FRENCH SUPPLEMENT TO THE LANCET

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MALARIA DURING THE WAR.

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THE epidemic of malaria which broke out in the armies operating in Macedonia will probably rank high among the great military epidemics known to history. Such an outbreak, occurring as it has in so unhealthy a country as the Balkans, and under the circumstances peculiar to a great army in the field, could not fail to create a striking impression and to give rise to serious investigation. Like so many other exotic diseases, it has made its appearance during the great war at the very time that a large number of medical men have been in a position to recognise and to study it.

It is proposed here to attempt a summary of the researches on malaria carried out by French medical officers, with reference almost exclusively to the malaria of Macedonia.

Severity of the Macedonian Malaria.

All the medical officers lay special stress on the severe type of the disease. Armand-Delille¹ drew attention to this feature from the very onset of the epidemic.

Professor Laveran has rightly remarked that this peculiarity was well recognised by military epidemiologists. Among numerous instances he recalls the well-known epidemic of "Walcheren fever," which decimated the British Army in 1808. Groll also insists on the constant severity of malaria in epidemic form.

Armies in the field obviously provide all the circumstances favouring a virulent malarial infection: the soldier is forced to take up insufficiently protected quarters in very unhealthy districts; he is over-fatigued and often badly fed; thus he is exposed to particularly virulent infection at a time when his resistance is below normal.

There has been much discussion as to what is the predominant factor in the virulence. Ravaut proved that quinine was administered very unsystematically to patients, and concludes that Macedonian malaria was, above everything, a malaria badly treated. This circumstance has certainly played an important part in the severity and the chronicity of the disease, but it is probably not the only factor. We are driven to assign a predominant rôle to the exceptional intensity of the virus in Macedonia during the summer of 1916. In addition to the fact that the troops had to be stationed in districts such as the valleys of the Vardar, the Struma, and the Butkova, where anophelines were innumerable, it must not be forgotten that the hospital centres, at any rate so far as the French Army was concerned, were also situated in very unhealthy regions. The best-known example of this in the Army of the East was afforded by the hospitals at Vertékop—the translation of which is "fever of the head"—maintained there in spite of the personnel being as much attacked by the disease as were the patients. In short, from the front right down to the base at Salonika not a single patient was safe from risk of infection, whether during his evacuation to the base or during his treatment there. It can be realised that the repeated and continued inoculation and reinoculation played a predominant part in the severity of type exhibited by the disease.

The serious feature which chiefly struck the medical officers detailed to treat malarial patients in Macedonia was the resistance of the infection to specific treatment by quinine. This is, of course, a well-recognised characteristic in all severe infections with malignant tertian malaria. It is to be found also in North Africa, where we have come across numerous examples of resistance to the drug.

In our opinion, the malaria in Macedonia during the summer of 1916 showed its severity particularly in the con-

siderable proportion of cases with an initial fever of typhoidal type, in the equally large number and early onset of grave complications of all varieties, in the altogether exceptional frequency of acute and early cachexia, and, finally, in the quite abnormal series of complications found only in subjects who are steeped in malarial infection. This explains the abundance and the interest of the clinical notes published on the subject.

*Clinical Studies.**

In 1916 the earliest cases of primary fever occurred during the second ten days of June. This agreed with Sir Ronald Ross's forecast, made in November, 1915, as a result of his mission to Macedonia, to the effect that malaria would commence on June 15th.

All the medical officers lay stress on the severe type of these primary attacks, which very often assumed the form of continued fever of typhoidal type. Mauban² studied in detail the initial symptoms in primary attacks, and emphasised the violence in onset of the fever and the varieties of pain associated with it—headache, backache, aching lower limbs, profound weakness, digestive and very frequently respiratory troubles, and rapid increase in size of the spleen. Armand-Delille³ has analysed the various clinical types in such primary attacks: the gastric disturbance due to pyrexia, the continued fever, quotidian remittent fevers, and the mild types attenuated to a mere febrile malaise.

Certain constant symptoms of malaria were manifested with exceptional severity, as, for example, anæmia. Paiseau and Lemaire investigated the hæmatology of the anæmia associated with primary malaria, and found in addition to the normal type a certain number of rare varieties, such as pseudo-leukæmic anæmia, pernicious anæmia, and certain hæmorrhagic forms, particularly remarkable in that the anæmia was accompanied not only by purpura simplex, but by purpura hæmorrhagica with epistaxis, hæmaturia, &c.

Malarial cachexia is usually the final result of a much-prolonged infection, but in the exceptional circumstances in Macedonia it has been fairly common to find patients dying of premature cachexia after only a few weeks of illness, during the course even of a primary infection. This phenomenon corresponds with that described by Kelsch under the name of hydræmic cachexia. It is characterised by a severe anæmia, accompanied sometimes by œdema unassociated with albuminuria. The asthenia is profound, and the digestive disturbance, diarrhoea, and vomiting often intractable. The fall in arterial blood pressure is frequently conspicuous. The researches of Paiseau and Lemaire⁴ suggest that this condition results from the association of progressive anæmia with suprarenal and hepatic insufficiency.

The *intestinal symptoms*, as studied by Abrami and Foix,⁵ were most often represented by crises of bilious diarrhoea accompanying the bouts of malaria. The bout was sometimes represented by diarrhoea alone. At other times a dysenteric diarrhoea was encountered, its distinction from true dysentery being difficult.

Peripheral circulatory disturbances were frequent and were observed in all degrees, from erythromelalgia to symmetrical asphyxia of the extremities, passing sometimes into symmetrical superficial gangrene (Raynaud's disease). Paiseau and Lemaire even reported a case of bilateral gangrene of the lower extremities.⁶

De Brun⁷ met with a diffuse and confluent erythema, usually morbilliform, sufficiently often to regard it as a normal symptom of malaria. Jaundice, pulmonary complications, and acute nephritis were also noted and studied in the course of this outbreak.

² Mauban: *Paris Médical*, Nov. 3rd, 1917.

³ Armand-Delille: *Journal Médical Français*, December, 1917.

⁴ Paiseau and Lemaire: *Cachexie aiguë du paludisme primaire*.

⁵ Abrami and Foix: *L'enterite des paludéens*. Réunion des Soc. Méd. de l'Armée d'Orient, Nov. 7th, 1916.

⁶ Paiseau and Lemaire: *Gangrène palustre*, Bull. Soc. Méd. H. p., Feb. 9th, 1917.

⁷ De Brun: *L'erythème paludéen*, *Paris Méd.*, August 11th, 1917.

¹ Armand-Delille, Paiseau et Lemaire: *Paludisme Macédonien*, Bull. Soc. Méd. Hôp. de Paris, March, 1916, and Oct. 13th, 1916.

Malignant attacks.—Malignant attacks occurring in Macedonia during the summer of 1916 were remarkable not only for their large number, but also for the variety of their clinical forms. Side by side with the classical comatose cerebral type were to be found other rarer varieties: convulsions, coma with hemiplegia, paraplegia, or aphasia; algid types simulating cholera, bilious types, and bilious hæmoglobinuria. It has been possible to draw certain conclusions from these facts.

The part played by *acute adrenal inflammation* in the production of the algid types is demonstrated by the histological investigations of Paisseau and Lemaire,⁸ who found in patients who had succumbed to this variety of the disease very important lesions, sometimes degenerative, sometimes hæmorrhagic, of the adrenal capsules, which at the same time showed a great accumulation of hæmatozoa. The clinical conditions can be correlated exactly with the adrenal insufficiency, the profound asthenia, the arterial hypotension ending in progressive heart failure, the phenomenon of the "tache cérébrale," the profuse vomiting and diarrhoea, and the abdominal and lumbar pain.

This adrenal syndrome is sometimes less pronounced, as in certain cases of malarial asthenia in which the patient can scarcely stir through weakness and the arterial tension is very low, the condition improving only very slowly.

Finally, and more rarely, pigmentation of the skin and of the mucous membranes is noted, the picture then being one of true Addison's disease. Adrenal insufficiency appears therefore to play an important part in malignant malaria.

Meningeal symptoms are sufficiently frequent in malaria for an actual *malarial meningitis*⁹ to be described (G. Paisseau and T. Hutinel). At first, in the mildest degree, there may be only a change in the cell content of the cerebro-spinal fluid; at a more marked stage clinical meningeal symptoms of a more or less pronounced character occur (Porot). Finally, Armand-Delille, Paisseau, and Lemaire have shown that the malignant convulsive type is accompanied almost always by meningeal symptoms dominating the clinical picture; for example, stiffness of the neck, contractures, Kernig's sign, and marked cytological reaction of the cerebro-spinal fluid—so that this variety may be considered as a true acute meningitis.

Numerous cases of *bilious hæmoglobinuric fever* were observed and studied in Macedonia (Carnot, Armand-Delille, Paisseau and Lemaire, Amblard, Porak¹⁰). No definite conclusions have been reached as to its much discussed ætiology. The majority of French writers admit its malarial origin, but some dispute and others admit the influence of quinine in its production. Carnot regards it as due to a rapid and simultaneous destruction of red corpuscles and of parasites. Hæmoglobinæmia has been observed in a certain number of cases, but the laking of the blood occurs at a very early stage and disappears quickly.

Secondary Malaria.

The persistence of complications among malarial patients repatriated from the Balkans has afforded opportunities, especially in France, of studying the secondary complications of the disease.

Carnot, Armand-Delille and Lemaire, and Paillard¹¹ have studied the different *types of fever*, commencing with the first relapse, and have described the interminable quotidian or tertian cycles, and the series of grouped attacks occurring at first each week, then once a fortnight, and then once a month. Marcel Labbé¹² and Paillard have drawn attention to the subfebrile states occurring in malarial patients apart from the true febrile attacks. Paillard regards this as proof of insufficient treatment with quinine.

Complications affecting the sense organs occurred fairly often. *Affections of the larynx*, studied by De la Mothe, were motor in character, paralysis of the muscles of the glottis resulting in aphonia. Chaverne recorded *ocular affections* dependent on the nervous mechanism, such as keratitis, iritis, and very frequently hemianopia. Such defects of

movement as occurred were dependent on the extrinsic and intrinsic muscles producing the various forms of strabismus and of errors of accommodation. Circulatory phenomena were equally frequent, notably conjunctival hæmorrhages, retinal hæmorrhages, and chorio-retinitis. All these complications were related to the febrile attacks as regards the time of their occurrence.

Psychical affections were extremely common among severely infected patients. Porot and Gutman¹³ studied them in detail, and insisted on the fact that the malarial psychoses are always at first confusional in type, coexisting very often with somatic nervous upset, and that they occur in patients whose general health is always profoundly disturbed. These acute confusional states may pass finally into dementia, or into conditions of asthenia and depression, melancholia, mania, &c.

A few cases of rare complications have been recorded, such as the mammitis reported by Carnot, and the instance of acromegaly observed by Richet, junior.

Studies in Parasitology.

A study of the parasitology showed that Macedonian malaria was due almost entirely to the parasites of benign tertian and of malignant tertian fever, that of quartan fever being most exceptional.

The reports of the various laboratories showed that, while the parasite of malignant tertian was predominant during the summer to the extent of over 85 per cent. of the cases, it was almost completely replaced by that of benign tertian fever during the months of March, April, May, and June. This was noted both among patients in France and among those remaining in Macedonia. This fact had been well recognised, but observation on so vast a scale gave it the character of a general rule. It does not, however, appear that this phenomenon has given any conclusive evidence on the much-discussed question of the identity or duality of the two parasites. Wurtz and Armand-Delille, who agree with the view constantly upheld by Professor Laveran, find in this phenomenon a proof of the transformation of a single species. Other writers agree with Marchoux in considering that a double infection is involved.

The biology of the hæmatozoa may afford a very satisfactory explanation of the rhythm of the malarial cycles and of the mechanism of relapses. Carnot,¹⁴ for example, has put forward an original hypothesis which represents the malarial paroxysm as a defensive reaction on the part of the patient. In proof of this he cites experimental evidence of a destructive action of the serum towards the parasites at the end of a paroxysm. This schizontolytic crisis is related to the schizontolytic properties of the serum described by Abrami. By an improvement in the technique of Ross's thick-film method of blood examination Tribondeau has made it suitable for general use in the clinical diagnosis of malaria; instead of hæmolysis by distilled water he employs alcohol diluted one-third, followed by fixation with absolute alcohol. This method preserves not only the gametes but also the young forms of the hæmatozoon, and allows of differential diagnosis of the organism in almost every case.

Prophylaxis in Malaria.

The epidemic of 1916 gave rise to a most difficult problem—that of the value of preventive treatment with quinine—for the general results obtained raised doubts in the minds of medical officers. This measure of prophylaxis had been ordered at the right time, there was at no time any lack of quinine, and the most exact and stringent orders had been issued by headquarters. Nevertheless, even if the mortality from malaria was diminished by these precautions, the effect on the morbidity was less evident. In this must be recognised merely the confirmation of the opinion of colonial medical men, who agree in general with Craig that preventive treatment with quinine is only one of the factors in the fight against malaria, and that by itself it may be insufficient.

On these grounds the Under Secretary of the Service de Santé appointed, at the suggestion of M. Sergeant, an organisation which, under the name of the Mission of Antimalarial Prophylaxis, rendered eminent service in Macedonia and obtained results of great interest in the protection of armies in the field against malaria.

⁸ Paisseau and Lemaire: Accès pernicieux et surrénales aigues. Bull. Académie de Médecine, Sept. 17th, 1916. Soc. Méd. Hôp., Nov. 13th, 1916. Presse Médicale, Dec. 4th, 1916.

⁹ Paisseau and Hutinel: Ménigite palustre, Soc. Méd. des Hôp., June, 1918.

¹⁰ Carnot: Paris Médical, March 3rd, 1917; Armand-Delille, Paisseau, and Lemaire: Soc. Méd. Hôp., June 15th, 1917.

¹¹ Carnot: Accès palustres de Macédoine, Paris Médical, July 28th, 1917. ¹² Marcel Labbé: Réunion médicale de la XVème région, 1917.

¹³ Porot and Gutman: Psychoses du paludisme, Paris Médical, Dec. 29th, 1917.

¹⁴ Carnot: Société de Biologie, June 16th, 1917.

Treatment of Malaria.

No essential change has been introduced in antimalarial treatment. The opinions expressed and the different methods proposed are summarised below.

Quinine treatment.—In the treatment of malaria the points to be considered are the method of administration of quinine, the time of administration, and the dosage.

As to the *method of administration*, quinine may be given intravenously, intramuscularly, and by the mouth.

The method of *intravenous injection* is generally regarded as a procedure only for exceptional cases. Its dangers appear to have been exaggerated, and the technique recommended by Jeanselme and Manaud,¹⁵ consisting in the slow injection by a serum syringe of 1 g. of quinine bichlorhydrate dissolved in 100 g. of saline, appears capable of completely removing such dangers. Carnot and de Kerdrel have shown that the intravenous method is the method of choice in dangerous malignant attacks. On the other hand, this method is not superior to the others in its sterilising power, doubtless on account of the rapidity of elimination of quinine introduced directly into the circulation. The indications for its use are, therefore, special and precise.

The general use of *intramuscular injections* has brought to light a certain number of difficulties. Even when it does not produce abscesses, which have, in fact, been fairly frequent and often severe, the caustic action of the quinine is painful. Although, however, this method should not be employed as a routine, nevertheless it is indicated as the only one practicable for patients with gastric irritability who are the subjects of malignant attacks.

Many writers give preference to *administration by the mouth*. Reference must be made to the opinion held by Marchoux as to the value of giving the least soluble forms of quinine, their efficiency being the greater because they are eliminated more slowly; the sulphate, and, above all, the alkaloid itself, being more active than the other salts. According to Marchoux, chronic malaria must be treated by oral administration.

The effective *dose* of quinine was generally fixed at 1 g. per day for constant treatment. A majority, however, of the medical officers (Soulié, Gutman¹⁶) advise a dose of 2 g., especially in infections due to the parasite of malignant tertian fever; some even advocate a dose of 3 g. for two or three days.

The *time of administration* of quinine appears to have lost much of the importance imputed to it at a period when it was sought to make the absorption of the drug coincide with the presence in the peripheral circulation of the young parasites which are alone susceptible to it. This end cannot be attained in those cases in which the fever is continuous from the onset, as the successive generations of parasites are too numerous. The same is true at the stage when the paroxysms become so irregular that it is difficult in practice to administer the drug at the proper moment. The methods employed vary according as the case is one of primary fever, or of attacks at the so-called secondary stage of malaria.

At the onset, when the aim is to sterilise the patients by preventing the appearance of the resistant forms, the gametes, it has been usual to adopt the classic method of administering quinine in large and continued doses. Mention should, however, be made of the technique employed by Abrami, who prefers to administer the quinine in very large doses at the febrile periods only, in order to destroy in succession the generations of parasites passing into the circulation.

In secondary malaria comparatively little use appears to have been made of the method of discontinuous dosage, based on the weekly periodicity of the recurrences. The method chiefly adopted has been that advocated by Ravaut by which two days' treatment with 1 or 2 g. of quinine a day is alternated with two days of injections with strong doses of cacodylate. Castaigne and Paillard give 2 g. of quinine a day for three days each week.

These methods of treatment have the disadvantage of working in the dark. For this reason the method advocated by Marchoux¹⁷ is of the greatest interest. It is based on the observation that the parasites pass into the blood-

stream two or three days before the rigor, the delay being due to the need for their multiplication to an extent sufficient to provoke the rigor.

With regular examination of the blood at intervals of three or four days it is possible to administer the quinine at the right moment and to destroy the generations of parasites in succession as they appear in the circulation. Not only can the recurrence of rigors be anticipated, but the patients can also be rendered sterile with a minimal expenditure of quinine. Marchoux considers that the destruction of four generations of parasites would suffice to sterilise the system.

Accessory treatment.—In association with quinine, iron and arsenic are the standard drugs for the treatment of malaria. Medication with arsenic has been specially studied, and many writers recommend its systematic use. In France the combined arsenic-quinine treatment advocated by Ravaut, Réniac, and de Kerdrel¹⁸ is specially popular. On two successive days 0.20 to 0.30 g. of arrhénil are injected, followed on the next two days by 2 g. of quinine chlorhydrate by the mouth. This treatment gives excellent results, and has in all cases a remarkable effect on the general health.

Carnot¹⁹ has made a general study of arsenical medication in malaria. He avoids the use of atoxyl and gives preference to injections of arsenobenzol. The lesions of the suprarenal glands noted in malaria justify the use of adrenalin intravenously or subcutaneously, particularly during the rigors and in weak and unstrung subjects, and especially at the commencement of infection. Ravaut, who finds frequent evidence of suprarenal insufficiency in secondary malaria, agrees with Perrin and Edelmann²⁰ in advising the use of adrenalin at this stage.

From the aggregate of the studies published on the therapeutics of malaria there emerges the conclusion that no method of treatment is capable of producing within a short period permanent sterilisation of the patient.

Three methods of treatment deserve mention by reason of their originality or of the results obtained:—

1. Abrami²¹ treats the complications of primary malaria by quinine in very large doses—3 g. of quinine daily, preferably by injection and in two doses, until the temperature no longer exceeds 100.4° F.; the daily dose is then diminished to 2 g. by injection, and is continued until the second day after the temperature has reached the normal. The originality of the method consists in the fact that the quinine is not given during the period of apyrexia, but that the sterilisation is effected by successive doses at the onset of a paroxysm.

2. Ravaut and Carnot have recommended treatment with arsenic. Ravaut alternates the injection of 2 g. of quinine a day for two days with the injection of 0.20 to 0.30 g. of arrhénil for a further two days. This course is followed for one month, and if necessary renewed for three weeks longer after an interval of ten days. Carnot gives six injections of arsenobenzol in a month at the rate of one dose of 0.30 to 0.45 g. every five days, and then gives a protective dose of 0.45 g. once a fortnight, then once a month.

3. Marchoux makes a practice of examining thick blood-films twice a week; in the case of malignant tertian fever and during active stages on alternate days. If the result is positive 1 g. of the alkaloid is given at once. It is extremely rare for an attack to develop between two examinations. These examinations are carried out in a dispensary at which the patients attend regularly. By this method it is possible to employ them on active work during the whole course of treatment.

DISTRIBUTION OF SOLDIERS, TEMPORARILY UNFIT THROUGH MALARIA, IN AGRICULTURAL COLONIES.

BY PROFESSOR E. JEANSELME.

THE malaria of the East is a most obstinate disease which resists the most energetic treatment for many months. If the convalescent is returned too quickly to his unit he has a relapse which makes it necessary to readmit him to hospital,

¹⁵ Jeanselme and Manaud: *Injections Intraveineuses de Quinine*, Presse Médicale, March 31st, 1917; and Carnot and de Kerdrel: *Paris Médical*, 1917, No. 1.

¹⁶ Gutman: *Presse Médicale*, March 10th, 1917.

¹⁷ Marchoux: *Le Paludisme de Salonique*, Bull. Acad. de Médecine, August 3rd, 1917.

¹⁸ Ravaut, Réniac, de Kerdrel: *Le Paludisme d'Orient ou de Marseille*, Presse Médicale, August 16th, 1917.

¹⁹ Carnot: *Paris Médical*, Nov. 3rd, 1917.

²⁰ Perrin and Edelmann: *Paris Médical*, Sept 21st, 1918.

²¹ Abrami: *Le paludisme primaire en Macédoine*, Presse Médicale, March 22nd, 1917.