PATHOLOGICAL PROCESSES IN MALARIA AND BLACKWATER FEVER

BY

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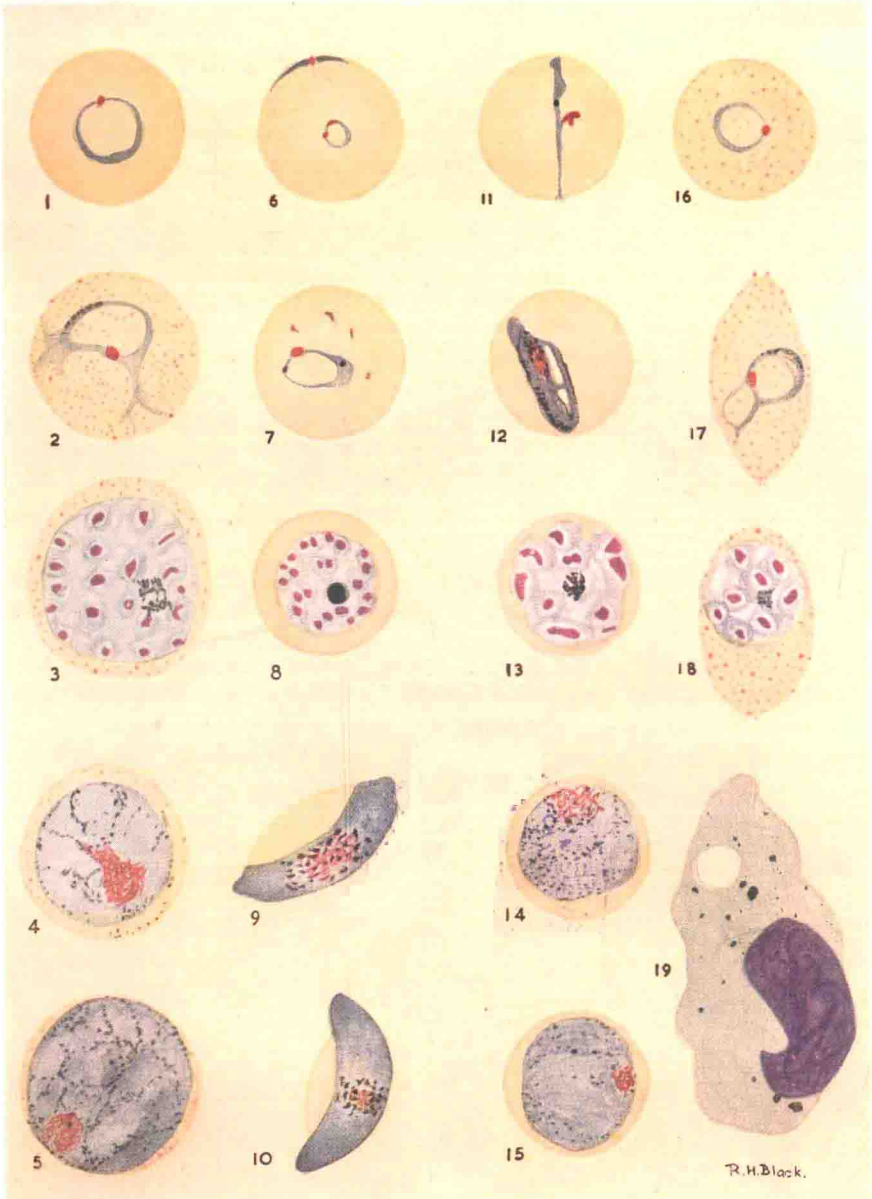

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To My Wife

INTRODUCTION

THIS book has grown out of a series of lectures given over the past two years to post-graduate students of tropical medicine. Its object is to define as far as possible the basic physiological and pathological processes which determine the reaction of the animal body to invasion by the malaria parasite and the appearance of blackwater fever. The discussion centres around most of the important organs affected with the exception of the lungs and the gastro-intestinal tract. Reference to the latter has been largely omitted because the changes occurring in them are primarily the same as those in other organs.

It was hoped at one stage that it would be possible to present a coherent picture of malaria as a whole, but the lack of information is too great at present to permit this. Certain processes have, however, been found common to the development of lesions in all the organs, notably generalized anoxaemia, vascular endothelial damage and general and local circulatory changes which result in the production of tissue anoxia.

If this book does no more than point out some of the appalling gaps in our knowledge, and stimulate some intelligent research, I believe it will have served a useful purpose.

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BRIAN MAEGRAITH.

Liverpool,
August 26, 1947.

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THIS Chapter contains a very brief account of some of the main features of the clinical manifestations of malaria, and is meant to act as an introduction to the disease for those unfamiliar with it. It is not in any sense intended to be more than this. Detailed descriptions of the signs and symptoms associated with pathological changes in certain organs will be found in the Chapters dealing with the various organs concerned. A short note on treatment has been added for the sake of completeness. *P. ovale* infections are not described.

Man acts as the intermediate host in the life cycle of the malarial plasmodia which infect him. Infection occurs in natural circumstances as a result of parenteral introduction of sporozoites by the infective mosquito. There is some evidence that infection may in rare instances be acquired across the placenta, giving rise to so-called 'congenital' malaria. The bite of one mosquito may introduce sufficient sporozoites to establish the disease. In such natural infections it is often assumed that the sporozoites are injected directly into the blood stream, but there is no proof of this, and it is apparently not essential to the establishment of the disease, since Boyd and Stratman-Thomas (1934) have shown that infection can be obtained by the introduction of sporozoites into blister fluid. Gordon and Lumsden (1939) watched the mouth parts of mosquitoes in the act of biting the web of a frog's foot and observed two methods of feeding, one by direct insertion of

the fascicle into a capillary and the other by absorption of blood from pools formed by the injury to the vessels resulting from the insertion of the fascicle. These experiments indicate that the mosquito does not have to rely on direct capillary penetration and that such penetration is largely fortuitous. Presumably, therefore, the direct injection of sporozoites into a vessel must be equally fortuitous.

Artificial infection may be achieved by causing infected mosquitoes to bite suitable subjects or by the intravenous injection of suspensions of sporozoites prepared from the glands of infected mosquitoes (James, Nicol and Shute, 1927). Shute (1937) reported successful infection after injection of as few as fifty sporozoites.

Infection may also be acquired artificially by injection of trophozoites intravenously, intramuscularly or subcutaneously for therapeutic purposes. Accidental infection has followed blood transfusion from infected donors or stored blood and from the use of a communal syringe, e.g. by drug addicts (Biggam, 1929; Hutton and Shute, 1939; Black, 1940; Sharnoff, Geiger and Selzer, 1945). Shortt and Menon (1940) have reported successful infection in monkeys and chickens following the oral administration of defibrinated infective blood. Infection has also been established by the injection of a single trophozoite or merozoite in *P. knowlesi* and *P. cathemerium* malaria (Coggeshall and Eaton, 1938; Stauber, 1939), and Kitchen (1941) reports the transmission of *P. vivax* malaria with as few as ten trophozoites. The latter points out that a successful take after injection depends not only on the dose of inoculated material and its stage of development but also very much on the recipient and his state of natural or acquired immunity to the introduced plasmodia.

The interval between inoculation of the infective material and the appearance of the disease (taken either as the first appearance of parasites in the peripheral blood or as the first rise of temperature to 100° F.) is known as the incubation period. In trophozoite induced malaria the length of this interval is roughly in inverse proportion to the dose administered. It is possible with a sufficiently heavy inoculum to obtain immediate infection. Boyd and Kitchen (1936) have recorded 'passive paroxysms' in some heavily inoculated cases, related to the division of the injected brood of parasites (Boyd, 1941).

The incubation period of sporozoite induced malaria, whether naturally or artificially acquired, is usually called the 'intrinsic' incubation period, to distinguish it from the time required for parasitic development in the definitive host. Shortly after injection sporozoites disappear from the blood stream which becomes free from all parasites

for some days until the appearance of trophozoites. This silent phase has been explained on the grounds of the existence of an exo-erythrocytic tissue phase of the parasite, intervening between the sporozoite and the known asexual cycle. It is not possible by increasing the dose of inoculum to reduce this period to less than a certain minimal time, the length of which depends on the species of Plasmodium involved. By subinoculation of blood from the inoculated subject to a non-infected recipient, it has been ascertained that the blood of the former is never infective before the fifth day from inoculation, although it is commonly infective by the seventh to the ninth day, depending on the species of Plasmodium (Raffaele, 1937; Fairley, 1947).

The incubation period is usually considered to end with the appearance of fever. Parasites may become first detectable in the blood at the time of the appearance of fever, but they are frequently present a day or two before the rise in temperature, and occasionally appear later. According to Ross, the parasite concentration in the blood must reach a certain critical level before fever develops. Boyd (1938) found this pyrogenic level was about 10 parasites per cu.mm. in the case of induced *P. vivax* malaria. The level was higher in cases in which the appearance of parasites in the peripheral blood preceded the rise in temperature. It is dependent to some extent on the immune reactions of the host, as can be seen particularly well in *P. falciparum* infections. In negroes very high parasite densities may be recorded before the temperature rises. Kitchen (1941) quotes one case, for instance, in which 71,000 parasites per cu.mm. were present on the first day of the fever and in which parasites were present three days before the febrile attack. Such initial high densities are uncommon in white subjects, in whom the appearance of fever commonly precedes that of the parasites. In both *P. falciparum* and *P. vivax* infections the pyrogenic level is usually higher in relapses presumably because of the development of some acquired tolerance to the parasite (Kitchen, 1941).

The fever and associated signs and symptoms of an overt malarial attack usually show a periodicity which is dependent to a large extent on the growth and maturation of the parasite as it undergoes its asexual cycle. The febrile paroxysm appears about the time of maximum segmentation and rupture of the mature schizonts with liberation of free merozoites into the plasma. In the early stages of an attack the developing broods of parasite are often not closely synchronized and the fever is irregular, but after a few days the parasites 'fall into step' and the broods mature within a few hours of one another. Synchronicity is most evident in *P. vivax* infections, least in *P. falciparum*,

Symptoms appear as a rule only during the stages of the completion of schizogony and the liberation of merozoites. Where the cycle of schizogony takes 48 hours, as in *P. vivax* and *P. falciparum* infections, the classical periodicity of fever is tertian, the paroxysms occurring every third day, but in these infections daily or quotidian paroxysms are also very common, indicating two broods of parasites maturing on alternate days. Quotidian periodicity may follow a single inoculation and cannot therefore be explained in terms of successive infections. The classical periodicity in *P. malariae* infections, in which the plasmodia mature every 72 hours, is quartan, i.e. the paroxysms appear every fourth day. In this infection, however, almost every conceivable variation of periodicity from quotidian to quartan has been recorded.

After the short irregular interval immediately following the onset of symptoms, some kind of periodicity is usually established in *P. vivax* and *P. malariae* and less often in *P. falciparum* malaria, but the periodicity is by no means fixed, so that a tertian fever may change suddenly into quotidian and vice versa. Such changes of periodicity may be produced artificially by various methods of treatment, e.g. the administration of vaccine fever therapy has been shown to change quotidian periodicity into tertian (Plötner, 1944), probably by eliminating one brood of parasites. Periodicity may also be upset by altering the habits of the patients with regard to their periods of activity and rest (Young, Coatney and Stubbs, 1940).

The duration of an attack of malaria depends on both the patient and the strain of parasite. *P. vivax* and *P. malariae* infections tend to be long; for instance, Kitchen (1941) quotes a case of uninterrupted quartan malaria which continued for over 300 days. *P. falciparum* infections are usually shorter. Spontaneous cure is followed in more than half the cases by return of symptoms at intervals after weeks or months or even years. All three infections may lie latent for long periods. The relapse follows the pattern of the primary attack in most cases, except that the periodicity of the symptoms is determined from the onset and the length of the attack is usually shorter.

P. VIVAX MALARIA (Benign Tertian)

Incubation period and prodromal symptoms

The incubation period of benign tertian malaria varies from 10 to 17 days. In artificially induced malaria the length of this period depends to some extent on the dose of sporozoites inoculated into the subject. Stratman-Thomas (1941) states that parasites appear in the peripheral

blood most commonly 13 days after inoculation, but they may appear as early as the eighth day if the dose of sporozoites is sufficiently large. Occasionally the incubation period in both natural and artificially induced *P. vivax* infections may extend into months (Boyd and Kitchen, 1938; Shute, 1946).

During the last few days of the incubation period the patient may suffer from prodromal symptoms, particularly headache, limb pains and backache, anorexia, slight nausea and even vomiting. He frequently complains of shivering feelings, which, in relapsing cases, often have the same periodicity as the paroxysms which subsequently develop. The prodromal symptoms in *P. vivax* malaria are, however, seldom severe and may be absent altogether.

The attack

The incubation period terminates with the onset of the disease, which is usually defined as the point at which the body temperature first rises to 100° F. or above. This does not often occur before the tenth day following infection. Parasites may be detectable for the first time in the peripheral blood one or two days before or after the febrile onset.

The onset may be accompanied in a relapse by a rigor and febrile paroxysm, but this is unusual in the primary attack, in which the fever becomes continuous or irregularly remittent for the first few days, during which rigors are uncommon. As the disease progresses, however, the regular paroxysm makes its appearance and usually by the end of the first week the pattern of intermittent febrile paroxysms separated by apyrexial and often symptom-free intervals is established. The periodicity of these paroxysms may vary for some time but eventually they become tertian or quotidian and usually remain so, although in some cases changes in the rhythm may occur spontaneously from time to time.

The paroxysm and interval

In the experience of most observers, paroxysms of benign tertian malaria develop in the *post meridian* hours. Kitchen found this to be so in 90 per cent of his cases, 70 per cent of which started the paroxysm between 3 and 9 p.m. (Stratman-Thomas, 1941). The paroxysms develop in three well-defined stages, i.e. the cold stage or the chill; the hot or fever stage and the sweating stage.

The *cold stage* is characterized by a subjective feeling of intense cold, associated with a rapidly rising body temperature and various degrees

of shivering and rigor. Chills are uncommon in the primary attack during the initial irregular fever but accompany the febrile paroxysms as soon as they are established. In the relapse, however, they are present with the first paroxysms. They may be present at every paroxysm, or, in quotidian fever, may appear only in association with every other febrile attack. The temperature at the start of the shivering is usually below 100° F. and may have reached 104–106° F. by the completion of the cold stage. In the primary attack the severity of the rigor and the height of the temperature reached in the cold stage may increase for the first one or two weeks before reaching a maximum, and, similarly, the total length of the cold phase may increase from 10–15 minutes to a maximum of 45–60 minutes as the disease progresses.

The cold stage begins abruptly. The patient complains of feeling bitterly cold and begins to shiver, frequently passing into a violent rigor. The skin is pale and may be slightly cyanotic in the extremities. There may also be some apparent cyanosis of the mucous membranes. The body temperature rises rapidly. The pulse is small and fast although the blood pressure may rise. Anorexia, nausea and vomiting are common and sometimes accompanied by epigastric pain and discomfort. By the second week of the illness the spleen is usually palpable and tender and may often appear to enlarge slightly during the paroxysm. Polyuria is common in the cold stage and the urine is of low specific gravity and concentration and may contain albumin.

The *hot stage* follows the cold. The rigor ceases and the patient feels uncomfortably hot. The skin becomes flushed, hot and dry. The temperature may continue to rise or remain at the level reached at the end of the cold stage. The pulse is full and bounding and the blood pressure tends to fall, the diastolic pressure falling proportionately faster than the systolic. Respiration is rapid and there may be some unproductive coughing. Nausea and vomiting are common, and the patient frequently complains of thirst. He is restless and may be excited and delirious and occasionally passes into light coma. He is usually euphoric and disorientated and complains of severe throbbing frontal headache and pains in the limbs and back.

The hot stage lasts two to six hours and is succeeded by the *sweating stage*. Sweating appears first on the face, usually on the sides of the forehead, but rapidly becomes generalized. It is commonly profuse and sweat literally pours off the patient, who begins to feel better immediately. The temperature has usually begun to fall before sweating occurs, but in any case, once the sweating has begun, it falls rapidly, reaching normal or below in two to four hours. After the sweating

stage the patient is exhausted and frequently passes into deep sleep from which he wakes considerably refreshed and subjectively much better.

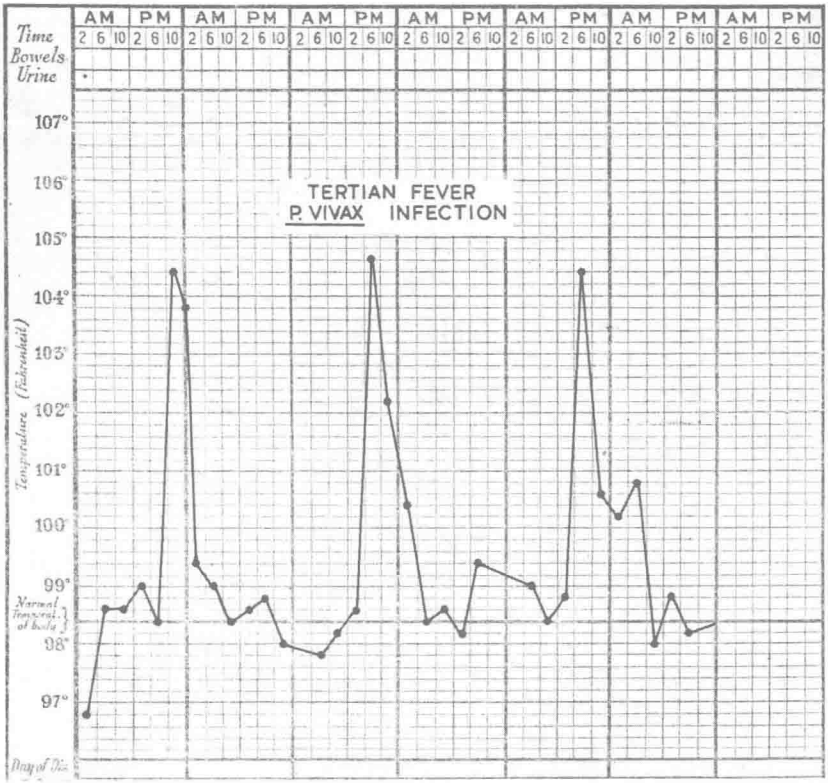

CHART 1—Tertian fever in *P. vivax* infection. In this case synchronization of maturation of parasitic broods was well developed; the asexual cycle was completed every 48 hours.

The temperature remains normal or below until the start of the next paroxysm. This interval is usually symptom-free. Occasionally the temperature in the interval may rise above normal.

Other signs and symptoms

Paroxysms, as explained above, will repeat at regular intervals during the clinical activity of the disease. In addition to the paroxysms, however, there are other symptoms of importance. The spleen enlarges during the disease and is often palpable by the second week. It enlarges slightly in some cases during the paroxysm. Anaemia develops as the disease progresses and may in exceptional cases become very severe, although it is usually not pronounced (see Chapter III). The

blood picture may show macrocytes and other changes not unlike those of pernicious anaemia, but the bone marrow response is essentially normoblastic and the colour index is unity or slightly less. Oedema occasionally appears in the legs after the disease has lasted some weeks. Kidney complications are rare, but polyuria is common during the early part of paroxysm. There may be a short period of oliguria in the hot stage. Jaundice may appear in very severe cases, but it is less common than in *P. falciparum* infections. *Herpes labialis* is very common. In the primary attack this complication occurs after the disease is well established, but in relapses it may precede by a day or two the onset of malarial symptoms. It is usually confined to the mouth and lips, but may spread to the nose and laterally to the ears. Herpes subsides with the malarial attack.

Course of the disease

A single untreated attack may last for two months or longer before it subsides. Termination of the attack is indicated in most cases by reduction in the severity of the paroxysms, which become irregular and finally cease, and may be replaced by periodic small rises of temperature accompanied by the usual paroxysmal symptoms. Kitchen (1941) considers that a symptom-less and fever-free period of about three weeks should pass before the primary attack may be considered over. In about 50 per cent of cases renewed clinical activity occurs subsequent to the subsidence of an attack, following a period of quiescence, the length of which is determined by many factors including the strain of infecting parasite and the total duration of the infection. It is customary to refer to such recurrences as 'relapses,' although James has attempted to divide them artificially into 'recrudescences,' 'relapses' and 'recurrences,' depending upon the length of time elapsing between the termination of the primary attack and the reappearance of symptoms. Relapses have been reported two years or more subsequent to the primary attack. The clinical features of the relapse are indistinguishable from those of the primary attack, except that the total duration of clinical activity is usually shorter in the former.

P. MALARIAE MALARIA (Quartan)

Incubation period and prodromal symptoms

The incubation period of quartan malaria is longer than that of benign tertian, in some cases extending to 30 to 40 days between inoculation and onset.