatment is promptly given the disease will soon end fatally.

In untreated acute malignant tertian malaria the general condition of the patient deteriorates much more rapidly than in the other forms of the disease. Persistent bilious vomiting (bilious remittent fever) is common, and the patient may quickly pass into a state of low muttering delirium (typhoid remittent fever).

The red corpuscles infected with the malignant tertian parasite show a marked tendency to stick to one another and to the endothelial lining of the capillaries, thereby occluding the lumen of the minute blood vessels. When this occurs, as is only too likely to be the case in untreated patients, there

develop pernicious signs of the most diverse character depending on the site of the capillaries most damaged. Unfortunately, the brain capillaries are often involved, thus giving rise to the cerebral forms of the disease, one of the commonest manifestations of which is coma. The alimentary canal may be particularly involved, resulting in the gastric form of the disease associated with severe epigastric distress and incessant vomiting of blood-stained material, or in the dysenteric form associated with diarrhoea and the passage of blood. It is important to note that in these very severe forms of the disease the skin may be cold and the patient collapsed, although the rectal temperature is raised.

Rules for Guidance in Diagnosis

From the foregoing brief summary of the disease it is clear that clinical diagnosis, especially in the severest cases, is merely a matter of surmise in the absence of a blood examination. In these times, when so many cases are arriving at the main ports and are being distributed all over the country, it is imperative for the saving of life that medical practitioners should be on the look out for the disease and should know how to proceed. For their guidance the following rules are suggested.

1. Every sick individual recently returned from a malarial country should be suspected to be suffering from malaria, even in the absence of a history of previous attacks, unless some other diagnosis is obvious. This generalization applies even though the patient's temperature is normal at the time he is seen.
2. Ascertain whether the patient is obviously anaemic and whether the spleen is palpable; if these signs are present the suspicion that the case is one of malaria is strengthened, but their absence does not exclude malaria.
3. Make thin and thick blood films according to the directions given above and send them to a pathological laboratory for examination.
4. If the patient is ill, or if several days must elapse before the pathologist's report can be received, treat the patient on the assumption that he is suffering from malaria.
5. If the pathologist's report turns out to be negative, no harm has been done beyond the wastage of a certain amount of an antimalarial drug; whereas if it turns out to be positive the prompt treatment may well have prevented a catastrophe. In the event of a positive report the treatment of the acute attack must be followed by suppressive treatment as described below.

Treatment

There are two drugs which are invaluable in the treatment of malaria: (1) quinine, an alkaloid from cinchona bark; and (2) mepacrine, a synthetic compound. There is also another synthetic compound, pamaquin, which possesses certain special therapeutic properties, but, as it has no curative action on malignant tertian malaria and is highly toxic, it is unsuitable for general practice and need not be considered here. Unfortunately, although everybody of experience is agreed about the value of quinine and mepacrine, there is not a similar unanimity of opinion regarding the way in which they should be used. Little seems to be gained by discussing here the merits and demerits of the numerous courses of treatment that have been recommended, and it seems best to confine ourselves to methods which have been employed with uniform success for many years in the treatment of thousands of cases at the Liverpool School of Tropical Medicine.

Quinine

In the ordinary case quinine is best given in solution by the mouth. In Liverpool the following mixture, which is known as *mistura tropica*, is used:

R Quinin. sulph. gr. x
Acid. sulph. dil. mxx
Aq. chlorof. ad ʒss

A tablespoonful—i.e., 10 gr. of quinine—is given thrice daily for 4 days. If the patient is gravely ill, with persistent vomiting, oral treatment should be preceded by an intramuscular injection of quinine. The best salt for this purpose is quinine bihydrochloride, which is 50% soluble in water. Ampoules containing 10 gr. of quinine bihydrochloride in solution are supplied by the wholesale houses, and the contents of one of these ampoules should be injected into the muscle with aseptic precautions. Except in cases of cerebral malaria with

coma, it is rarely necessary to give more than one injection, and treatment should be completed by the oral route as outlined above.

The outlook in cerebral cases with deep coma is notoriously grave, and in such cases an intravenous injection should also be given. The contents of the ampoule containing 10 gr. of quinine bihydrochloride should be diluted with 1/2 to 1 pint of hypertonic saline (3%) and run very slowly into the vein. If within 12 hours the patient has recovered consciousness and is able to swallow, the usual oral treatment should follow. If, however, he is still unconscious the intravenous injection should be repeated; but, as already stated, the outlook in such cases is bad—a fact which indicates the urgent necessity for diagnosis and treatment before this calamity develops.

In our experience, provided the patient is not comatose and moribund, this line of treatment invariably causes the parasites to disappear from the blood, the temperature to subside, and the general condition to improve enormously within 3 or 4 days; if this has not happened there is something wrong with the diagnosis, and some other cause for the illness must be sought.

Although this short course of quinine treatment cures the attack in a dramatic manner the infection is not sterilized, and if nothing more is done a relapse will occur within a few weeks in a large number of cases. With the object of preventing relapses and enabling the patient to return to work in safety, "suppressive" treatment must be administered. This consists in the oral administration of a small dose of quinine daily or of larger doses on each of two consecutive days each week. In Liverpool it is our custom to discharge the patient from hospital a few days after the treatment of his acute attack and to instruct him to take 20 gr. of quinine—i.e., one tablespoonful of *mistura tropica* twice daily—each Saturday and Sunday, for a period of 8 weeks. No other treatment is necessary, and the vast majority of patients are able to carry on their ordinary activities perfectly well and without further trouble. A few may have occasional slight relapses while taking this suppressive treatment, but these are not serious, and are dealt with by the subsequent week-end doses. Some cases, especially those of simple tertian and quartan malaria, relapse after the end of suppressive treatment, and in such cases treatment must be continued.

Mepacrine

This synthetic compound is supplied in tablets suitable for oral administration. The course for the treatment of the acute attack is 1 tablet (0.1 g.) thrice daily for 7 days. Its action is similar to that of quinine, and the 7-day course suffices to cause parasites to disappear from the blood and the signs and symptoms to subside. In the very severe cases referred to above, mepacrine treatment should be preceded by one or two intramuscular or intravenous injections of quinine bihydrochloride, as the salt of mepacrine suitable for injection may not be obtainable. With the object of preventing relapses, suppressive treatment must be administered in the form of 2 tablets (0.2 g.) of mepacrine each Saturday and Sunday for 8 weeks.

Conservation of Quinine.—In these days it is very desirable to conserve the limited stocks of quinine, and consequently whenever possible mepacrine should be used instead of quinine. Even if quinine is administered for treatment of the acute attack, mepacrine should be given for the subsequent suppressive measures, and the more so as there is some evidence to suggest that this drug is a more efficient suppressive than is quinine.

Toxic Effects of Quinine and Mepacrine

Apart from temporary tinnitus and deafness and sometimes slight gastric disturbance, there are no ill effects from quinine in the doses mentioned. Mepacrine is a dye, and even in the doses recommended may produce a yellow discoloration of the skin, which must not be mistaken for jaundice; the discoloration usually fades in the course of a week or two after the drug is stopped, but it may persist for as long as three months. A few patients suffer from mild gastro-intestinal effects, and very occasionally mepacrine acts as a cerebral excitant and produces mental disturbance and even mania, but these unpleasant effects are temporary, and soon disappear when the drug is stopped.

FACTORS INFLUENCING THE INCREASED INCIDENCE OF PULMONARY TUBERCULOSIS IN GLASGOW

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Following our previous investigation into the increased incidence of and mortality from tuberculosis in Glasgow (*Journal*, Sept. 27, 1941, p. 436), we have recently carried out a detailed investigation into the first 1,600 confirmed cases of pulmonary tuberculosis notified during the year 1941, with special reference to the effect of occupation and hours of work.

The Rise in Notifications

During 1941 the number of notifications of pulmonary tuberculosis again rose in Glasgow from the previous year's high level of 1,908 to 2,066. Table I compares the age and sex distribution of the cases notified during the two war years, 1940 and 1941, with the average of the last two peace years, 1938 and 1939.

TABLE I.—Age and Sex Distribution

Age	Males			Females		
	Average 1938-9	1940	1941	Average 1938-9	1940	1941
-15 years ..	118	92	134	84	111	136
-25 " ..	236	287	300	341	437	454
-35 " ..	165	218	214	181	214	219
-45 " ..	147	164	184	65	82	82
-65 " ..	222	206	230	65	53	69
65+ " ..	25	31	32	10	13	12
Total ..	913	998	1,094	746	910	972

The table demonstrates that the notifications of pulmonary tuberculosis in 1941 for males show an increase of 9.6% over 1940 and 19.8% over the average of 1938-9. The relative female figures are 6.8% and 30.3%. A feature of the table is that the under-15 age group has shown a marked increase in both sexes, and there has also been an increase in the over-45 age group confined to males. The number of cases recorded in the age groups 15-45 in males and 15-35 in females has only slightly increased during the past year, but exceeds 1938-9 by 27.3% for males and 28.9% for females.

Tables II and III give the total deaths from pulmonary tuberculosis, along with their distribution in age groups, for the years from 1938 to 1941.

TABLE II.—Total Deaths

	1938	1939	1940	1941
Males	534	537	664	615
Females	426	435	518	540
	960	972	1,182	1,155

TABLE III.—Age Distribution

Age	Males			Females		
	Average 1938-9	1940	1941	Average 1938-9	1940	1941
-15 years ..	25	25	34	27	26	30
-25 " ..	109	138	103	170	217	228
25+ " ..	401	501	478	233	275	282
Total ..	535	664	615	430	518	540

The figures show that the male death rate during 1941 is 13% above the average in 1938-9, although it has shown a slight fall since 1940; whereas the female death rate still continues to rise in all age groups, being just over 25% higher in 1941 than in 1938-9.