CLINICAL FEATURES AND TREATMENT OF MALARIA IN BRITISH TROOPS IN WEST AFRICA

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"The symptoms of this fever, it is to be regretted, are so various and irregular, in different cases and under different circumstances, that a mere nosological definition of them would afford no precise information and might mislead those it was intended to instruct." Since Boyle in 1831 wrote these words in his gloomy *Account of the Fevers of Western Africa* the prognosis of subtertian malaria has greatly altered, but the diversity of its manifestations has not. Modern textbooks may claim to provide more than a mere nosological definition, but they tend to emphasize the severer and rarer types of the disease to the exclusion of its commoner and milder, though no less protean, forms. As the latter are prevalent in troops in West Africa at the present time and are not uncommon in those returning to this country, we believe that a fresh description of them may be of value. Pernicious types will receive little notice, as in our experience they occurred infrequently, and methods of investigation requiring more than the simple use of the microscope will hardly be mentioned.

The description is based on over 1,200 cases seen and treated by one or both of us in two military hospitals in West Africa in 1941 and 1942. Where figures are given these refer to 846 unselected cases in 584 patients from one hospital in each of which the diagnosis was confirmed by the finding of malaria parasites in the blood. In 380 cases the parasites were diagnosed as *Plasmodium falciparum*. In the remainder no diagnosis of the type of parasite was attempted, but it can be assumed for the purpose of this paper that all or nearly all were due to *Pl. falciparum*, since in no instance did the appearance of the parasite or the clinical features of the disease suggest the contrary, and workers in the district concerned agree that other types of malaria are rare, occurring, when they do, usually in visitors who have been infected elsewhere.

Our account deals with a group of white males aged 18 to 51 who had been passed as fit for overseas service, who were in most cases in a malarious district for the first time, and amongst whom the observance of antimalarial precautions and the taking of a suppressive drug were enforced, so far as they could be, by disciplinary measures. Further, in British West Africa subtertian malaria is for the most part hyperendemic and, on account of the climate and the varying habits of the principal anopheline vectors (*A. gambiae*, *A. gambiae* var. *melas*, and *A. funestus*), infections, though commonest in the wet season, occur all the year round. Conclusions based on the study of a particular type of patient in an area with particular characteristics are not necessarily applicable to other types of patient in other areas.

Previous Descriptions

We know of no previous account of the clinical features of malaria in white troops in West Africa. Small groups or single cases of the disease, acquired in West Africa but treated in England, have been described by Fawcitt (1940), Fawcitt and Walters (1941), Murray and Shute (1942), and Anderson and Bradshaw (1943); and treatment has been discussed by Hughes (1942), Hill (1942a, 1942b), and Hughes and Murgatroyd (1943).

The Clinical Types of Malaria

Malaria has been described as the great mimic of other diseases. To illustrate this fact, which is of great importance in diagnosis, we have divided our cases into clinical types, according to the principal feature of the attack, much in the same way as did Falconer and Anderson (1917) and Manson-Bahr (1920) in their respective descriptions of malaria in the Salonika and Egyptian Expeditionary Forces of the last war. While the exact pathogenesis of these types can only be a matter for speculation, it was noticeable that patients who had repeated attacks showed no predilection for a particular type of the disease.

The "types" described below accounted for 818 of our 846 cases. The remainder consisted of 24 particularly mild cases in which the patients had no fever and complained only of headache and slight malaise, and 4 cases with jaundice as the principal feature, which will be mentioned under the heading "Complications."

I. The Febrile Type

In this type (684 cases) fever itself was the main feature. The onset was usually quite sudden, with chilly feelings or shivering, soon followed by feverishness. During the hot stage, which lasted from 10 to 36 hours, the temperature was raised to 103 or 105°, and the patient complained of burning heat and great discomfort or was quite prostrated. In most cases this stage ended with profuse perspiration, a fall in temperature, and a sense of great relief, to be succeeded by an apyrexial interval, whose length was from a few to 36 hours and which often varied inversely with that of the preceding hot stage. While afebrile the patient felt quite well or complained only of slight headache. In some cases there was no apyrexial interval, and symptoms continued till the fever was controlled by an antimalarial drug.

During the febrile stage headache, backache, and generalized aches and pains were usually present. Pain in the back of the neck and aching across the shoulders, associated sometimes with stiffness in these regions, were common complaints, as were also aching in the eyeballs and pain behind the eyes, aggravated by moving them. Vomiting occurred in about a third of these cases in the febrile stage, and in some instances was very distressing, being accompanied by much retching. Some patients complained of abdominal pain, either diffuse or localized in the left hypochondrium or epigastrium, and others of pains in the chest which suggested intercostal myalgia or pleurisy or were of an indefinite nature. In some of the cases included in this type the symptoms were milder, and the patients had often remained at duty for several days before reporting sick.

Rigors occurred on only 22 occasions, and are therefore rare in malaria of this type. Their occurrence should suggest the possibility of the onset of blackwater fever and call for the keeping of a close watch on the patient and his urine.

II. The Gastro-intestinal Type

Gastric, diarrhoeic, and dysenteric forms were recognized.

(a) *Gastric*.—Vomiting was the principal feature in the 11 cases of this type. Epigastric discomfort, at times amounting to actual pain, and constipation were usual, and headache and backache were complained of on occasion. The fever was mild in all instances, and the vomiting differed from that which occurred in the febrile stage of cases of the previous type in that, though more persistent, it was less distressing and was not associated with retching. The symptoms were continuous or irregularly intermittent, except in one case in which they recurred on alternate days. Some of these patients were sent to hospital with a diagnosis of "dyspepsia" or "acute gastritis." In all instances the symptoms cleared up rapidly when antimalarial treatment was instituted.

Illustrative Case.—Sgt. T. was admitted to hospital with a history that four nights previously he had complained of nausea and vomiting, and these symptoms had continued all the next day. Two days before admission he had been free from symptoms and felt well till the evening, when nausea and vomiting returned. The symptoms had continued all the next day, and were associated with epigastric discomfort and complete anorexia. On the day of admission he felt better but weak. No malaria parasites were found in films of his blood. That night he complained again of epigastric discomfort, vomited repeatedly, and his temperature rose to 100.4°. On the following day his spleen was palpable, malaria parasites were present in blood films, and quinine bisulphate gr. 10 t.d.s. was prescribed. He made a rapid and uninterrupted recovery.

(b) *Diarrhoeic*.—The principal feature in the 60 cases of this type was simple diarrhoea, accompanied in most instances by colicky abdominal pain of varying severity. In a third of the cases this began suddenly, and was associated with headache of mild severity and vomiting of short duration. In the remainder diarrhoea, mild colicky abdominal pains, and a feeling of malaise had been noticed for several days before the patient felt ill enough to report sick. These patients had few symptoms apart from their intestinal ones, and were sometimes sent to hospital merely for the investigation of a diarrhoea which had failed to respond to the usual remedies. None had high fever and 11 of them had no fever while in hospital. The stools were watery, did not contain blood or mucus, and varied from 5 to 18 or more in the 24 hours. In the majority of cases the diarrhoea was continuous, but in some it occurred on alternate days. The stools were examined microscopically in every case; in the majority nothing abnormal was detected, but in about a quarter of them pus and red blood cells were present. They were cultured on a number of occasions, but no organisms of pathogenic significance were isolated.

Illustrative Case.—Pte. B. was admitted to hospital with a history of diarrhoea and colicky abdominal pain for six days. His motions had been watery and had numbered between seven and ten daily. He had never noticed blood or mucus, and did not complain of other symptoms. His temperature was 100.6°, pulse 74, and respirations 20. He had mild angular conjunctivitis, the lower edge of the liver was palpable and tender, but no other abnormal signs were present. During the first two days in hospital no malaria parasites were found in blood films; microscopical examination of the stools showed some pus and red blood cells only, and culture of them revealed no abnormality. On the third day malaria parasites were found and treatment with quinine was begun. The temperature became normal in 48 hours and the diarrhoea disappeared on the third day of treatment.

(c) *Dysenteric*.—In 12 cases of this type diarrhoea, with blood and mucus in the stools, was the main feature, and was accompanied by headache, fever of moderate severity, and abdominal pain. The onset was almost always sudden; the fever and constitutional disturbance were greater than in cases of the previous type and the diarrhoea was more profuse and distressing, as many as 30 motions being passed in 24 hours. Backache was complained of in a few cases; vomiting was unusual, and tenesmus quite exceptional. The stools were cultured repeatedly, but no pathogenic organisms were discovered.

Illustrative Case.—Sgt. G. was admitted to hospital with a history of diarrhoea, with blood and mucus in the stools, 25 having been passed in the previous 24 hours. He had complained of headache on the evening before admission and stated that he had had a temperature of 102° at the same time. On admission his temperature was normal and his tongue slightly furred; no other abnormality was discovered on physical examination, and no malaria parasites were

found in blood films. The stools contained pus and red cells, but no pathogenic organisms were grown on culture. On the following day his condition was unaltered until the evening, when he complained again of headache and generalized aching and his temperature rose to 101°. On the third day his temperature was normal, but bloody diarrhoea continued and films were still negative for malaria parasites. On the fourth day malaria parasites were found in blood films, and quinine bisulphate gr. 10 was administered thrice daily. Three days later his bowels acted normally and thereafter he made an uninterrupted recovery.

We saw no case of malaria of an appendicular type in West Africa. We did, however, see one of true appendicitis in a patient with malaria. Since returning to this country one of us has seen a typical case of malaria simulating acute appendicitis. The presence of a leucopenia was the main differentiating feature, and the condition cleared up rapidly when treatment with quinine was started.

III. The Respiratory Type

In 39 cases the main clinical feature was an acute or subacute bronchitis, patients with a previous history of chronic or recurrent bronchitis being excluded from this group. The symptoms varied from the acute respiratory distress of an asthmatic attack to a moderate degree of cough and expectoration. Some fever was the rule, but in a few instances it was insignificant in degree or absent. The attack usually began abruptly with headache, backache, and generalized aching. After a variable period respiratory symptoms appeared. The cough, at first dry and unproductive, soon became looser, but expectoration was seldom profuse. Wheezing and vomiting occurred in some instances. Rales and rhonchi were heard on physical examination, and in a few cases the clinical picture suggested the presence of a bronchopneumonia; but radiographs of the chest did not confirm these clinical findings.

Illustrative Case.—S/Sgt. P. was admitted to a hospital with a history of a few hours' feverishness, headache, generalized aching, and vomiting. His temperature was 102°, pulse 88, and respirations 24. He was wheezing and had considerable respiratory distress. On examination of the chest numerous sibilant rhonchi were heard in all areas. Malaria parasites were present in a blood film, and quinine bisulphate gr. 10 t.d.s. was prescribed. Seven hours later he had a profuse perspiration, but wheezing continued and he was given a hypodermic injection of adrenaline with good effect. He was better next morning, with only slight wheezing, and expectorated abundant frothy sputum, but the same evening his acute symptoms returned. On the following day the sputum became mucopurulent and the spleen was palpable, but the symptoms abated. On discharge 12 days after admission he complained of slight cough only and the spleen was no longer palpable.

IV. The Myalgic Type

In 10 cases the main feature was muscular pain and stiffness. In six of them there was no fever and in three no more than slight fever. The onset was usually acute, with pain localized to the affected muscle or muscles, and constitutional symptoms were slight or absent. On examination the affected muscles were tender and in spasm, and active or passive movement caused acute pain. The muscles most often affected were the lumbar, the intercostal, and those of the neck, either singly or in combination. Rest, salicylates, and heat provided temporary relief; but only when malaria parasites were demonstrated in the blood and the appropriate treatment was administered did complete recovery ensue.

Illustrative Case.—Sgt. T. was admitted to hospital complaining of pain and stiffness of the right side of the neck that had come on suddenly two days previously. There were tenderness and spasm of the right sterno-mastoid and of the cervical portion of the right trapezius, and the condition differed in no way from an ordinary acute torticollis. No other abnormal physical signs were noted, and a blood film revealed no malaria parasites. Salicylates by mouth and radiant heat and massage were prescribed without beneficial effect. Two days later, as no improvement had taken place, further blood films were examined: malaria parasites were demonstrated, and quinine bisulphate gr. 10 t.i.d. was administered. The pain was much improved in 48 hours and the condition cleared up completely in five days. The patient had no other symptoms and was afebrile throughout.

V. The Cerebral Type

The 2 patients in this series had cerebral symptoms. The first was conscious, but was completely disorientated, had some motor aphasia, and was afflicted with severe muscular

twitchings. The second was delirious and gravely ill, with a dry brown tongue, a paralytic squint, and a left extensor plantar response. Both recovered completely.

General Features

The following features applied to some extent to all types of case.

Onset.—This was sudden in the majority of cases, but in a minority (152) was preceded by a prodromal period, lasting from a few days to a few weeks, of malaise, headache, lassitude, backache, or diarrhoea.

Symptoms.—The main symptoms of the attack, irrespective of type and in order of frequency, were headache (770), backache (486), shivering (253), vomiting (234), feverishness (233), pain in the back of the neck (184), generalized aching (180), slight cough (169), sweating (153), and simple diarrhoea (134). Constipation (61) was the exception.

Temperature.—Quotidian intermittent fever was seen in 45 cases; tertian intermittent in 49; subtertian intermittent in 53; irregularly intermittent in 87; remittent in 75; continuous in 27; "low fever" (pyrexia not exceeding 100°) in 91; and no fever throughout in 50. In 366 cases the fever did not last long enough to be of any special type.

Pulse Rate.—Relative bradycardia was a principal feature of the disease as seen by us in West Africa. An analysis of the pulse-temperature ratio is as follows:

Temperature	Corresponding Average Pulse Rate per Minute	No. of Observations made
105°	102.0	59
104°	97.2	177
103°	91.6	177
102°	86.5	177
101°	83.9	177
100°	79.2	177

Urine.—Albuminuria, varying from the presence of a trace to a heavy deposit in the boiled specimen, was reported on 10 occasions, and reduction of Fehling's solution in 17 cases. Both were transient features.

Physical Signs

The spleen was palpable on admission in 315 cases, at some time during the acute attack in 462 cases, and on discharge approximately two weeks after admission in 137. Tenderness in the splenic region was noted in 114 cases. The liver was abnormally palpable in 32 cases, the greatest degree of enlargement being to three inches below the costal margin; and tenderness of the liver on palpation was noted in 61. Diffuse abdominal tenderness was noted in 19 cases and slight abdominal rigidity in 7. The tongue was usually moist and clean, and was never more than slightly furred in uncomplicated cases. Angular conjunctivitis in some degree was not uncommon, and a faint icterus of the conjunctivae without noticeable involvement of the skin was seen occasionally. Rhonchi were heard in the chest in 136 cases, sometimes accompanied by rales.

Complications

Chronic Malaria.—Out of 584 patients 6 were considered, after several acute attacks, to be suffering from chronic malaria. Such patients usually complained of chronic headache, fatigability, and general ill-health. They looked sallow, had some degree of splenomegaly—the spleen being harder in consistency than that commonly felt in acute attacks—an anaemia of slight to moderate degree with leucopenia and a relative lymphocytosis, and had often lost weight. In many instances of so-called "chronic malaria" the objective signs were slight, the symptoms appeared to be mainly emotional, and simple psychotherapy was more needed than drugs.

Blackwater Fever.—Four patients out of 584 developed this complication, and two of them died.

Jaundice.—Definite jaundice was seen in 11 cases and slight icterus of the conjunctivae in 14. Three types of jaundice were recognized: (i) The acute haemolytic jaundice of blackwater fever. (ii) Slight icterus of the conjunctivae only, which was present during the acute attack and was presumably due to slow haemolysis. (iii) Jaundice, usually of moderate severity, with clay-coloured stools and dark urine, indistinguishable

clinically from catarrhal jaundice or infective hepatitis. In four cases this was present on admission, and in two it appeared during treatment with mepacrine. As in at least two cases, not included in this series, similar jaundice appeared during treatment with quinine, it is unlikely that mepacrine was responsible for it.

Herpes labialis occurred in 41 cases and herpes nasalis in 5.

Generalized urticaria occurred in 3 cases—in two during treatment and in one at the onset of the attack.

Severity and Prognosis

In less than 10% of these cases could the patient be described as severely ill and in less than 1% as dangerously ill. Of those described as severely ill the majority were simply patients who responded unusually slowly to treatment, and these probably corresponded to the 12% of patients shown by Howie and Murray-Lyon (1943) to absorb or metabolize abnormally quinine given by mouth, as disclosed by the irregular occurrence or absence of positive Tanret reactions in the urine. Out of 584 patients 14 (2.4%) were invalided home, the indications being chronic malaria (7), recovery from cerebral malaria (2), recovery from blackwater fever (2), anaemia (1), persistent jaundice (1), and haemolytic jaundice of uncertain origin (1). There were no deaths from uncomplicated malaria. Two patients out of 584 died from blackwater fever—a mortality rate for the whole series of 0.34%.

We believe our account to show that, given favourable conditions, malaria in West Africa at the present time need not enjoy the evil reputation that it has. The disease is potentially a very dangerous one, and its apparent mildness may occasionally prove its most subtle danger; but unnecessary exaggeration of the dangers of the average case causes needless alarm and contributes to disability from "tropical neurasthenia."

Diagnosis

Films were usually taken at 12- to 24-hourly intervals, and in 968 cases parasites were found at the first examination in 57%, at the second in 22%, at the third in 5%, at the fourth in 3%, and at the fifth and sixth in under 1% (an "examination" for this purpose meaning the search of a thick film for not less than 10 minutes); while in 13% parasites were not found and the condition was treated as "clinical malaria."

When the clinical findings are equivocal it is wise to examine repeated blood films, but the above figures show that parasites will usually be found, if they are going to be, in the first two or three examinations. With us the apyrexial interval was as favourable as any other time for the finding of parasites, for out of 816 positive films 389 were taken when the patients were afebrile.

While films are being taken for the diagnosis of equivocal cases in hospital the administration of a suppressive drug should be discontinued, as the parasites are then more likely to be found. We have never seen any harm come of this practice. Patients in hospital for any other purpose should continue to take their suppressive drug, and patients undergoing surgical operations should be given 10 gr. of quinine or 0.1 g. of mepacrine daily. If this is not done an attack of malaria two or three days after the operation is not uncommon, and at best adds considerably to the patient's discomfort.

Treatment

In a district of the type described here it is likely that most residents become and remain infected with malaria. Many of them must be regarded as living in a state in which the forces of infection and of resistance are in a somewhat precarious balance, and a clinical attack may result from anything which serves even temporarily to reduce the powers of resistance—such, for instance, as a surgical operation, an intercurrent infection, or an interruption of suppressive treatment. Since there is at present no known drug treatment that will terminate human infections and there is reason to believe that immunological processes play a considerable part in their control (Coggeshall, 1943), the objects of treatment in such an area must be to aid natural resistance to the disease and by the use of drugs to suppress or abort clinical attacks.

While little is known of the nature of the immunological processes involved, it is reasonable to suppose that they will be aided by the maintenance of a high standard of general health, and in practice measures to this end do appear to be important. In our experience ambulant patients or those treated in their own quarters did not regain a feeling of well-being as quickly as those kept in hospital for an adequate period, and they had a greater tendency to early relapse, though the same course of drugs may have been administered in each case. We had an impression that the same applied to patients receiving an unnecessarily large dosage of drugs. Whatever drugs are given patients should, except in an emergency, be treated in hospital and should remain there for a minimum of 12 to 14 days. It is false economy to treat patients otherwise or to cut short their convalescence.

We believe that this principle could be carried further and that the provision of convalescent camps in West African stations is a measure which would save its own cost by reducing disability from malaria. Such camps should be situated in relatively healthy areas, preferably with facilities for bathing and other recreation; and convalescence in them should be planned, and should include graded exertion so that return to normal duty does not involve a sudden unaccustomed strain. The *Medical History of the War, 1914-18*, describes the provision of such camps as "a practice which obtained recognition during the war," and states that convalescence should last at least three weeks.

Treatment of the Acute Attack

In the height of the fever patients were nursed in blankets. Warm sponging, drying, and changes of clothing as often as necessary added considerably to their comfort. The disadvantage of sedatives is that they usually produce profuse sweating without relief of symptoms. We began by treating all our patients with a full course of quinine, mepacrine, and pamaquin, under the assumption that the more "thorough" the treatment the less likely was the occurrence of relapses. This assumption was not justified, for we found that our return cases were no less numerous than anyone else's. We next tried treating the patients in one ward with quinine followed by pamaquin, and those in another with mepacrine followed by pamaquin. We found that patients in the quinine-pamaquin ward became apyrexial and free of symptoms quicker than those in the mepacrine-pamaquin ward, but thought that return cases were less common in the mepacrine-pamaquin ward than in the quinine-pamaquin one. We next abandoned pamaquin for routine use because:

(i) It is doubtful whether pamaquin has any anti-relapse value in malignant tertian malaria (Sinton and Bird, 1928).

(ii) The destruction of gametocytes, which pamaquin does achieve, is of little importance in Europeans in a hyperendemic area where there is a huge reservoir of infection in the native population.

(iii) Cyanosis and abdominal colic occurred in a few of our patients under treatment with pamaquin.

(iv) Haemoglobinuria had been reported in patients under treatment with pamaquin (Sinton, Smith, and Pottinger, 1930; Mann and Smith, 1943), and we heard of a few recent cases of blackwater fever during administration of this drug.

(v) We were unable, as was not the case with quinine and mepacrine, to demonstrate to ourselves that in the treatment of our patients pamaquin had any value other than the destruction of gametocytes.

After abandoning the use of pamaquin we settled on a routine course of quinine by mouth for two days (sometimes extended to three if the fever had not fallen to below 100° at the end of 48 hours), followed by mepacrine for six days. This modification produced no evident deterioration in our results; patients who had been treated by the earlier methods stated that they felt better after the modified course, and the proportion of cases returning within three months was distinctly less after this treatment than after the previous ones. Quinine was given as a solution of such salts as were available, in doses of 10 gr. t.i.d. if necessary in an acid mixture. Mepacrine was given in doses of 0.1 g. t.i.d. If vomiting occurred we substituted for the usual quinine mixture quinine bihydrochloride in tablet form, and found that this could be taken in most cases.

We used quinine by injection in all cases considered to be suffering from pernicious forms of the disease, in a few cases in which even tablets of quinine bihydrochloride were vomited, and in very occasional and quite exceptional cases (less than 1%) which did not appear to be responding to quinine by mouth. The routine use of quinine injections, as suggested for instance by Wingfield (1943), even granted that a higher proportion of severe cases may be seen in England, seems to us excessive and unnecessary.

As our patients were kept in hospital for 12 to 14 days in any case we did not give quinine and mepacrine simultaneously; but there is no objection to this practice, and as mepacrine acts slowly it may with advantage be begun 24 hours before quinine is discontinued. If mepacrine alone is used the initial doses should be greater than 0.1 g., but the optimum dosage for this purpose remains to be determined. We have recently used an initial dose of 0.8 g. followed by 0.1 g. t.i.d. in a few cases in England with good results.

As soon as the course of treatment was completed our patients returned to their usual suppressive dose of quinine or mepacrine.

Treatment of Pernicious Attacks

These must always be regarded as medical emergencies, and should be treated promptly and, in the initial stages, by injection. We do not propose to enter into the controversy as to the best route for the injection of quinine. We used both intravenous and intramuscular injections on occasion without encountering ill effect. In a patient who is conscious and can take quinine by mouth and absorb it (as shown by the Tanret test in the urine) nothing was gained, in our experience, by giving more than two or at most three parenteral injections. In comatose patients or those unable to take or absorb drugs given by mouth, parenteral injections must be continued till the symptoms are controlled. Intravenous glucose and saline may be necessary to prevent dehydration. In a few cases we tried reconstituted plasma as suggested by Fawcitt, and considered the results promising. In patients with cerebral malaria who failed to respond to other measures therapeutic lumbar puncture seemed to be of value.

Suppressive Treatment between Attacks

The taking of a small dose of so-called "prophylactic" quinine has been customary among Europeans on the West Coast for at least a century, and is strongly recommended by most local practitioners of experience. This measure is undoubtedly of some value, and is considered essential for troops under active-service conditions. In practice the results are not quite according to theory, and a varying degree of individual susceptibility appears to be of importance; for some individuals can go for long periods with no suppressive drugs and have little or no malaria, while others have repeated attacks in spite of them.

In dealing with troops under active-service conditions exceptions cannot be made, and the taking of a suppressive drug on parade and under the supervision of an officer is enforced. It is likely that mepacrine will replace quinine for this purpose in troops in West Africa, and according to Hill (1942a, 1942b) doses of 0.1 g. daily can be taken with good effect and without the appearance of toxic manifestations. It is important that persons leaving malarious districts of this type should be instructed either to continue with their normal dose of suppressive drug for at least two months after they have left the area, or to continue this dose for two weeks and then take mepacrine 0.1 g. thrice daily for five or six days.

Summary

846 unselected cases of malaria in British troops in West Africa, every one confirmed by the finding of parasites and presumably almost all subtertian in type, were divided according to the principal clinical feature of the attack into febrile, gastric, diarrhoeic, dysenteric, respiratory, myalgic, and cerebral types.

While its apparent mildness may occasionally prove the disease's most subtle danger, under the conditions stated, which included compulsory personal antimalarial precautions and taking of suppressive drugs, the prognosis in ordinary cases was excellent, while pernicious attacks and complications were very rare. Only 2 patients died, both from blackwater fever, and 14 were invalided home.

After various modifications in treatment the routine use of pamaquin was abandoned. The most generally useful course of drugs in uncomplicated cases was found to be quinine gr. 10 t.d.s. by mouth for two or three days, and mepacrine 0.1 g. t.d.s. for six days, the two drugs being with advantage "overlapped" for 24 hours. The patient's usual dose of a suppressive drug was resumed as soon as the course was finished, and an adequate period of convalescence was regarded as of the greatest importance.

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DESPECIATED BOVINE SERUM (D.B.S.): A SUBSTITUTE FOR HUMAN PLASMA

BY

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The use of plasma in surgical treatment is increasing rapidly, and further studies of the condition of hypoalbuminaemia and its relation to post-traumatic and post-suppurative cachectic states and to delayed wound-healing envisage a still greater demand for plasma protein therapy. The panels of donors and blood banks organized throughout the country have hitherto provided a convenient supply of a protein solution, but the investigation of an alternative source is indicated in view of the future need for this material.

Any plasma substitute must have the following characteristics: (a) it should be retained in the circulation and eventually be metabolized; (b) it should exert an osmotic pressure equivalent to that of plasma; (c) it should be non-toxic, free from antibodies, and non-antigenic. An attempt to produce such a material was made by Bayliss in 1916, when he introduced 6% gum-acacia in saline as a substitute for blood in the treatment of shock (Bayliss, 1917). This material had a very considerable efficiency, but it was only partially metabolized. Much of it remained permanently in the tissues, and many unpleasant sequelae occurred (Hanzlik and Karsner, 1920; Maytum and Magath, 1932; Yuile and Knutti, 1939; Andersch and Gibson, 1934).

Other organic substances suggested have been isinglass (Taylor and Waters, 1941), pectin (Hartman *et al.*, 1941), gelatin (Gordon *et al.*, 1942), and methyl cellulose (Hueper, Martin, and Thompson, 1942); but they must be absolutely pure, and in the case of the first three this standard is very difficult to obtain. Furthermore, the effective metabolism of such foreign material is very much in doubt. More recently periston (polyvinyl pyrrolidone) has been put forward in Germany (Hecht and Weese, 1943); it has a very high osmotic action, and the claim is made that it will remain in the circulation for two days and be excreted in 3 to 4 weeks. All these substances may have some beneficial effect in maintaining blood volume in shock and haemorrhage, but will have little or no value in restoring loss of blood protein.

The substance most nearly approaching human plasma protein in character, and one which is available in quantity, is animal plasma protein. Unlimited quantities may be obtained in the abattoirs in the form of animal serum. A comparison of the protein constituents of human blood with those of the blood of the animals of which practical use may be made is shown in the following table (Howe, 1925):

	Human	Cow	Horse	Sheep
Total protein, g. % ..	7.49	7.43	6.10	5.74
Fibrinogen " ..	0.30	0.72	0.34	0.36
Globulin " ..	2.73	3.50	2.49	2.31
Albumin " ..	4.45	3.21	3.27	3.17
Albumin/globulin ratio	62.0/38.0	47.8/52.2	56.6/43.4	57.1/42.9

In total protein, bovine blood most nearly approaches human blood, but there is a much higher percentage of fibrinogen, which, however, is eliminated in the preparation of the serum. Howe's figure for the total protein of bovine blood refers to elderly animals, bullocks usually having a much higher content than this (see below). The albumin/globulin ratio is lower, too, in bovine blood, which might result in a lower osmotic pressure than with human serum, as the albumin fraction, having a smaller molecule, exerts the greater pressure. As bovine serum is obtainable in the largest quantity, however, this material has been utilized in the following investigation.

Administration of Animal Sera

The infusion of animal sera of full protein content has up to the present been generally unsatisfactory, owing to the high percentage of unfavourable reactions. Kremen and his co-workers (1942) recently gave crude bovine serum an extensive clinical trial in 120 cases, and have declared it unsuitable for general use for the following four reasons: (1) all recipients must be tested by an intradermal dose, positive reactors (approximately 50%) to which do not take the serum well; (2) approximately 60% of the recipients have an immediate reaction after infusion of less than one pint; (3) serum sickness developed in 60% of those cases to which it was possible to administer any quantity of the serum; (4) the rate of administration was so slow as to be practically useless in shock. These authors attempted, furthermore, to absorb the agglutinins on to washed human red cells by mixing these with the serum; but this was only partially successful, and there was a tendency to haemolysis of the human red cells. The incidence of immediate reactions decreased somewhat, but serum sickness was just as prevalent.

Characteristics of Crude Bovine Serum

Crude bovine serum is orange in colour and of a slightly higher viscosity than human serum. We have found the total protein content to vary between 7.5 and 9.5 g.%, the higher figure being obtained in bullocks (Folin and Ciocalteu's colorimetric method). The values for sugar, chlorides, non-protein nitrogen, and potassium were approximately the same as for human serum. *In vitro* tests showed that when bovine serum was mixed with 50 different samples of human red cells of all groups agglutination occurred rapidly. The titre of this agglutination factor in bovine serum is almost constantly 1/16, and this would not permit of more than 200 c.cm. being administered rapidly with safety to any human being. Furthermore, haemolysis of the human red cells is very definite after a period of one hour. These tests bear out the statement of Kremen *et al.* as to its unsuitability for human administration.

Removal of the Globulins

As most of the antibodies are known to be attached to the globulins, removal of this fraction might leave a solution of albumin which could safely be given to man. To this end we took samples of bovine serum and precipitated the globulin fraction by half saturation with sodium sulphate. The resulting filtrate was then dialysed in cellophane cylinders against water, leaving behind a solution of albumin. This albumin was passed through a Seitz filter and collected in sterile bottles. A test of the solution showed that there was no agglutination of human red cells. The pH was 7.8.

This albumin solution was administered slowly to two volunteer patients suffering from advanced carcinoma of the