The Nature and Detection of Apyrexial Malaria.

By Colonel R. H. Firth.

To this Journal an important and suggestive article was contributed by Major G. E. F. Stammers, R.A.M.C., and Captain G. I. Davys, L.M.S., entitled "Apyrexial Malaria Carriers." It is questionable whether the significance of this condition is quite appreciated by us; certainly, anyone having the practical experience of analysing critically the statistics and epidemiological data connected with malaria incidence among troops cannot fail to be impressed with the view that, in this question of malaria incidence, its prevention and control, there is a potential factor as to which we apparently know little and have possibly ignored too long. The factor seems to be the condition which may best be described as dormant malaria. If this assumption be correct, either wholly or in part, the need for its early detection is obviously an important step in the procedure by which we hope, and are endeavouring constantly, to control or minimize military inefficiency from paludal infection. As an elementary and supplementary effort towards emphasising attention to this subject the following considerations are submitted.

Our first difficulty is to define or explain what we mean by

1 Vol. xviii, p. 268.
dormant malaria. Circumstances have precluded one making any exhaustive examination of the literature on malaria, but such examination as one has made affords little information; in fact, the conclusion drawn is that the condition has been ignored by most writers, but referred to by a few, notably by Christophers, Stephens, and Plehn. For practical purposes, we may say that dormant malaria is that apyrexial period in a malarial infection during which the parasites are still in the peripheral blood or deeper organs, but not present in the asexual stage in sufficient numbers to cause the clinical phenomena of fever or ague.

In spite of the large amount of work which has been done on malaria and the great attention which all our officers are devoting to its nature and prevention, it is open to doubt whether the current teaching on the subject emphasizes enough the distinction between incubation, recrudescence, and relapse in malaria cases. Each of these is a state associated with malarial infection and, so far as relates to the condition of dormancy, each suggests a distinctive phase. By incubation, one refers to that apyrexial stage intervening between the time of the introduction of the sporozoites by the mosquito to the time when the asexual parasites are present in sufficient numbers to produce the first attack of fever. We all know that this period ranges from one to seven days in the malignant tertian infections, and from twelve to eighteen days in the benign quartan infections. The taking or not of quinine will affect this period; in many cases, if the amount of quinine taken be efficient the infection may terminate at this stage, or if the dosage be insufficient the attack its merely deferred. We need precise information as to this last contingency among soldiers who have been under prophylactic cinchonization. It has been part of my duty to examine critically the malaria returns of garrisons and units; the notable rise in numbers of malaria admissions during October and November suggests that we have here evidence of delayed or prolonged incubation, in other words, insufficient prophylaxis.

By recrudescence of infection one means that increase in the number of asexual parasites sufficient to produce an attack of fever, these asexual forms having already existed in the infected person. We can conceive a phase of dormancy in recrudescence, during which the asexual parasites are multiplying, although not present in sufficient numbers to cause fever. How long this dormancy may exist will vary according as to whether the host is under quinine treatment or not. In untreated persons this may
run from seven to fourteen days, and in the treated cases this afebrile or latent period may range from extreme irregularity to one or more months. A serious practical question is the great difficulty of detecting asexual forms in the peripheral blood during these periods of dormancy in recrudescence of infection. It is some time now since one did much examination of blood smears, but one is told the best chance of detecting the few asexual forms to be found in this condition lies in the use of the thick film method of Ross. One has had no experience of it, as it is a development later than my laboratory days.

We come now to the more difficult question of relapse of infection by malaria. Few writers recognize the essential distinction to be drawn between a relapse and a recrudescence of infection; there is reason to think that most men confuse the two events or regard them as identical. There is much to suggest that there is a definite difference. In attempting to argue that there is such a difference one is conscious of one's own ignorance and lack of recent experience in this field of work; but the more one thinks over what little one does know, the more one is impressed with the idea that some common clinical incidents of everyday life are not wholly explicable by the orthodox or simple conception of a recrudescence of infection. The problem is, how can one explain such a case as this? A man contracts malaria and presents the classical symptoms, his blood swarms with asexual parasites. Assuming that he is not treated with quinine he will acquire, after ten days or so, and does acquire a certain amount of immunity, and sexual forms make their appearance in his peripheral blood, followed by a cessation or abatement of his pyrexia. These sexual forms increase and ultimately replace the asexual forms. Such a man may remain free from any ague attack for a considerable time when suddenly, following a chill, he develops an attack of fever simultaneous with the appearance of asexual forms in his peripheral blood. Cases of this kind are not uncommon, and exemplify what may be termed a relapse rather than a recrudescence of infection. The sequence of events may be described biologically as a relapse to schizogenesis after a mutation from schizogenesis to sporogenesis. It would be interesting to know whether such an explanation is supported by collateral technical evidence. If it is, then the synchronous appearance of zoites and gametes in the peripheral blood of a malaria-infected person, who has been free from attacks for some time, would be the signal that a relapse was imminent. Discussing
The Nature and Detection of Apyrexial Malaria

this view with men who claim to have considerable experience of malaria, one has elicited only unsympathetic comment; in spite of this, one has failed to hear a satisfactory alternative explanation, therefore the idea is put forward for what it is worth.

If the foregoing arguments are sound, it follows that the question of malarial apyrexia or dormancy assumes a serious importance, quite apart from other evidence, such as that given by Stammers and Davys. We therefore must endeavour to detect these dormant forms of malaria as, if we ignore or overlook them, we are leaving certain points in our defences unguarded. The question is, How can we best detect them? It is clear that the ordinary routine of peripheral blood-smear examinations will fail us. Looking through recent malaria literature, one finds a suggestion by Thomson which deserves notice in this connexion. As the outcome of his work on the leucocytes in malarial infections, Thomson has formulated the following conclusions: (a) That during the course of active malarial fever the number of the leucocytes in the peripheral blood is below normal, and varies more or less inversely with the body temperature; (b) that in malarial fever the curve showing the percentage of total mononuclear leucocytes is an exact inverse of the temperature curve; (c) that in apparently cured malarial cases transient periodic leucocytoses occur in the peripheral blood, and these leucocyte fluctuations arise mainly from a polymuclear leucocyte variation; (d) that these leucocyte phenomena seem to be an infallible index of previous malaria, and are not observable in any other disease. We have, therefore, in this procedure of a total leucocyte count for leucopenia or leucocytosis coupled with a differential leucocyte count a valuable means of detecting dormant forms of malaria. Owing to the violent fluctuations often met with, a single daily count will be of little value. The counts must be made at five or six-hour intervals, covering two or three days. A case of apyrexial anaemia of an obscure nature came under notice in my own family recently in which there was no reason to suspect malarial infection. A series of blood examinations indicated a definite fluctuating leucocyte count, with a high mononuclear percentage at the leucopenic stage. This leucopenia varied from 3,300 to 6,800 per cubic millimetre. The subsequent history of the case confirmed the view of malaria in that parasites were found later in the

peripheral blood, though absent during the earlier stages, and the pyrexia developed a true paludal type, succumbing readily to quinine. The person in question was living in a mosquito-free area, and it was possible to exclude definitely any conception of recent infection. There was a history of old infection with a long interval devoid of fever.

In cases of this kind corroborative evidence is to be obtained as to destruction of blood by means of a test suggested by Plehn.\(^1\) It utilizes the greater or less presence of urobilin in the urine. This pigment is not found in the urine of healthy persons, but can be detected in pneumonia, enterica, suppurative hepatitis and cases of anemia, whether secondary or primary. According to Thomson, urobilin does not occur during the dormancy of incubation in malaria, but shows itself with the onset of pyrexia, and reaches its maximum some two days after the fever. Its detection is very easily carried out by adding to the urine an equal volume of a saturated solution of zinc acetate in a test-tube and shaking vigorously. Next add from 5 to 10 drops of iodine, such as is used in Gram's stain, and then stir or shake. The mixture is next filtered through filter paper, and if urobilin is present the filtrate shows varying intensities of fluorescence in proportion to the quantity of urobilin. At one time I constantly used this test on a relative in whom a small liver abscess was suspected. Thomson says that the urobilin content remains at a high level during the dormant period of malarial recrudescence, and that during the dormant period of relapse it tends to fluctuate violently, rising at first to a high level and then falling. There is reason to expect a higher elimination of this pigment in the malignant than in the benign infections by malaria. Quinine may raise the output at first, but once a person is cinchonized the drug does not affect the pigment elimination. The rationale of the urobilin test is obvious. It is but a measure of the amount of hæmoglobin eliminated by the urine, which disintegrated pigment is but an index of the degree of blood destruction taking place, or which has taken place in some part of the body. The ratio of the one to the other is known and may be put at 1 grn. of urobilin from each 25 grn. of hæmoglobin broken up. Of course, the presence or absence of urobilin is not a specific index of malaria, and is in no way equivalent to the detection of parasites in the blood; but as an indirect clue to what metabolic changes are going on in the body, the presence of

The Nature and Detection of Apyrexial Malaria

Urobilin in the urine constitutes a valuable test for the existence of malaria in apyrexial states. By itself the urobilin reaction has little value. A positive result indicates that blood pigment is being destroyed somewhere, and assuming by other evidence the elimination of other diseases, if there is no pyrexia the patient is in all probability in the malarial apyrexial or dormant state. Conversely, if there be no urobilin, then either blood destruction is not going on, or if it is then the liver is still capable of coping with the products of haemoglobin disintegration. If malaria be suspected, then in such a case other evidence must be sought.

These aspects of this question are brought forward to focus attention on the apyrexial malarial state, and incidentally to call attention to means by which the condition can be detected. That detection is necessary is obvious; and once detected the suspected individual must be regarded as potentially a menace and handled on recognized principles. The logical deduction to be drawn from the facts is, that one more duty is added to the sphere of our activity; it is incumbent on us to carry it out.

Postscript.—Since writing the above, information reaches me that the urobilin test, as suggested by Plehn, has been extensively employed in India in the examination of apyrexial malaria by Major Harvey, Captain Knowles, and Captain Acton, all of the Indian Medical Service. Their work in this direction is said to confirm largely the views of Plehn, whose article on the detection of dormant malaria deserves serious consideration by all engaged in the treatment and control of malaria. The later work of the above-named Indian workers should be of great value as helping towards a clearing up of this vexed question.