MEDICAL PRACTICE

Clinical Progress

Malaria

Epidemiology

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Recent reports of the World Health Organization have shown that malaria as an indigenous disease has disappeared from Europe and from the U.S.A., from most of the U.S.S.R., from Israel, Lebanon, large parts of India, from Singapore, Hong-Kong, Taiwan, South Africa, Australia, Chile, most of Argentina and Venezuela, most of the islands of the Caribbean, and from Mauritius. Nevertheless, the whole of tropical Africa, parts of North Africa and Central America, many countries of South America, some areas of the Middle East, and most of the countries of south-east Asia and of the south-west Pacific are still malarious. Thus, despite immense gains from malaria eradication campaigns, very large parts of the world are still sources and reservoirs of plasmodial infection.[1]

Epidemiology

The danger of imported tropical diseases and malaria in particular has been emphasized by B. G. Maegraith[2] and many others. The term "imported malaria" has a definite epidemiological meaning; it refers to cases of infection acquired outside the area where it has been found. "Introduced malaria," on the other hand, is due to a local transmission by mosquitoes, subsequent to a case imported from outside the country concerned. Malaria may also be transmitted intentionally ("induced") as a therapeutic measure (malariatherapy for neurosyphilis) or it may be seen as an accidental disease following blood transfusion or (as it happens with some drug addicts) the use of syringes containing small quantities of infected blood.

In the U.S.A. alone during the past five years there were over 13,000 cases of malaria, with a peak in 1969 of over 3,800 cases. Most of these cases occurred in military personnel returning from south-east Asia; the remainder were seen in teachers, students, merchant seamen, tourists, and Peace Corps volunteers. A smaller but still substantial proportion of imported malaria is being reported every year from the U.S.S.R., France, Germany, Hungary, Portugal, and other European countries,[3] and this is related to the phenonmenal increase of the speed and volume of international travel.[4] In 1968 there were about 140 million international tourists and their numbers are growing by about 10% per annum.[5] Last year nearly six million British people went abroad for their holidays—one fifth of them outside Europe—and about the same number of foreign visitors came here.

Many parts of the tropical world have now become accessible to visitors unaware of the fact that these are also endemic areas of malaria, and not forewarned that simple precautions may be fully adequate to prevent the infection, while ignoring them may have serious consequences.[6] Some 2,000 cases of imported malaria have been recorded in England and Wales over the past 15 years. About half of these infections originated in Africa, while the other half (mainly *Plasmodium vivax*) came from Asia.[7] The annual incidence of malaria over the past decade is shown in the Table.[8] In Scotland about 20 cases per year have been notified over the relevant period.[9]

Though malaria has been a notifiable disease in Britain since 1919, it is not often reported even when the infection is diagnosed correctly. The mean figure of 100 cases per year

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Annual Incidence of Malaria in England and Wales Contracted Abroad

Year	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970
No. of Cases	82	88	128	93	88	71	62	92	130	113	123*

* Provisional figure

during the past decade is probably well below the actual incidence. Several cases that came recently to the notice of the Ross Institute were never notified.

Clinical Manifestations

The incubation period in malaria covers the time between the infection and the first appearance of clinical signs, of which fever is most common. For mosquito-transmitted infection this period varies according to the species of plasmodium. Usually about 12 days are required for the development of *P. falciparum* infection, 13 to 15 days for *P. vivax* or *P. ovale,* and up to one month for *P. malariae.* With some strains of *P. vivax* the incubation period may be delayed for several weeks or months; this may also occur in persons who have been taking suppressive antimalarial drugs. Even before the onset of clinical symptoms scanty parasites may appear in the blood. Preceded by various premonitory signs such as headache, malaise, nausea, etc., a classical attack of maleria consists of several short febrile paroxyms preceded by a rigor and recurring every two days (tertian periodicity of vivax or ovale malaria), or every three days (quartan malaria); falciparum malaria produces either daily or irregular fever and rigors are not a common feature.

Typical paroxysms consisting of a "cold stage, hot stage, and sweating stage" are far from constant; variations of the classical clinical course are common, particularly in children.[10] Intermittent fevers with periodic paroxysms are infrequent in *P. falciparum* infections, the protean symptoms of which may be very misleading. Because of the high rate of multiplication of *P. falciparum* the symptoms of this infection may appear with dramatic suddenness and severity.

COMPLICATIONS

Four groups of complications are generally recognized (though this classification is far from definite, as many symptoms may overlap): (1) cerebral malaria; (2) gastrointestinal malaria; (3) hyperpyrexia with delirium and convulsions; and (4) algid malaria, with low blood pressure and cardiovascular failure

Anaemia and hepatic symptoms, with jaundice, renal, respiratory, and other involvement, develop often when the parasites are numerous in the peripheral blood, but exceptionally also when they are scanty, because of their accumulation in the internal organs. Rapid diagnosis and immediate, adequate treatment are necessary in every case of falciparum malaria, especially in nonimmune persons. In vivax, ovale, and quartan malaria such complications are uncommon, though renal involvement has been associated with quartan malaria. Malaria due to the last three infections is rarely fatal by itself but can be serious, especially in children. In these infections malaria attacks may recur more or less regularly but with decreasing severity for several weeks.

RECURRENCES AND RELAPSES

Recurrences of acute falciparum malaria incompletely treated are generally milder than the initial attack and disappear, often spontaneously, within one year to eighteen months; however, in immune persons from endemic areas parasites may persist in the blood much longer, with very mild if any clinical symptoms. It is unusual for vivax and ovale malaria to relapse after three years following the primary attack; on the other hand, quartan malaria is much more persistent and relapses may be seen 5, 10, or even 40-50 years later. In fact, some persons with untreated or poorly treated quartan malaria may become asymptomatic carriers of plasmodia for life and can transmit the infection whenever they serve as blood donors.

Fatal Falciparum Malaria

There are three potentially serious aspects of imported malaria in any country where the relative absence of tropical diseases has not prepared the medical profession to appreciate their significance and consequences. The first is the severity of some *P. falciparum* infections in nonimmune persons; the second is the complication by a relapsing latent malaria infection of any acute disease, delivery, or surgical intervention (particularly splenectomy) occurring in a person who previously inhabited an endemic area; the third is the possibility of transfusion malaria when the donor of whole blood is an asymptomatic carrier of plasmodia.[11]

Among the 468 cases of malaria quoted in the Table there were 22 deaths (an overall fatality rate of 4·7%.) Among the 2,000 cases of malaria notified in this country between 1954 and 1969 360 patients were infected with *P. falciparum,* of whom 58 died.[12] This appalling fatality rate of 16% compares unfavourably with that of 1·25% reported during 1965-68 in the U.S.A. in 960 patients with falciparum malaria treated in hospitals. Specialized care in military hospitals in that country reduced the mortality to 0·3%. Most of these deaths could have been avoided if the diagnosis had been made without delay and the correct treatment instituted promptly.

A typical case of *P. falciparum* malaria occurs generally as follows:

A tourist (or a businessman, a technical adviser, or school-child) returns to the U.K. from a happy holiday (or an important visit) to Africa, South America, or the Far East. During his stay abroad he was exposed to bites of mosquitoes but did not take any prophylactic antimalarial drugs, or if he did, ceased taking them on arrival home. (It is also possible that on his journey by 'plane he spent only a few hours in a central African town while the aircraft was delayed by engine trouble.)

About two weeks after his return he starts feeling unwell and complains of fever, headache, general malaise, muscular pains, diarrhoea, and some vomiting. He does not bother to see his doctor, or, if he does, the doctor, finding no prominent symptoms and not knowing that the patient had recently been abroad, makes a provisional diagnosis of "influenza" or "gastroenteritis" and prescribes symptomatic treatment, often including some antibiotics. No blood film is made, or if this has been done the laboratory technician misses the scanty parasites present in the red blood cells of the thin film. Within a day or two the patient suddenly shows signs of involvement of the central nervous system (or renal failure, pulmonary oedema, severe haemolysis, and jaundice). On emergency admission to the hospital the diagnosis is easily made, as the peripheral blood is heavily parasitized.

The specific antimalarial and general treatment starts promptly enough but even the best therapeutic intervention may fail if more than 5% of erythrocytes are infected. With luck the patient may recover fully, but a fair number of patients die of various complications despite a striking reduction of the level of parasitaemia.

This course of events is not rare, as shown by a series of cases described during the past few years. At least two people die in this country every year of malaria, though such deaths could be easily avoided. Evidently the primary responsibility rests with the general practitioner who, faced with an obscure pyrexial illness, should think of a tropical disease, find out if the patient has been exposed to it, demand a blood examination, and ask for advice and help from a specialized tropical centre in London, Liverpool, or Edinburgh.

Transfusion Malaria

Accidentally induced malaria as a result of blood transfusion is not uncommon in several countries and may become more frequent as the demand for blood increases. The available though incomplete records covering the period 1950-68 and based on data gathered in 35 countries gave the figure of 655 cases, of which over one half were due to *P. malariae*, with *P. vivax*, *P. falciparum*, and *P. ovale* in the decreasing order of frequency.[3] There is a definite relationship between the incidence of imported malaria and the number of cases due to blood transfusion.[13] In the United Kingdom only eight cases of transfusion malaria have been described over the past 30 years, but probably such occurrences were more common in this country and elsewhere and not diagnosed or not reported.[14]

Prevention of transfusion malaria depends on the elimination as a whole-blood donor of anyone who ever had malaria in the past or who has ever been exposed to malaria during a specified period prior to blood transfusion. This type of screening is quite effective when strictly applied. Detection of malaria infection in a suspected donor is notoriously difficult. Microscopic examination of a blood film is of little value, since asymptomatic parasitaemia is usually very scanty. Nevertheless, methods of indirect diagnosis of malaria by the use of immunofluorescence tests offer the best possibilities for routine screening of latent malaria infections.

Laboratory Diagnosis

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A diagnosis of malaria can be made with certainty only in the laboratory, and, as with most other infective diseases, this can be done either directly, by demonstrating the presence of the infective organism, or by serological methods, which are chiefly of retrospective value in diagnosis.

Demonstration of Malaria Parasite

The surest and certainly the most convenient way of demonstrating malaria parasites is by the use of stained thin or thick blood films taken from the patient. Parasites are usually most numerous in blood taken during or soon after the paroxysm, though in urgent cases one should not delay taking blood films, as some parasites are often present at all stages of the cycle. Several examinations can, and preferably should, be made at different times, especially if it is desired to find different stages of the parasite to aid in identification of the species. Even experienced malariologists may have difficulty in species differentiation when the blood films show only the young ring stages. Nevertheless, it is important to remember that in primary infections with *Plasmodium falciparum* the fever is nearly always irregular and that even in fatal infections parasites are sometimes quite scanty in the peripheral circulation. The parasites may develop mostly in the viscera and only a few small ring forms may be present in the blood, which can be easily missed by the inexperienced. Similarly, if the blood films have to be sent to a distant laboratory for staining and microscopical examination treatment of an acutely ill patient should not be delayed if there is any suspicion of malaria from the clinical and geographical histories. There is little risk of toxic reactions from modern antimalarial drugs, nor of the masking of other infections to confuse the diagnosis, while a delay of a few hours in starting specific therapy in a patient with *P. falciparum* malaria may decide the difference between recovery and death.

MAKING BLOOD FILMS

The most important prerequisite to making blood films is to have scrupulously cleaned glass slides.

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New, unused slides are nearly always available, and it is usually sufficient to polish these shortly before use with a dry, dust-free cloth. If there is any suspicion that they may be greasy they may be rinsed briefly in alcohol, or better a mixture of equal parts of ether and ethyl or methyl alcohol, before polishing. Even a trace of grease will cause uneven spreading of a thin blood film and detachment of a thick film. Of almost equal importance is the need for a suitable slide tray in which the clean slides may be taken covered to the bedside and in which the blood films may be laid to dry horizontal and protected from dust and dirt. The presence of small amounts of foreign matter can greatly increase the difficulties of reading the films. The need for the provision of suitable slide boxes for sending unstained or stained films to other laboratories should also be mentioned here, as this detail is often neglected.

Blood films are usually made from capillary blood taken from the finger or ear lobe, but they may also be made from blood obtained by venepuncture if this is being done. A minimum of at least three thin films and three thick films should be made on each occasion the patient is examined: one of each for staining and examination as soon as possible, a pair to be kept in case the staining of the first is unsatisfactory and modification of the staining technique is indicated, and a pair to be sent unstained to a reference laboratory (see below) for checking or confirmation of the diagnosis. For making good thin films it is essential to use a *small* drop of blood, the size of a large pin head, placed at the end of a slide. As a spreader the clean smooth edge of another slide is used, held at an angle of about 45° to the first slide; the film is made by pushing the spreader *away* from the drop of blood. By this means a film should be made with the red blood corpuscles only one layer deep and almost touching but not overlapping each other. This is well illustrated in the book by Shute and Maryon,[15] which gives further details of techniques in malaria, and which should be in any laboratory concerned with its diagnosis.

To make a thick film a drop of blood, about three times the size of that used for a thin film, is placed on a slide and, using the corner of another clean slide, spread to cover about three times its original area. This must be done rapidly without excessive stirring to avoid the formation of strands of fibrin in the film. The traditional advice about the thickness of the film is that it should just be possible to read small print through it when dry. With these criteria the volume of blood which can be examined in a unit of area is about 10 to 20 times that of a thin film. Though the staining and interpretation of thick films is more difficult than for thin films, it is certainly worth making them on each occasion, if only to be sent to a reference laboratory.

Because their subsequent treatment is different it is preferable to make thin and thick films on separate slides, though if many slides are being made as in a survey they are sometimes made on one slide. Finally, each slide should at once be labelled legibly with the name or number of the patient and