B

THE NEW SYDENHAM SOCIETY.

INSTITUTED MDCCCLVIII.

VOLUME CXLVI.

B

PALUDISM.

BY

DR. A. LAVERAN,
PROFESSOR OF MEDICINE IN THE SCHOOL OF VAL DE GRÂCE.

TRANSLATED BY

J. W. MARTIN, M.D., F.R.C.P.E.

LONDON:
THE NEW SYDENHAM SOCIETY.

1893.

TRANSLATOR'S PREFACE.

The work of which a translation is now offered to the members of the New Sydenham Society may be considered as the chief of a series of most valuable treatises which M. Laveran has written upon the subject of paludism. It deals with and summarises the important investigations he has conducted, and describes his discovery of the malarial hæmatozoon which has made his name famous. The accuracy of his description of the different forms of the organism, and his account of the long series of cases in which it was found, confirm its reality as a factor in the malarial process. When it is demonstrated that these organisms disappear *pari passu* with the cure of the disease M. Laveran's position is very considerably strengthened.

It is too much to say that the discovery of these parasites puts an end to all future investigations of paludism. Far from it; the composition of the blood, coupled with that of the possible products developed by these organisms, must be further examined and explained. Thus the full knowledge of their bearing upon the malarial process will entail further and elaborate investigation. I do not think, however, that anyone can peruse M. Laveran's work without it being at once apparent that his discovery is in all likelihood the correct one.

His researches have been confirmed by many other observers. Such able writers as Vandyke Carter and Hehir fully substantiate them, as do various authorities in America. At the seventh International Congress of Hygiene, held in London in 1891, Professor Cruikshank spoke to the presence of Laveran's organisms in man as evidence of the existence of malaria, and their detection as invaluable as a diagnostic sign.

It is to be hoped that before long the whole life-history of these parasites may be demonstrated, and, moreover, that charts will be published showing the areas of distribution of the

malarial process with greater accuracy than has at present been attempted.

I have endeavoured to render M. Laveran's views as accurately as possible, without adhering too rigidly to a literal translation.

J. W. MARTIN.

EDINBURGH.

PREFACE.

At the end of the year 1880 I pointed out the existence of new parasites in the blood of patients suffering from palustral fever, and I have returned at different times to the description of these parasites to confirm my first observations, and on some points to make them complete.

The parasites which I described as being those of marsh fever differed very much from those which had been previously described, and they did not belong to the class of schizophytes, to which all pathogenic microbes seem to belong; consequently my first assertions were received everywhere with much scepticism.

Since 1880 investigations confirmatory of mine have been multiplied, and I believe I can say without exaggeration that to-day the existence of the hæmatozoon of paludism is admitted in all parts of the globe where the disease is endemic.

In 1889 the Academy of Sciences conferred the very high honour upon my work of bestowing upon me the Bréant prize.

I shall be pardoned, I hope, if I quote here a part of Professor Bouchard's report, as it constitutes a document too important in the history of the hæmatozoon of paludism to be omitted.

"The Commission[1] by a unanimous vote bestow the Bréant prize (interest of the endowment) on M. A. Laveran, Professor in the School of Val de Grâce, for his discovery of the hæmatozoon of paludism. This discovery, which was made ten years ago, has been verified by observers of the most different views in almost every country where intermittent fever prevails. The parasite, which is the pathogenic agent of an endemic the most ancient, the most extensive, and the most serious of all that scourge humanity, differs fundamentally from the parasites which are at present known of other infectious diseases. It is at least the first example of a disease being caused in man by a sporozoon. No

[1] Commissioners: MM. Marey, Richet, Charcot, Brown-Séquard, Verneuil; Bouchard, reporter.

one to-day will support the ideas formerly held which attributed palustral disease to various forms of algæ or to bacteria.

"The discovery of M. Laveran comprises the whole pathogenesis of intermittent fever; it may be said that it has changed the pathological anatomy of this disease. In fact, the characteristic pigment of the lesions of palustral infections is effected by the parasite, and is contained in the parasite itself." (Academy of Sciences, public meeting of December 30th, 1889, p. 65.)

The existence of the hæmatozoon of paludism is no longer seriously disputed, but several points concerning the history of this parasite are still obscure and require to be re-examined, taking into consideration the numerous works which have been published within the last few years.

What I have proposed to do in this new work is as follows:

Introduction.—Brief *résumé* of researches anterior to mine on the parasitic nature of paludism, and state of the question in 1880.

Chapter I.—Description of the hæmatozoon of paludism.

Chapter II.—Review of researches subsequent to mine.

Chapter III.—Nature of the parasites of palustral blood. Analogous hæmatozoa found in different animals.

Chapter IV.—The hæmatozoon which I have described is really the agent of paludism. This parasite is polymorphous, but unique.

Chapter V.—Pathogenesis of the phenomena of paludism.

Chapter VI.—Means of protection on the part of the organism. Treatment and prophylaxis.

In the first chapters I have reproduced in part some articles which appeared in 1889 and 1890 in the 'Archives of Experimental Medicine and Pathological Anatomy.' I had only to complete that work with the help of the most recent publications.

I have not thought it necessary to return to the clinical description of the phenomena which paludism produces; there would be but little to add to the chapters devoted to this question in my 'Traité des fièvres palustres.'

Terminology is of great importance in science, and it must be admitted that, in general, medical terminology leaves much to be desired. There are more than twenty different terms for the phenomena produced by palustral endemia. It seems to me that it is high time to make a choice from among these terms, and no longer leave the matter to individual taste. The word *paludism*, proposed by Professor Verneuil, appears to me excellent. It is short; it recalls the chief origin of the fevers, and does not give

a false idea of the nature of the phenomena, as some other terms—for example, intermittent fever.

One might hesitate between *palustral* and *paludal*. Paludal might be perhaps more exact, but the word palustral has been accepted long ago, and for this reason I have adopted it, employing it generally as a qualifying adjective—thus, palustral anæmia, palustral cachexia, &c.; sometimes as a substantive, a palustral designating a patient suffering from paludism.

Apart from the figures interspersed in the text, several plates represent the hæmatozoon of paludism under the different aspects which it has in fresh blood, or in preparations of dried and stained blood.

The hæmatozoa of tortoises and of birds, which approach more than any other the hæmatozoa of paludism, are also represented in several plates.

The photographs reproduced in Plates V and VI have been taken by M. Yvon, from my preparations. The photographs of hæmatozoa are difficult to execute, and I thank M. Yvon very sincerely for having so kindly placed at my disposal his great experience of microscopic photography.

A. LAVERAN.

PARIS; *March 1st*, 1891.

CONTENTS.

CHAPTER VI.

ON MARSH FEVER AND ITS ORGANISM.

INTRODUCTION.

The conditions which favour the development of paludism, and those which are necessary to the multiplication of most of the lower animal and vegetable organisms, are exactly the same ; and the parasitic nature of paludism has long been suspected, as the writings of Vitruvius, of Varron and Columellus show.

Lancisi and Rasori admitted that paludism was produced by certain animalcules, which, engendered by the putrefaction of the marsh, are found in suspension in the air of marshy places, and are capable of penetrating the blood. These ideas were so common in Italy at the beginning of this century, that the fever-producing animalcules had received from the people a name—that of *serafici* (death-producing).

According to Virey, infusoria are the principal cause of the insalubrity of a marsh. Boudin considered it due to the vegetable organisms which abound in marshy localities, and principally to the marsh-flower, the vegetable species giving off into the atmosphere toxic volatile principles which are capable of giving rise to paludism.

Bouchard attributed these phenomena to a species of poison secreted by some of the animalcules which abound in a marsh.

This is pure hypothesis, without more foundation than the opinion of Boudin ; it has been observed that the marsh-flower, in especial, could not account for the occurrence of paludism.

According to J. K. Mitchell, Mühry, and W. A. Hammond, the spores which abound in the air of marshy localities are the cause of paludism.

J. Lemaire, who published in 1864 'Researches upon the Microscopic Organisms found in the Air of Marshes,' was obviously

inclined to think that the microphytes and the microzoa which exist in the air of marshy localities are the cause of paludism, but he does not name any one species in particular.

Similarly, Massy of Ceylon, Cunningham of Calcutta, and Corre of Senegal attribute it to the microscopic organisms in the air or in the water of marshes as a whole, and do not specify what is the pathogenic micro-organism.

From 1866 to 1880 these researches were conducted with more precision, and on several occasions it was announced that the parasite of paludism had been discovered.

The observers who look for the microbe of paludism in the air, the water, and in the soil of unhealthy localities are naturally led to attribute it to the micro-organisms which predominate where the observations are made.

In 1866 Salisbury described little vegetable cells of the species of *Palmella* as the cause of paludism; these, he said, he had found constantly in the urine and in the sweat of patients suffering from fever in the Ohio or Mississippi district.

In 1867 Binz pointed out the existence of bacteria in the blood of patients suffering from palustral fever, and he announced that he had induced paludism in animals by injecting into their veins putrid matters of vegetable origin.

In 1869 Balestra described an alga found in the water of the Pontine marshes as the pathogenic cause of palustral fever.

In 1876 Lanzi and Terrigi, following up experiments made on animals, in the blood of which they injected water taken from the marsh of Ostia, arrived at the conclusion that paludism is due to a brownish bacterium which might be the cause of the pigmentation of the organs of those attacked.

In 1878 Eklund described, under the name of *Limnophysalis hyalina*, a micro-organism which he had often met among the algæ of marshy and fever-producing places, and which appeared to him as deserving to be considered the parasite of paludism.[1]

In 1879 Klebs and Tommasi Crudeli, following up researches which were undertaken to verify the assertions of Lanzi and Terrigi, arrived at the conclusion that the cause of paludism is *a bacillus*.

I consider that it is unnecessary to describe here all the micro-organisms which have been successively honoured with the title of the parasite of paludism, not one of which has stood the test of control researches; the works of Klebs and Tommasi Crudeli are the only ones that deserve our attention, the *Bacillus malariæ*

[1] For more details see my 'Traité des fièvres palustres,' pp. 31—51.

having, in fact, been admitted by a great number of observers when I began my researches.

Klebs and Tommasi Crudeli, after having established the presence of the bacillus in the air, in the water, and in the soil of palustral localities, tried to cultivate these bacilli. Mud from a marsh was exposed to the free air at a temperature of 36° to 40° C. in a manner so as to dry only the surface and leave the subjacent layers humid, which appeared to be the condition most favorable to the development of the agent of paludism; a small quantity of this mud was introduced into a cultivation fluid, and this first culture served to inoculate other liquids which were injected into the subcutaneous tissue of rabbits. Klebs and Tommasi Crudeli were said to have succeeded by this process in setting up in the animals under experiment phenomena analogous to those of paludism.

According to these observers, the bacillus which is found in the soil under the appearance of oval spores, mobile and strongly refractile to light, is developed in culture fluids and in the bodies of inoculated animals under the form of long filaments, at first homogeneous, afterwards transversely segmented.

These experiments, and the conclusions to which Klebs and Tommasi Crudeli came, are subject to numerous and grave objections. The cultivation liquid was evidently very impure; the bacillus described as being the pathogenic cause of paludism presented no single characteristic to distinguish it from the numerous bacilli of the soil; and further, the assertions of the authors with regard to the phenomena produced in animals are very questionable: the thermometric tracings given as being those of intermittent fever were very little characteristic—the same applies to the anatomical lesions observed in the rabbit; and it must also be added that at the present time it still remains to be demonstrated that these animals are susceptible to paludism.

Researches, undertaken in Italy by Perroncito, Ceci, Cuboni, Marchiafava, Valenti, Ferraresi, Piccirilli, appeared at first to confirm those of Klebs and Tommasi Crudeli.[1]

Cuboni affirmed that this bacillus was peculiar to paludism, and that he had succeeded in cultivating it; Marchiafava and Ferraresi were said to have established that the blood of patients suffering from intermittent fever examined during the cold stage

[1] Klebs and Tommasi Crudeli, "Studien ueber die Ursache des Wechselfiebers u. ueber die Natur der Malaria" ('Arch. f. exper. Pathol. u. Pharmakol.,' vol. xiii). Tommasi Crudeli, the 'Practitioner,' November, 1880, p. 321. Cuboni and Marchiafava, 'Arch. f. exper. Pathol.,' vol. xiii, 1881.

contained always, and at times in great quantity, the *Bacillus malariæ* at its stage of complete development, while during the height of the fever the bacilli disappeared from the blood, and only their spores were found.

In 1882 Ceci published the results of experiments made in the laboratory of Klebs ('Archiv f. experim. Path. u. Pharm.,' vols. xv, xvi), and the conclusions of his work agreed with those of Klebs and Tommasi Crudeli; the author was said to have succeeded in setting up the phenomena of palustral fever in dogs and rabbits by injecting into their veins the culture fluids prepared from palustral earth.

Such was the state of the question at the time when I published the first results of my observations on the parasites of paludism; it is, I believe, useful to recount it at the beginning of this work in order to let the reader appreciate the results of my work, and to judge of the progress which has been made since 1880 in the knowledge of the nature and causes of paludism.

Another problem remained very obscure in 1880—that of palustral melanæmia. As the study of palustral melanæmia was the cause of my researches, and as it is intimately connected with the history of the parasites of paludism, it merits some attention.

The brown coloration of the spleen, of the liver, and of the brain has been pointed out by all observers who have had the opportunity of making autopsies on subjects who have died of pernicious attacks; but the first observers being deprived of the aid of the microscope did not know to what to attribute this particular coloration, which they noticed only in those cases where it was very pronounced.

Lancisi, Stoll, Bailly, Monfalcon, demonstrated that there often existed in persons who had died of paludism an abnormal pigmentation of the liver and brain. Popken and Fricke, Chisholm, Thussinck, Anderson, Prick, Drake, Annesley, Stewardson, attributed the abnormal pigmentation of the spleen, liver, and brain to the alterations most associated with paludism.[1] Maillot pointed out on several occasions the brown tint of the spleen in those suffering from fever, and he rightly compared this coloration to that of chocolate and water. Out of twenty-two autopsies of pernicious fever mentioned in his 'Traité des fièvres intermittentes' (Paris, 1836, pp. 285—287), the dark tint of the grey substance of the brain is mentioned eight times; in five cases that coloration had assumed almost a blackish hue.

According to Haspel, the pigmentation of the spleen, the liver,

[1] See my 'Traité des fièvres palustres,' p. 100.

and the brain is one of the most constant changes in paludism ('Malad. de l'Algérie,' Paris, 1850, t. i, p. 335; t. ii, p. 318).

Meckel first recognised that the brownish tint of certain viscera in patients who had died of palustral fever was the result of an accumulation of pigment in the blood.

Virchow, Heschl, Planer, and Frerichs in especial have given good descriptions of palustral melanæmia. Frerichs described well the changes produced by melanæmia in the different organs—liver, spleen, lungs, kidneys, brain. He even shows in the brain, besides particles of pigment, colourless and hyaline concretions which obstruct certain capillary vessels ('Traité des malad. du foie,' French translation, p. 493). Frerichs had never thought of the parasitic nature of these latter elements, which are, moreover, indistinguishable in the conditions in which he studied them, that is in organs examined at least twenty-four hours after death.

According to Frerichs, it is in the spleen that the most part of the pigment is produced; the stagnation of the blood in the venous sinuses of the spleen is, he thinks, the principal cause of that alteration.

Frerichs, and after him Griesinger, gave to the accumulation of pigment in the capillary vessels of the brain an important part in the pathogenesis of the brain-changes in paludism—pernicious fevers with delirium, somnolence, and coma.

The articles on melanæmia ('Dictionnaire encyclopédique des sciences médicales'), and of the 'Dictionnaire' of Jaccoud, written by B. Ball and by Hallopeau, show that although when they were written (1873—1876) the study of the pathological anatomy of melanæmia was well understood, the causes and nature of the lesion were still very obscure. Melanæmia was considered neither as a constant lesion of paludism nor as a lesion peculiar to this malady; as for the formation of pigment, there are several theories, which I think it unnecessary to give here.

In two treatises on palustral melanæmia ('Arch. de Physiol.,' 1875, and 'Arch. gén. de Méd.,' 1880) Kelsch came to the conclusion that melanæmia was a lesion peculiar to paludism; according to this observer the pigment was formed in the blood, but the mechanism of this formation was still obscure, and the question was now more important than ever, Why does palustral fever produce pigment, while other fevers more dangerous—*e. g.* typhoid, typhus—are not accompanied by melanæmia?

On arriving at Bona in 1878 I had the opportunity of making several autopsies on subjects who had died from pernicious

attacks, and I was struck with the fact that melanæmia was a lesion peculiar to and very characteristic of paludism; my attention was naturally directed to this lesion, which I had never met in any other disease.

Melanæmia is specially very pronounced in individuals who died from acute paludism (pernicious attacks); the colour which it gives to certain organs, particularly to the spleen, the liver, and the grey substance of the brain, is almost always sufficient to show from microscopic examination if death is the result of paludism.

I shall state here shortly the alterations which are observed in acute paludism: in chronic paludism lesions are complex; the alterations of the blood are complicated with congestions and inflammations which, in palustral cachexia, are highly noticeable. These inflammatory lesions, principally the vascular cirrhoses, are, moreover, well explained by the existence in the blood of parasitic elements.

Some observers have been able to maintain that occasionally no single characteristic alteration was found in individuals who had died of pernicious fever.

This assertion does not stand a strict examination, and could only be put forward at a time when the importance of melanæmia was not known. It might be affirmed, on the contrary, that in these cases there always remain lesions specially pronounced in the spleen and liver. The spleen increases in volume and weight, but the increase is not always considerable; in one patient who died of a pernicious attack the spleen did not weigh more than 400 grammes. The shape of the organ is modified, the edges are rounded; the spleen tends to take a globular form, which is explained by the softening, the pulpiness of the splenic parenchyma. It often happens that the mere act of grasping the spleen to pull it out from the abdomen causes rupture of the distended and thin capsule; the fingers sink into the splenic pulp.

The colour is characteristic; instead of the normal red colour the spleen shows in the inner parts, as well as on the surface, a brownish tint which has been compared to chocolate and water.

If you examine a drop of splenic fluid with the microscope you will find in the midst of the blood, and the elements proper to the spleen which are separated, the existence of pigmented elements in great numbers, and free granules of pigment; the pigmented elements are either leucocytes loaded with pigment, or hyaline bodies of irregular shape: one finds in those preparations

of the spleen pigmented granules much more numerous than in blood taken from the vessels of other organs.

The liver is generally increased in volume and weight; its consistence is often diminished, but the only constant and characteristic alteration consists in a greyish-brown or slate-coloured tint which is taken by the hepatic parenchyma.

By histological sections of a piece of the liver made after hardening, it is easy to see that the blood-capillary vessels enclose pigmentary elements in great numbers, which distend them more or less.

Histological examination of the kidneys reveals also the existence of pigmentary elements, especially in the Malpighian glomeruli; a certain number of pigmented elements circulating with the blood are evidently arrested there.

Melanæmia is often sufficiently well marked in the grey substance of the brain to allow one to see it with the naked eye; the grey substance of the convolutions takes a dark grey or violet tint, which can be compared to that of certain dark-coloured hortensias. The histological examination of the sections of the brain after hardening by the ordinary process shows that the capillaries enclose a large number of pigmented elements; the pigmented granules are in some cases regularly disposed along the length of the brain capillaries, the appearance of which is quite characteristic.

In the other parts of the brain, in the pons, in the medulla, the capillaries also enclose numerous pigmented elements. If the grey tint is more apparent in the grey substance of the convolutions, it evidently depends on the abundance of the capillaries in that substance. The medulla of the bones has a brownish tint due to the presence of pigmented elements, similar to those found in the spleen. The other tissues have a normal tint, but by histological sections it is easy to see that the capillary vessels contain pigmented elements more or less numerous, and that melanæmia is really, as the etymology implies, a general alteration of the blood, which is only more pronounced in the spleen, in the medulla of bones, and the liver than in the other viscera, which is naturally all the more apparent as the tissues are more vascular.

When one examines a drop of blood taken from the dead body of a palustral subject in the ordinary conditions of autopsy—that is to say, twenty-four hours after death—one sees in the midst of the blood numerous pigmented bodies. Many of these elements are melaniferous leucocytes, the nuclei of which can be coloured and stained with carmine; but beside these leucocytes, hyaline pig-

mented irregular bodies are seen, which can only be coloured slightly, or not at all, by carmine, and which do not contain any nuclei. These latter elements have great analogy in their dimensions, and often in their shape, with melaniferous leucocytes, and it can easily be understood that they may have been confused with them. If the blood is taken shortly after death the parasitic elements characteristic of paludism can be recognised.

CHAPTER I.

Description of the hæmatozoon of paludism—Different aspects under which it is seen—Methods of examination of the blood—Attempts at cultivation and inoculation in animals.

In 1880, as I was trying to account for the mode of formation of the pigment in the palustral blood, I was led to see that besides melaniferous leucocytes, spherical hyaline corpuscles without nucleus could be seen, and also very characteristic crescent-shaped bodies.

I had proceeded thus far with my researches, and was still hesitating whether these elements were parasites, when on November 6th, 1880, on examining the pigmented spherical bodies mentioned above, I observed, on the edge of several of these elements, moveable filaments or flagella, whose extremely rapid and varied movements left no doubt as to their nature.

I published in 1881 the observation of the patient in whose blood I saw the flagella for the first time ('De la nature parasitaire des accidents de l'impaludisme,' Paris, 1881, p. 58); this observation is given at the end of this book (Observation 22).

The very fact that I can quote the day on which I observed the flagella for the first time shows how characteristic these elements are. It was natural to suppose that these parasitic elements, for the most part pigmented, were the cause of palustral melanæmia, and also the cause of the phenomena of paludism. Numerous facts soon came to confirm this hypothesis.

The parasite of palustral blood is seen under rather varied forms, which may be classed under the four following types:

1st. Spherical bodies.

2nd. Flagella.

3rd. Crescent-shaped bodies.

4th. Segmented bodies and rose-shaped bodies.

1st. *Spherical bodies.*—This is the most common form, and the one most often met; I have noticed it, in the examination of palustral cases, 389 times out of 432. These elements often possess amœboid movements which alter their shape more or

less. They are composed of a hyaline, colourless, and very transparent substance, and have variable dimensions: the smallest have scarcely 1 μ, the largest have a diameter equal to or even greater than the diameter of a red blood-corpuscle; some of the elements have a diameter twice as large as that of blood-corpuscles.

The contours are shown by very fine lines; on preparations stained with osmic acid and colouring reagents, a double contour may be found, which is not seen in elements observed in fresh blood. The smallest only contain one or two granules of pigment, or even none at all. They have the appearance of little colourless clear spots in the blood-corpuscle.

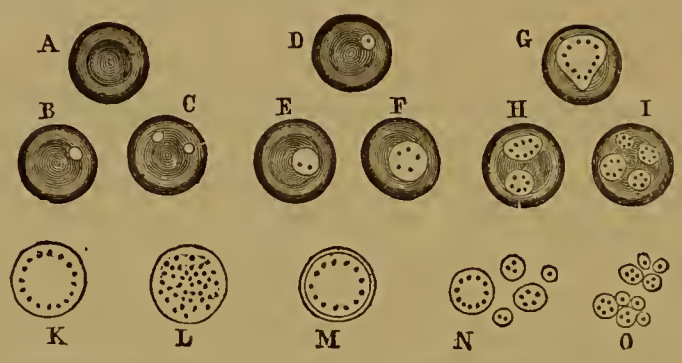


FIG. 1.—A. Normal red blood-corpuscle. B, C. Blood-corpuscles with spherical bodies of very small size not pigmented. D, E, F. Blood-corpuscles with spherical bodies of small size pigmented. G. Blood-corpuscle with a spherical body distorted by amœboid movements. H, I. Blood-corpuscles with several spherical bodies pigmented. K. Spherical body, pigmented, fully developed. L. Spherical body containing grains of pigment in movement. M. Spherical body on which a double contour is distinguished. N. Free spherical bodies. O. Spherical bodies massed together. (× 1000.)

In proportion as these elements enlarge the number of granules of pigment increases; these granules make a fairly regular circle, or else they are arranged irregularly, and often possess very rapid motion. This motion has neither the constancy nor the regularity of the Brownian movement, with which, in other respects, it has a certain analogy; it diminishes or increases in rapidity, it stops sometimes, to commence again, without the physical condition of the preparation being modified. On their first appearance one is inclined to believe that the pigmented corpuscles possess a movement of their own; but it seems almost certain that it is a movement imparted to them.

The amœboid movements of spherical bodies coincide often with the motion of the granules or pigment; these distortions, which

take place rather slowly like those of amœbæ, are easy to see when the same element is in the centre of the field of the microscope, and is drawn say every minute. These spherical bodies are at times free in the serum (K, L, N, O, Fig. 1), at times adherent to the red blood-corpuscles (B, C, D, E, F, G); on the same blood-corpuscle sometimes two, three, or four of these bodies are found (H, I).

These parasites evidently live at the expense of the blood-corpuscles, which grow pale in proportion as the parasitic elements which adhere to them increase in size; there is a time when the blood-corpuscle is only distinguished by its contour; its characteristic colour has disappeared, its transparency is the same as that of the parasite, and soon the corpuscle disappears completely.

The red blood-corpuscles attacked by parasites have often a diameter considerably larger than that of the normal blood-corpuscle; the characteristic yellowish colour and their disc-like shape also disappear, the blood-corpuscles becoming, so to speak, dropsical. Are, then, the parasites enclosed in the blood-corpuscles, or are they simply adherent to them? This question, which after all is secondary, is difficult to answer by direct observation.

Our knowledge of the structure and composition of the blood-corpuscles in man makes it difficult for us to understand how these parasites can enter them. The probability is that they simply adhere to the blood-corpuscles by pressing upon them. What makes this supposition more likely to be true is that the parasitic elements are often found in the blood in a free state, and that at all periods of their development.

The spherical bodies may be multiplied by means of segmentation or by budding.

On examining minutely one of these elements possessing amœboid movements, it sometimes happens that this body is seen to divide into three or four similar but smaller elements; these elements separate themselves and become free. Some kinds of sarcoid balls are sometimes formed on the edges.

After a variable time, seldom extending over half an hour or three quarters of an hour, the movements of the granules of pigment stop, and the spherical bodies take their cadaveric form; the contours are more or less irregular, the pigment collects in certain points; the bodies are still easily distinguished from the melaniferous leucocytes by the absence of a nucleus.

Some observers have described a nucleus in the spherical bodies; if it exists (which is not yet proved), this nucleus is

very difficult to see, and is not coloured by the methyl aniline blue, as is the case with the nuclei of leucocytes.

Figs. 2 to 18, Pl. I, inserted at the end of this book, represent diseased red blood-corpuscles to which from one to four spherical bodies adhere, first without pigment, then with black granulations. The red corpuscle increases in size and becomes pale (15, 16), then completely disappears. Figs. 19 and 20 show free spherical bodies in their complete development; figs. 21 and 22 show small spherical bodies, free, isolated, grouped, and massed together.

In fig. A, Pl. II, I have represented spherical bodies free or adherent to blood-corpuscles, just as they are seen in fresh blood. Fig. B in the same plate shows spherical bodies in the different degrees of their development, with the appearance they present in the preparation of blood, dried and stained by methyl aniline blue. Lastly, fig. A in Pl. III shows spherical bodies in their different stages of development, either free or adherent to the blood-corpuscles, as they appear in preparations of dried blood submitted to the double staining of eosine and methyl aniline blue.

Marchiafava and Celli make claims in relation to the discovery of these elements, to which I must refer in analysing works which are subsequent to mine. These observers assume that I had not seen the largest pigmented forms of spherical bodies, and that I had not described the amœboid movements; on that account I think it my duty to reproduce here some passages from my earlier publications.

In a communication to the Academy of Sciences (sitting October 24th, 1881), after having spoken of crescent-shaped elements, of spherical bodies containing mobile pigmented granules, with or without flagella, and of free flagella, I also mentioned as parasitic elements of palustral blood *small elements which scarcely measure the sixth part of the diameter of one blood-corpuscle, and which only enclose one or two granules of pigment.* I add that these bodies, sometimes isolated, sometimes grouped together in threes and fours, now free in the blood, now adherent to blood-corpuscles, seem only to represent one of the phases in the development of larger spherical bodies.

I also mention the red blood-corpuscles which seem fenestrated, and are nothing but blood-corpuscles to which small hyaline bodies without pigment adhere, making colourless spots on the blood-corpuscles (Acad. des Sciences, 'Comptes rendus,' t. xciii, p. 628).

In a communication made to the Medical Society of the Paris

hospitals on April 28th, 1882, I pointed out *the existence of small transparent elements, the smallest of which only measured* 1 μ, *and only contained one or two granules of pigment. These bodies are sometimes free, sometimes adherent to red blood-corpuscles, sometimes three or four of these bodies are found on the same blood-corpuscle. At an ordinary temperature these elements show amœboid movements.*

A coloured plate accompanying this work, which was communicated in 1882 to the Medical Society of Hospitals, represents small elements, free, isolated, or grouped together, and other elements, one, two, and three in number, which adhere to blood-corpuscles.

In the 'Revue scientifique' of April 29th, 1882, the small elements, which only measure 1 μ, are also described and represented in a free state or within the red blood-corpuscles; in this work I also show that these elements present amœboid movements at an ordinary temperature.

In the second edition of the 'Nouveaux Éléments de Pathologie médicale' (in conjunction with Teissier, Paris, 1883) these small elements are also described and represented (op. cit., t. i, p. 93, and fig. 12).

In my 'Traité des fièvres palustres' (Paris, 1884), fig. 7 represents small elements free or adherent to blood-corpuscles; the smallest do not even measure 1 μ, and only contain one granule of pigment; one of them does not contain any at all. I point out (p. 167) the frequency of red blood-corpuscles which show small colourless spots, at p. 168. I note the amœboid movements of the bodies which I then described under the name of body No. 2. Fig. 11 also represents small elements free or adherent to red blood-corpuscles.

At p. 203 (op. cit.) I write, "The primitive embryonic form of the parasites of paludism seems to be represented by the little spherical transparent bodies which I described under the name of body No. 2, of small volume, and which are presented in fig. 7. These little bodies are free or adherent to red blood-corpuscles, at the expense of which they evidently live, for the red blood-corpuscles which support them grow paler in proportion as they increase in size, and at last disappear. At first these elements are hyaline, transparent, and non-pigmented, and the blood-corpuscles to which they adhere simply show little clear spots; soon a granule of pigment is formed within, then two and three, and very soon the pigmented granules become so numerous that it is difficult to count them."

The existence in the blood of the smallest of these elements is

frequently noticed in the course of clinical observations published in this book; particularly Obs. 21, 32, 35, 36, 41, and 42, which were collected in 1881 and 1882.

We shall see further that in 1884, after the publication of my 'Traité des fièvres palustres,' Marchiafava and Celli still maintained that the elements which I had described were only degenerated red blood-corpuscles. This fact alone should enable people to estimate fairly the claims of these authors.

2nd. *Flagella.*—When a preparation of blood is carefully examined, in which spherical bodies of ordinary size are found in a free state, mobile filaments or flagella are often seen upon the edge of these elements; these flagella move very quickly, and give to the neighbouring blood-corpuscles very varied movements: the blood-corpuscles are diminished, folded, and yet they always resume their form as soon as the flagella are a little removed. These movements can be compared to those of small eels which are fixed by their tails and seeking to get free. The flagella are so fine and so transparent that in spite of their length for microbes, three or four times the diameter of the blood-corpuscles, it may be 21 to 28 μ, it is very difficult to see them when they are at rest. The flagella are liberated from the spherical bodies; the act of their freeing themselves can sometimes be seen.

The number of flagella which adhere to one spherical body is variable: sometimes only one of these elements is distinguished (C, Fig. 2); at other times two, three, or four (A, B): the move-

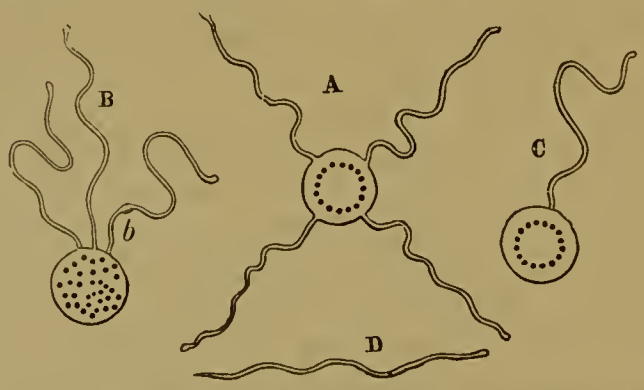


FIG. 2.—A. Spherical body with four flagella. B. Spherical body with three flagella, one of which shows a slight swelling. C. Spherical body with one flagellum. D. Flagellum free. (About × 1000.)

ments of each flagellum are independent of those of neighbouring flagella.

When the flagella are three or four in number they are

sometimes rolled up, so that it is very difficult to say what their number and dimensions are.

The movements of flagella may be seen in the blood after it is taken from the vessels, especially when the outside temperature is very high, but generally it is much easier to make the observation after fifteen to twenty minutes. Perhaps the movements stop under the influence of the cooling of the blood on coming out of the vessels.

The free end of the flagellum often presents a little pyriform swelling, only discernible when this very mobile end is exactly in the line of vision. These swellings at the extremities have been shown in all the flagella A and B (Fig. 2).

Besides these, small swellings sometimes appear which seem to move along the flagella (B, Fig. 2); I have several times seen a pigmented particle which seemed to come from the interior of the spherical body and moved along the flagellum, causing a slight swelling as if the flagellum had been hollowed out of a canal.

Sometimes the flagella are placed symmetrically, at others they are grouped together at one point of the spherical body.

In observing a spherical body provided with flagella, such as A and B in Fig. 2, it is difficult not to think that it is an animalcule provided with pseudopodia, all the more so because the flagella often give more or less extensive movements to the spherical body. It is generally an oscillating movement in one place without the spherical body leaving its place, but if the layer of blood is rather thick it undergoes a real movement of transition.

The varying number of flagella and their irregular disposition do not accord with the idea of a parasite provided with pseudopodia, but the real reason for giving up that idea is that at a given time the flagella leave the spherical bodies and circulate among the blood-corpuscles. The flagella when they have become free are difficult to follow; instead of moving in one particular place, as when they were adherent to the spherical bodies, they move rapidly in the field of the microscope: the fixed point furnished by the pigmented spherical body is also missed. It is evident that each flagellum then lives an independent life.

After the flagella have become free, the pigmented bodies to which they adhered alter their shape and remain motionless, the granules of pigment accumulating in one or more points.

It has been attempted to minimise the importance of flagella by saying that they are very rare in palustral blood. It is certain that these elements are observed more rarely and with more diffi-

culty than the spherical and crescent-shaped bodies; the flagella are only produced in one phase of the evolution of the parasites of paludism, they are invisible in a state of rest, and in addition they rapidly disappear under the influence of quinine. Out of 432 palustral patients whom I examined, I found flagella in 92 only.

Flagella are represented in Pl. I (figs. 29—32); Pl. II (fig. A) gives a fairly exact idea of the very characteristic appearance which these elements take when they move in fresh blood among the blood-corpuscles which they displace.

The flagella are always found in the blood at the same time as the spherical bodies described above, and also often at the same time as the crescent-shaped bodies which will be described later on. I have never succeeded in seeing flagella come out of a crescent-shaped body; but these latter may, as we shall see, go through a slow transformation from an oval to a spherical form, and it is very probable that these spherical bodies give rise to flagella, as do the spherical bodies themselves.

The flagella, although rather rare in the peripheral blood (according to the researches of Councilman they are to be found much more frequently in the blood taken directly from the spleen), are not the less on that account the most characteristic elements among the different forms which are taken by the parasites of paludism.

I have often been asked to examine parasites, and I have always noticed that when I had only spherical elements or crescent-shaped bodies to demonstrate, there remained some doubts in the mind of the observer; if I succeeded in finding flagella all hesitation disappeared: an examination of a few minutes was sufficient to remove all doubts.

It is after having verified the existence of flagella in fresh blood that Professor Bouchard said, in the Academy of Sciences, "A recent note by M. Laveran leads me to point out the importance of a discovery which now goes back ten years, which, although contradicted for a long time, seems to me now unassailable" (Academy of Sciences, sitting January 21st, 1889).

Professor Straus has also been satisfied of the parasitic nature of the elements found in the blood of palustral patients from the day when he was able to observe the flagella; I had shown him previously the spherical and crescent-shaped bodies without succeeding in completely convincing him.

"I confess," says M. Straus, "that I was amongst those who still entertained some doubts of the truth of M. Laveran's discovery, so much is one inclined to mistrust new ideas which do

not belong to the ordinary stock of information; but these doubts have been completely dissipated. M. Laveran has kindly shown me at Val-de-Grâce preparations of blood taken from a soldier suffering from an attack of intermittent fever, who had returned from Tonquin. The several forms of the parasite described by him could be seen there very distinctly, specially *the flagellated bodies,* which are eminently characteristic; these spherical bodies, provided with vibrating flagella which possess extremely quick movements, and displace red corpuscles after the manner of whips, form one of the most striking pictures which can be seen under the microscope. This picture is as distinct and as characteristic as that of the blood of anthrax, or the blood of an individual suffering from filaria" ('Soc. de Biologie,' November 24th, 1888).

The observers, numerous at the present time, who have succeeded in finding flagella in palustral blood are unanimous in declaring that seeing the flagella in movement is absolutely characteristic, and that once seen it is impossible to doubt that these elements are living. The flagella are not generally seen in preparations of dried and stained blood. I have, however, seen some in these preparations, which proves that the flagella existed in fresh blood, the drying taking place very quickly on separation from the vessels.

3rd. *Crescent-shaped bodies.*—These are cylindrical elements more or less pointed at their extremities, and usually bent in crescent form (A, Fig. 3); the substance of these bodies is transparent, colourless except towards the middle, where granules of pigment similar to those of the spherical bodies are found.

The length of these elements is generally a little greater than the diameter of the blood-corpuscles, *i. e.* from 8 to 9 μ; it is worthy of note that one never finds crescent-shaped bodies of small size or of a size much greater than that just mentioned; the breadth is about 2 μ towards the middle. The extremities of the crescent are sometimes very pointed, sometimes rounded.

Their appearance in fresh blood is shown by a single very fine line, but it is easy to see in certain preparations which have undergone the action of osmic acid, or of colouring reagents, that there exists a double contour.

The granules of pigment whose presence is constant are almost always massed towards the middle, they are more or less heaped together; in exceptional cases the pigment is to be found at one of the horns.

A very fine line is usually seen on the side of the concavity, and this joins the two extremities of the crescent (B, Fig. 3).

These elements are free in the blood; when one is adherent to the blood-corpuscles (c, Fig. 3) it is by accident; if the cover-glass is struck ever so lightly so as to displace the blood-corpuscles, the crescent-shaped body is generally displaced and becomes free. Spherical bodies adherent to red blood-corpuscles, on the contrary, adhere very strongly to them, and it is impossible to free them in the way just mentioned.

By setting up a small current in a preparation of blood it is easy to ascertain that the crescent-shaped bodies have really the cylindrical form mentioned above; they turn on their own axis following the current, and show their different phases.

Fig. 3.—A, B. Crescent-shaped bodies. C. Crescent-shaped body joined to a blood-corpuscle. D. Crescent-shaped body. E. Oval body. (About × 1000.)

Besides these crescent-shaped elements others are also found which are scarcely curved, or even whose main axis is straight, and which have more or less the oval form represented by E (Fig. 3). By leaving a crescent-shaped body in the field of the microscope, it may be seen that after a certain time this body assumes an oval form. The oval body itself is changed after a variable time to a round body.

These elements do not possess motion; the pigmented granules which they contain are motionless, the changes in form mentioned above take place slowly, and have nothing in common with the amœboid movements; lastly, one never finds flagella on the sides of the crescent-shaped bodies.

The shape of these elements, their dimensions, which are always about the same and which are nearly equal to those of the red blood-corpuscles, the fine line which often unites the horns of the crescent, and which seems to belong to a blood-corpuscle which has been almost entirely destroyed, lead one to think that they are blood-corpuscles invaded by the hæmatozoa of paludism.

Sometimes this origin of the crescent-shaped bodies is very apparent; the fine line which unites the two ends of the crescent makes with the outward edge of the crescent a regular circle, which has exactly the dimensions of a red blood-corpuscle. It is to be noticed that no small crescent-shaped bodies are ever found in the blood-corpuscle in a state of development as may be ob-

served in the case of certain hæmatozoa in animals (*Drepanidium ranarum*, for example).

Some observers admit that the crescent-shaped bodies have nuclei.

The crescent-shaped bodies are shown in Plate I, figs. 33 and 34, as well as the oval and spherical bodies which are derived from them (figs. 37, 38).

Fig. A in Plate II shows crescent-shaped bodies as they appear in fresh blood; and fig. B in the same plate shows their appearance in a preparation of blood dried and stained with methyl blue.

Fig. A in Plate III shows the same elements in a preparation of dry blood and submitted to double staining (eosine and methyl blue).

4th. *Rose-shaped or segmented bodies.*—Beside the spherical bodies and flagella and crescent-shaped bodies, spherical elements pigmented in the centre and regularly segmented may be sometimes found in the blood of palustral patients. In my 'Traité des fièvres palustres' this variety of parasitic elements is mentioned on p. 177. This segmentation is represented in D, E, G, H, in Fig. 4. These elements were drawn at Constantine in September, 1881, and observed during an attack of quartan fever. I have also noticed these elements in some cases of quotidian fever; they seem to me very rare in tertian fever.

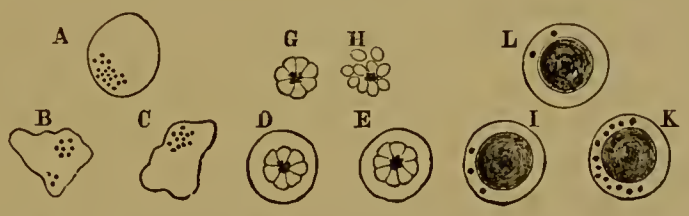


FIG. 4.—A, B, C. Hyaline bodies pigmented, motionless, and mis-shapen. D, E. Segmented and rose-shaped elements, pigmented at the centre. G, H. Elements resulting from the segmentation of rose-shaped bodies. I, K, L. Melaniferous leucocytes whose nuclei have been brought out by carmine. (About × 1000.)

This rose shape has, according to Golgi, a great importance; it represents the principal mode of multiplication of the parasite of paludism; moreover this mode of segmentation is different in the tertian and quartan fevers. I shall return later to this question; for the present it is sufficient to say that I have not often had the opportunity of meeting this rose-shaped form in palustral blood, which explains the very secondary place which I have assigned to it.

We have seen above that the spherical bodies may be multiplied by a kind of budding or by segmentation; the regular segmented bodies would therefore only represent one of the methods of multiplication of the hæmatozoa.

The different phases of the segmentation of a spherical body are shown in Plate I (figs. 23 to 28); the segmentation, which at first is only shown by a slight indentation of the outline of the element, grows larger and larger; at last the small spherical bodies resulting from the segmentation become free.

Fig. A, Plate III, shows a rose-shaped body in the preparation of dried blood and submitted to the double staining (eosine and methyl blue).

Lastly, irregular pigmented hyaline motionless bodies are found in palustral blood (A, B, C, Fig. 4); these evidently are only the dead forms of the parasites above described, and melaniferous leucocytes differing from them by their more regular form and by the presence of a nucleus which can easily be stained by carmine (I, K, L, Fig. 4).

Melaniferous leucocytes are presented in Plate I (figs. 39, 40, 41) with dead forms of parasitic elements (figs. 42, 43, 44); and in Plate II, fig. A, with the appearance they have in fresh blood.

Out of 480 palustral patients examined in Algeria, I have noticed the existence of parasites described above 432 times; negative facts were collected at the beginning of my researches, when I did not know exactly under what conditions to observe the parasites, and refer to some patients who had been submitted to quinine treatment, or else had not had any attack for some time—conditions very unfavorable to the search for parasites, as I have since discovered.

It was interesting to know if the parasites were more or less numerous in the blood before, during, or after the attacks. Out of 79 examinations made a little time before the attack, I have observed parasites 79 times. Out of 286 examinations made during attacks I have observed them 273 times. Out of 164 examinations made a few hours after the onset of fever I have observed them 141 times ('Traité des fièvres palustres,' p. 197).

It is, therefore, a little before the attacks or at the beginning that the examination of the blood should be made.

In certain patients, and particularly in certain cachectics who seem to have acquired very great tolerance for the parasites, the latter are found not only during the whole duration of the paroxysms, but also in the interval of the attacks, and certain forms (crescent-shaped bodies) only disappear slowly even when

the patient is submitted to treatment with quinine. On the whole there exist great individual differences.

I had the opportunity of examining in Paris a number of soldiers who had returned from the colonies, and were passing through or on furlough in Paris. These men came from Algeria, Tunis, Tonquin, Cochin-China, Senegal, and Madagascar. Every time I was able to make the examination of the blood under good conditions, *i. e.* at the beginning of an attack, I found parasitic elements, and the elements were the same whatever the native origin of the fever. Certainly these elements were often few in number, and it was consequently more difficult to observe them than in Algeria. It should be taken into account that the palustral patients seen in Paris have always been treated in a more or less systematic way. I have also found the parasites in some patients who had contracted paludism in France, in Rochefort principally.

Out of 432 cases in Algeria in which I ascertained the presence of parasites, I noticed—

Spherical bodies alone	266 times.
Crescent-shaped bodies alone . . .	43 "
Spherical and crescent-shaped bodies . .	31 "
Spherical bodies and flagella . . .	59 "
Spherical and crescent-shaped bodies and flagella .	33 "

The spherical bodies alone or associated with other elements have therefore been observed 389 times out of 432.

The crescent-shaped bodies alone or associated with other forms, 107 times.

The flagella, always associated with spherical elements, have been seen in 92 patients.

In most of the cases (95 times out of 107) the crescent-shaped bodies have been observed in the blood of patients suffering from palustral cachexia or recurring intermittent fever; when, as has been done in Paris, patients are observed who came from a distance and who have had numerous relapses of fever, or who are cachectic, it was to be expected that the crescent-shaped bodies would be more frequently found than in the palustral countries, in which there is often the opportunity of observing fevers in their primary attack.

If I do not modify the figures given in my 'Traité des fièvres palustres' concerning the frequency of the different elements, taking into account facts which I have observed since I left Algeria, it is because my first figures refer to all the forms of paludism, whilst in Paris I only observed one class of patients (those suffering from a relapse of intermittent fever); the intro-

duction of these facts into my statistics of Algeria might therefore have affected the conclusions at which I had arrived.

What relations exist between the different parasitic elements above described? I expressed as far back as 1862 the opinion that these elements, in spite of the variety of their shapes, constitute not parasites of different kinds, but successive states of the same polymorphic parasite.

The hyaline corpuscles, not yet pigmented, which make small clear spots on the red blood-corpuscles, represent probably the embryonic stage of the parasite; little by little their bodies increase, and their size is completed when they are equal to or even a little larger than that of the blood-corpuscle; at the same time the number of the granules of pigment increases. These elements, which possess amœboid movements, exist in a free state in the serum of the blood, or adhere to the red blood-corpuscles, at the expense of which they live, and which supply them with the pigment. The flagella are developed within the spherical bodies, and at a given time they become free.

The explanation of the crescent-shaped bodies remains still rather obscure, but the relation of these elements to the spherical bodies and to the flagella does not seem doubtful.

We shall see in the next chapter that several Italian observers admit the existence of two or three species of hæmatozoa of paludism, one being characterised by the crescent-shaped bodies.

Examination of palustral blood; technical details for the preparation and staining of the parasitic elements.—In studying the parasites of paludism, it is necessary that the choice of patients should be made under the most favorable circumstances. The parasites are most often absent from the blood of those palustral patients who have not had any attack for some time, or who have just been undergoing quinine treatment; a patient should therefore be chosen who is actually suffering from fever, or who is just affected, and who has not taken any quinine recently.

The easiest and most practical method for the search of the parasites of palustral blood, consists in the examination of the fresh blood obtained by pricking the finger.

Councilman and Golgi, who have examined the blood of the spleen in a certain number of patients, have noticed that the blood obtained in this way contained parasitic elements in larger number than peripheral blood. Hypodermic puncture of the spleen made with antiseptic precautions is not dangerous, but it is too delicate and painful an operation to bring into practice generally.

The preparation of the recent blood is made by the ordinary method; it is important that it should be very thin. It may be surrounded with paraffin, but this precaution may be dispensed with. The blood which coagulates on the edges of the preparation in contact with the air is a sufficient seal; it remains liquid in the centre for a variable time, but at any rate for a few hours, which is quite sufficient for ordinary examination. When it is wished to make an examination of the blood with high powers, or to study the movements of the parasitic elements, it is well to ring with paraffin in order to stop the movements which the drying of the blood gives to the blood-corpuscles.[1]

At the beginning of my researches I took minute precautions to prevent the introduction of all extraneous matters into the preparation. In practice these precautions are not necessary; the parasitic elements are too characteristic for one to compare them with the dust in suspension in the air.

The finger of the patient which is to be pricked must be clean, it must be washed very carefully in order to prevent the entrance of dirt into the preparation, which might interfere with the examination. The finger should be washed first with water, then with alcohol, and care should be taken to dry it completely before pricking. If the skin is ever so little damp, the blood spreads, mixes with the water, and the red blood-corpuscles are disfigured; on the contrary, when the skin is very dry the blood which comes out of the wound makes the drop very defined and very prominent; it is easy to collect, and the blood-corpuscles are not changed if the operation is quickly performed. I usually examine pure blood without the addition of any reagent.

At first after making the preparation the search for the parasitic elements is sometimes difficult; the blood-corpuscles form rouleaux, and often present their edges; in these conditions most of the parasitic elements, and particularly those which adhere to the blood-corpuscles, are invisible. If the preparation is sufficiently thin the blood-corpuscles will soon lie flat, which makes the search for the hæmatozoa much easier.

The parasitic elements are often in small numbers in the peripheral blood, therefore the observer who undertakes to find them must be patient, and repeat the examination of the blood several times before declaring the examination to be negative.

[1] Preparations may be sent to the R. C. P. Laboratories of either Edinburgh or London, the directors of each having kindly engaged to examine the specimens. —[Trans. note.]

A power of 400 diameters is sufficient for the investigation of the hæmatozoa of paludism. I ordinarily use the oculars 1 or 2, and the objectives 7 or 9 of Verrick; I have also used the objectives 10 and 13 with oil immersion by the same maker. The examination of the fresh blood must be made in daylight; artificial light and the Abbé condenser make the parasitic elements too transparent. The parasitic elements being usually pigmented, the black granules of pigment will give a useful point to start from.

By adding a drop of water to the blood the blood-corpuscles are destroyed, without altering, at least for some time, certain parasitic elements, specially the crescent-shaped bodies, which may easily be discovered by this means.

It is in the pure and fresh serum in the midst of the blood-corpuscles that the parasites are best studied; if the presence of the blood-corpuscles is sometimes inconvenient it often makes the observation easier, especially so far as flagella are concerned, these being so transparent that it is difficult to see them in the serum. The very varied movements which these elements give to the blood-corpuscles serve to show their presence, and to make their particular movements more apparent.

The very rapid movements of the granules of pigment in the spherical bodies, and the amœboid movements of the latter, can also only be studied in fresh blood; and in preparations of fresh blood, by means of a prolonged observation of a spherical body, some of the transformations it undergoes may be followed.

A hot stage (37° to 38° C.), useful for observing amœboid movements and flagella, is not necessary. All my observations in Algeria were made at the temperature of the laboratory.

The rapid drying of the blood by heat is an excellent means of preserving the blood and the parasitic elements which it contains. The cover-glasses with the blood spread in thin layers on their surface may be preserved a long time, sent away a distance, and stained a long time after the blood was collected; thanks to this method, I can examine in Paris blood which I obtained in Algeria. I am glad to have the opportunity of thanking those of my colleagues who have kindly sent me dried palustral blood, and specially M. Soulié, assistant professor in the school at Algiers, and M. Geschwind.

Heat in this case seems to me preferable to the vapours of osmic acid, which have also been recommended to fix the blood-corpuscles in their shape. Osmic acid is much more difficult to use than heat; a bottle containing a solution of osmic acid cannot be carried about, and it would be dangerous to leave that re-

agent in the patient's room. Besides, osmic acid is not satisfactory in these cases on account of its staining the fat granules black, consequently they might be confused with the granules of pigment in the parasites.

In making preparations of dry blood the following plan may be followed with advantage:

1st. A few cover-glasses are cleaned with great care, first in water and if necessary in water mixed with hydrochloric acid, then in alcohol.

2nd. The finger of the patient it is intended to examine is rendered physiologically clean and dried completely, then pricked with a needle passed through the flame.

3rd. A cover-glass is made to impinge on the drop of blood which escapes from the pricking; the drop of blood thus adheres to the glass.

4th. A second glass is applied immediately to the first glass so that the blood spreads in a thin and uniform layer between these two glasses.

5th. The two cover-glasses are then made to slide over one another and separated, and the blood, which makes a very thin layer on the surface of each glass, is rapidly dried.

6th. Each cover-glass is taken with the forceps and passed three times through the flame of a spirit lamp, care being taken not to turn the surface covered with blood downwards.

The cover-glasses thus prepared may be wrapped in paper and examined subsequently; the name of the patient and the date when the blood was taken should be written on the paper.

The blood, dried as we have just described, may be examined without any other preparation, without staining, and this method gives excellent results for the crescent-shaped bodies. The cover-glass is placed on a slide and surrounded with paraffin; the preparation is *mounted dry,* as they say; Canada balsam will make the elements much too transparent.

In some preparations of blood preserved for six or seven years by this process the crescent-shaped bodies are still quite visible: in time the elements become a little disfigured; they broaden out and become granular.

The pigmented spherical bodies, either free or adherent to the red blood-corpuscles, are also seen in preparations of dry blood when one is practised in these methods; but for the study of these elements in dry blood there is some advantage in using colouring reagents—namely, methyl blue or double staining with eosine and methyl blue.

Before submitting a preparation of blood to the colouring reagents, it is useful, in order to retain the blood-corpuscles in their shape better than they were simply by heat, to use (following the advice of Roux) a mixture in equal parts of alcohol and ether; a few drops of this mixture is poured on the glass and allowed to dry.

In order to obtain a staining with methyl blue, a few drops of concentrated aqueous solution of methyl blue is poured on the glass covered with dry blood; after thirty seconds it is washed with distilled water and the preparation dried, and also mounted dry.

The preparations mounted dry are surrounded with paraffin and wax, so as to prevent the dampness of the atmosphere affecting them; they may thus be preserved a long time.

The parasitic elements (spherical bodies free or adherent to red blood-corpuscles, the crescent-shaped bodies, the oval bodies and segmented bodies) take, in these preparations, a blue tint much paler than that of the nuclei of leucocytes; the blood-corpuscles preserve their normal colour (fig. B, Pl. II).

The double coloration of blood by eosine and methyl blue by the process of Metschnikoff gives very good results for the study of the hæmatozoa of paludism, and for that of the hæmatozoa of those animals which approach the parasites of paludism.

The blood is dried and the globules fixed as has been described above; the cover-glass on which the blood has been dried is put in an aqueous concentrated solution of eosine for thirty seconds, then washed with distilled water and dried; the cover-glass is afterwards placed in the concentrated solution with methyl blue for about thirty seconds, washed again with distilled water, and dried. It is mounted dry or in Canada balsam, after ascertaining that the double staining is satisfactory.

In the blood of birds, and of batrachians or reptiles, the nuclei of the blood-corpuscles are deeply stained blue; the hæmatozoa assume a tint of much paler blue than that of the nuclei of the leucocytes and of the blood-corpuscles, sometimes a faint violet, due to the mixture of the tints of eosine and methyl blue.

The blood-corpuscles altered by the presence of the hæmatozoa are coloured less deeply by eosine than the healthy blood-corpuscles.

Figs. A and B on Pl. III show the appearance of palustral blood and birds' blood containing hæmatozoa on preparations submitted to the double staining with eosine and methyl blue. I have not yet succeeded in staining flagella; some flagella may

at times be so differentiated in preparations of blood, but this is very rare.

In studying palustral blood, and specially in the study of the blood which has been dried and submitted to the action of different reagents, invariably some effects are produced; the accidental alterations must be taken into account, thereby avoiding the risk of confusing these alterations with those which are characteristic of the presence of hæmatozoa.

Ehrlich and Foa have observed that in certain cases the normal red blood-corpuscles, dried and submitted to the action of methyl blue, showed bluish tints or granulations stained by methyl blue.

Celli and Guarnieri, who point out this source of error ('Annali di Agricoltura,' 1889), have tried to stain fresh blood on its coming out of the capillaries with methyl blue dissolved in serum coming from serous effusion; the coloration of parasitic elements takes place slowly, the preparation must be left for an hour or even three hours in the damp chamber.

According to Celli and Guarnieri, the amœboid bodies stained in this way show a clear central space in which one or two corpuscles more highly stained are found; the peripheral part is stained rather quickly.

In this process, as in the process by drying, sources of error exist; the long stay in the coloured serum and the wet chamber may easily give place to alterations in the normal or parasitic elements.

A good method of staining, says Soulié, consists in collecting the blood to be examined on a piece of glass which bears a drop of an alcoholic solution of evaporated methyl blue; the colouring matter is slowly dissolved in the serum, the white corpuscles and other elements are stained without alteration ('Bull. méd. de l'Algérie,' 1890, p. 230). Care must be taken to use a sufficiently dilute solution, without which the methyl blue cannot be dissolved in the serum. Feletti has recommended a method of staining similar, if not identical (Congress of the Italian Society of Medicine, 1890).

Attempts at cultivation.—When pure blood is taken from a palustral patient and the presence of hæmatozoa ascertained, some drops should be put in broth, in gelatine, or jelly, or on potato, and it will be noticed that after a few days the broth is limpid, and no colony has been raised in the solid substances, even if these substances have been kept in an incubator at a temperature of 37° to 40° C.

In water and sterilised earth the results of the sowing are not absolutely negative.

As the ordinary media did not succeed for the cultivation of paludism, it might have been expected that these parasites could be cultivated in the blood.

The attempts I have made in this direction have, up to the present, given only negative results. One of these attempts at cultivating hæmatozoa in pure blood kept at a temperature of 38° C. has been made by M. Roux in the laboratory of M. Pasteur—that is to say, under the best conditions.

A very simple way of trying this culture in the blood consists in taking a drop of palustral blood with precautions on a cover-glass which is placed over one of the excavated slides which are used for the study of microbes in suspended drops; the slides are first sterilised in the flame. A little vaseline placed between the cover-slip and the slide prevents drying; for further security the preparation between various examinations may be left in the damp chamber.

On examining a drop of blood which has been taken on a cover-glass care should be taken to spread it a little; the parasitic elements are visible at the places where the layer of blood is thinnest, and principally at the periphery.

I have thus been able to preserve, for ten days or longer, preparations of palustral blood in which I distinguished parasitic elements in the middle of the blood-corpuscles scarcely altered. Once it seemed to me that the pigmented amœboid bodies had increased in number; but that was, perhaps, only an illusion which might be explained by the fact that the blood-corpuscles, having become paler, allowed the parasitic elements to be seen more easily.

Since I have adopted this procedure I have unfortunately had but few opportunities of studying fresh palustral blood; there are, on this point, further researches necessary: it is possible that by carefully examining blood in the suspended drops, and keeping the preparation at a temperature of 38° C. with the hot stage, one may succeed in following the changes of the parasite, and in finding out more exactly than has been possible till now the relations existing between its different forms.

Attempts at inoculation in animals.—Many veterinary surgeons agree in denying the existence of paludism in animals (Verheyen, art. "Fièvres Interm." du 'Dictionn. de Médecine vétérinaire' de Bouley et Raynal).

Certain epizootic diseases have been attributed to paludism because they have been observed in marshy districts. This is evidently quite insufficient as a proof. Marshy districts favour the propagation of many diseases besides paludism.

The watery cachexia or rot, which often makes great havoc in herds which graze in marshy fields, has nothing to do with palustral cachexia; it is said that it results from the presence of distoma or flukes in the bile-ducts.

Obédénare has compared an epizoon fairly common in oxen in the Danubian provinces to paludism; this epizoon is characterised by fever and hæmaturia.

Babes has recently studied that disease under the name of *Hémoglobinurie épizootique du bétail* ('Arch. f. path. Anat. u. Physiol.,' 1889); according to him the disease is caused by a diplococcus which penetrates into the blood-corpuscles and destroys them: the diplococci are specially found in great numbers in the kidneys, which explains the frequency of the hæmaturia.

The presence of the pentastomata in the bowels (very common in oxen in Danubian provinces) would favour the diplococcus penetrating into the blood.

The diplococcus described by Babes is evidently a parasite very different from the hæmatozoa of paludism.

Smith has described alterations in the blood in the Texan fever of the ox, which is probably of a parasitic nature, but which appears to have nothing in common with the hæmatozoon of paludism (Pfeiffer, 'Les Protozoaires pathogènes,' p. 57).

When I was in Algeria I often asked veterinary surgeons to send me parts of the liver and spleen of animals suspected of paludism; I made a histological examination of those parts in a small number which were sent to me, and I never noticed the lesions of paludism.

The facts of experimental paludism quoted by Klebs and Tommasi Crudeli, and Ceci, and Schiavuzzi will not stand criticism.

In 1883, when at Constantine, I tried to induce palustral fever in a rabbit by injecting into its veins culture fluids prepared with palustral earth (according to the method of Klebs and Tommasi Crudeli, and Ceci). The injection of these liquids, or of those directly collected from pools of water in marshy localities, into tho veins easily produces an attack of fever in the rabbit, but the attack is not repeated; the animals recover very soon, and when killed, after a certain time, the alterations which are characteristic of paludism aro not observed.

I was not more fortunate in my attempts at inoculating paludism in rabbits when I used blood taken from palustral patients for intra-venous injections.

We shall see further (Chap. III.) that some observers have likened certain hæmatozoa of birds to the parasites of paludism. These certainly resemble them very much, but should not be mistaken for them ; this question will be more carefully discussed when the hæmatozoa of birds are studied.

The fact that up to the present the parasite of paludism has not been cultivated in natural or artificial media, nor inoculated into animals, has been quoted more than once by the authors who disputed the existence of the new parasite. The argument would have some value if the question were about a schizophyte ; but the hæmatozoon of paludism not belonging to that class, it is not surprising if they should behave otherwise than micrococci or bacilli. It is impossible to cultivate the filaria of human blood in artificial media, yet nobody attempts to dispute the parasitic nature of filariosa.

We now possess, thanks to the work of men like Pasteur and Koch, an excellent method for the study of schizophytes. Ought one to be surprised if this method does not apply to sporozoa ? Evidently not. These new parasites require new methods of observation and experimentation. The study of the hæmatozoa of animals is naturally the preface to the more difficult study of the hæmatozoa of paludism. It will be necessary to choose species which are readily available for experiment, and in which the hæmatozoa are easy to observe ; it will be particularly interesting to see how the hæmatozoa of birds, for instance, so akin to those of paludism, are reproduced and propagated.

CHAPTER II.

Researches subsequent to mine—The hæmatozoon of paludism has been discovered by a large number of observers—Remarkable agreement of the descriptions that have been given of it in all countries.

Investigations based on my researches on the parasites of paludism, which were very rare from 1881 to 1886, have become more and more numerous in subsequent years.

In mentioning the researches which confirm mine I shall not follow the chronological order exactly. Several observers have published papers on that question which correct or supplement one another, and cannot be examined separately. The annual bibliography which will be found at the end of this volume will enable the reader to see the chronological order of these works.

At the end of 1880 I communicated the first results of my researches to my colleague, Dr. E. Richard, fellow-professor at Val-de-Grâce, asking him to verify them. M. Richard soon wrote to me that he had succeeded in discovering the parasites which had been observed at Constantine, in the blood of palustral patients at Philippeville (Province of Constantine).

In an article in the 'Revue scientifique' of January 27th, 1883, Richard gives a good description of the different appearances under which the parasitic elements are found in the blood of palustral patients, and concludes thus :—"After a year of research we are now strongly convinced that M. Laveran is right, and that the real microbe of paludism has been discovered by him."

We saw (p. 5) that the name of Marchiafava was in 1880 among those of the observers who defended the so-called *Bacillus malariæ*. From that time Marchiafava has completely given up that opinion, and has published in collaboration with Celli several works on paludism, on the analysis of which we will dwell at some length. From 1884 to 1889 the opinions expressed by these authors have varied very much, and it is essential to know the history of their variations in order to appreciate the value of certain claims made by Marchiafava or in his name.

In 1884 Marchiafava and Celli, in the treatise '*On the Alterations of the Red Blood-corpuscles in Malarial Infection and on the Cause of Melanæmia,*' assert that all the parasitic elements which I have just described as found in the blood of palustral patients must be considered as degenerated blood-corpuscles. Marchiafava and Celli deny absolutely that the new elements which I had the opportunity of showing them in Rome in 1882 are of a parasitic nature; they wish to explain the flagella themselves by a degeneration of the red blood-corpuscles.

Marchiafava and Celli are now inclined to believe that the cause of paludism is a micrococcus.

In a letter dated Rome, April 9th, 1884, M. Marchiafava, in thanking me for sending him my 'Traité des fièvres palustres' and forwarding me the above-mentioned treatise, is very careful to draw my attention to the fact that he and his colleague have arrived at conclusions very different from mine.

"In our view," writes Marchiafava to me, "the only elements that may be suspected of being parasites *are corpuscles deprived of pigment analogous to micrococci,* which are often found in large numbers in red blood-corpuscles, and are only visible in preparations of blood dried and stained with methyl blue. We believe that the pigmented forms which you have described are nothing but degenerated and pigmented red corpuscles."

At the Congress of Copenhagen in 1884, Marchiafava and Celli together with Tommasi Crudeli still urged that the elements I have described as the parasites of paludism only represented retrograde changes of red blood-corpuscles.

Thus there can be no doubt of this point: after the publication of the 'Traité des fièvres palustres,' four years after the publication of my first works on this question, Marchiafava and Celli refused to admit the parasitic nature of the elements which I had described in the blood of palustral patients, that of the spherical bodies as well as of the crescent-shaped bodies and flagella, and they considered then that the parasite of paludism was a micrococcus.

In 1885 Marchiafava and Celli in a second treatise, under the title of 'New Researches on Malarial Infection' ('Annales italiennes de l'Agriculture,' Rome, 1885), agree that parasitic elements may be found in palustral blood which affect the form I had previously described—pigmented bodies free or adherent to the blood-corpuscles, crescent-shaped bodies, and flagella endowed with movements extremely characteristic; they still insist on the small unpigmented elements, described in their previous publication, being a species of micrococci, but they confess that, contrary

to what they had first asserted, many of these elements are visible in fresh blood and contain granules of pigment; out of forty-seven parasitic elements represented, forty are pigmented.

It is sufficient to cast one's eyes on the figures given below (Fig. 5) from that treatise of 1885 to ascertain that the parasitic elements described by these authors are really those whose presence I had shown in palustral blood several years before; it is easy to recognise the spherical bodies adherent to the blood-corpuscles (included in blood-corpuscles, say Marchiafava and Celli), the elements with flagella, and the crescent-shaped bodies.

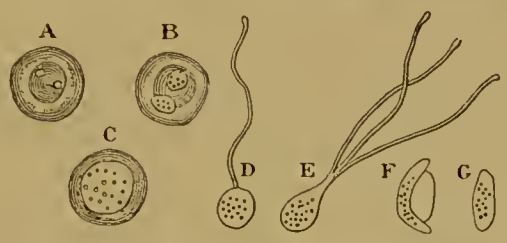


FIG. 5.—A, B, C. Blood-corpuscles containing plasmodia. D, E. Hyaline bodies, pigmented, with flagella. F. Crescent-shaped body. G. Oval-shaped body. (Figures taken from the treatise of Marchiafava and Celli.)

In 1886 a new treatise by the same authors was published in the same contributions as the previous one. They insist very strongly on the description of the elements endowed with amœboid movements and deprived of pigment, to which they propose to give the name of *plasmodia*, or *malarial hæmoplasmodia*. This name of plasmodia applied for the first time to parasitic elements of palustral blood may have induced some persons to believe that Marchiafava and Celli have found new parasites; in reality these authors have merely described under this new name (the unsuitability of which has been shown)[1] some elements which I showed as far back as 1880 and 1882. In order to prove their claims Marchiafava and Celli insisted on these two considerations,—that the plasmodia were non-pigmented elements, and were endowed with amœboid movements. I had said before them (see p. 18) that the elements described in my first publication under the name of bodies No. 2, and which correspond to plasmodia, were endowed with amœboid movements, and that the smallest of these elements did not contain any pigment. Marchiafava and Celli besides, in order to prove their case, have much

[1] Naturalists mean by the name of plasmodia a collection of similar entities which frequently may be observed in one of the phases of the development of the Protozoa; the hæmatozoa of paludism are not found in the state of plasmodia, so the generic name cannot apply to them.

exaggerated the frequency of the non-pigmentation of these elements; it is exceptional to find non-pigmented amœboid elements of the same size as some of those represented in the above-mentioned treatise.

In 1887, in a communication on malarial infection made to the Royal Academy of Rome, Marchiafava and Celli again assert that the elements endowed with amœboid movements and deprived of pigment (plasmodia) are the real parasites of paludism, whilst admitting that the pigmented elements are also parasitic; and it is not a question, as they have previously maintained, of a degeneration of red blood-corpuscles.

In 1888, in the 'Archives italiennes de biologie,' the same observers once more try to show that plasmodia are the real parasites of paludism, and that the plasmodia are very different from the parasites I have described.

In 1889 Celli and Guarnieri published, in the 'Annales italiennes de l'agriculture,' a work which is evidently a sequel to the preceding treatises although it does not bear the signature of Marchiafava.

This work shows a new evolution in the opinions of Celli; the authors classify as follows the parasitic elements of palustral blood: 1st, amœboid bodies; 2nd, sickle-shaped bodies, which they say give origin to flagella.

We have seen that in their treatises of 1886 and 1887 Marchiafava and Celli described, as being the parasites of paludism, small amœboid elements, non-pigmented (plasmodia), which, according to them, had nothing in common with my parasites; these authors had, till then, refused to admit that the plasmodia were, as I have always held, nothing but the first degree of development of the pigmented spherical bodies. Now Celli and Guarnieri accept this combination as demonstrated, the pigmented spherical bodies are put into the class of amœboid bodies with the small elements deprived of pigment; in the plate set apart to amœboid bodies, the elements are represented as being pigmented 27 times out of 30.

Celli and Guarnieri admit that some vacuoles, artificially made on dried red blood-corpuscles, have been more than once mistaken for the micrococci which Marchiafava and Celli suspected, in 1884, to be the agents of paludism; they admit, lastly, that the amœboid bodies, either pigmented or not, either free or adherent to red blood-corpuscles, the crescent-shaped bodies, and the flagella only represent different phases of the same parasites, probably a sporozoon.

There was only one admission remaining for Celli and Guarnieri to make, namely, that Marchiafava had been quite wrong in disputing so long the facts which I had advanced, and that the claims of that observer concerning plasmodia had no longer any foundation.

In spite of logic and truth Celli and Guarnieri again tried to maintain these claims. They are willing to admit that I was the first to discover the crescent-shaped bodies and the flagella, but if we are to believe them the largest share in the discovery of amœboid bodies was due to Marchiafava, seeing that I had only described (so they say) those that are free and motionless. Being unable to deny that I have spoken of amœboid movements, Celli and Guarnieri affect to believe that I mentioned them in connection with the crescent-shaped bodies, which is utterly wrong. I always said that the crescent-shaped bodies were motionless, and I only spoke of amœboid movements in connection with elements indicated in my first publications under the name of bodies No. 2, and which are no other than the amœboid elements of Celli and Guarnieri.

It may have been noticed (p. 19) that I have described as far back as 1882, not only free amœboid bodies, but also those among these elements which adhere to red blood-corpuscles; the latter elements are principally described and figured in a treatise printed in 1882 and presented to the Medical Society of Hospitals; it is sufficient to look at the plate published in that work to be convinced of the inaccuracy of the assertion of Celli and Guarnieri. Far from ignoring the importance of the elements which Celli and Guarnieri call amœboid bodies, I have always said that these were the forms oftenest found in palustral blood; it will be seen in my 'Traité des fièvres palustres' that I have observed these elements 389 times out of 432 cases.

Celli and Guarnieri say that they have seen crescent-shaped bodies being transformed into oval elements, afterwards into spherical elements, which gave out flagella. I have often tried to follow the changes of the crescent-shaped bodies; I have seen these elements take, after a variable time, an oval or rounded form; but I never saw flagella escaping from a body which, at the beginning of the observation, presented the form of a crescent.

Without disputing the fact pointed out by Celli and Guarnieri, I think that these authors were much too hasty in generalising and coming to the conclusion that the flagella were always derived from crescent-shaped bodies. I have often observed

flagella in blood which did not contain any crescent-shaped bodies, and I have seen the flagella escaping from bodies endowed with very apparent amœboid movements, belonging, no doubt, to the first class of the elements described by Celli and Guarnieri.

In a treatise on summer and autumn fevers, published in 1889, Celli and Marchiafava have admitted the importance of the crescent-shaped bodies, which they had till then disputed; according to them these bodies were only very seldom met with in palustral blood—once in 200 cases, according to a note in one of their works. Now these authors maintain that the crescent-shaped bodies are often found in the blood of patients suffering from autumnal fevers. Pietro Canalis had already pointed out this fact, which agrees with what I have said about the frequency of these elements in cachectics from paludism, or, at least, in patients who had had several relapses of fever.

In their last work on winter fevers (Rome, 1890) Celli and Marchiafava, discussing the question whether the parasitic elements of palustral blood belonged to one or to several species, conclude by saying that they adhere to the belief in the existence of a polymorphic parasite; "an hypothesis and supposition," they say, "which has always been upheld by us." This word *always* will undoubtedly appear strange to the reader who has just read the abstract of the works of MM. Celli and Marchiafava; I leave him to form his own opinion about it.

If we recapitulate the history of the works of Marchiafava and Celli we see that in 1884 these authors did not concede the parasitic nature of the elements described by me, and that they incline to believe that the cause of paludism was a kind of micrococcus.

From 1885 to 1888 Marchiafava and Celli tried to prove that the elements described by them in 1886, although under the name of plasmodia, are the real parasites of paludism, and that these plasmodia are very different from my parasites. At least in 1890 Celli, Marchiafava, and Guarnieri admit the existence of all the parasitic elements described by me, and to them as to me these elements only represent the different states of the same parasite, which is that of paludism.

One conclusion I think is that Marchiafava and Celli have simply been brought to verify, in 1890, the facts which I mentioned from 1880 to 1882.

Sternberg published in 1886 ('The Medical Record,' New York, 1886) a paper on the parasite of paludism, the conclusions of

which support those which we have just expressed in connection with the works of Marchiafava and Celli.

In 1881 Sternberg had undertaken some researches at New Orleans to prove those of Klebs and Tommasi Crudeli; he has remained in doubt as to the *rôle* of the *Bacillus malariæ* of these observers; in 1884 Sternberg had not, he says, much confidence in the new parasite which I had just described. In the meantime he went to Rome, saw the parasitic bodies whose existence I had demonstrated in the laboratory of Marchiafava, and he returned to America convinced that these new parasites were really those of paludism; he was not long in finding them himself in the blood of palustral patients in America. Sternberg has no doubt that the plasmodia are the same elements as those described by me in my first works under the name of bodies No. 2.

Golgi has published several treatises on the parasites of paludism, and he has studied particularly the segmented forms.

In a work published in 1886 ('Archives italiennes des sciences médicales') he gives the first results of his researches, which were carried on at Pavia, principally on patients suffering from quartan fever. Golgi asserts that he has found in the blood of nearly all his patients the hyaline corpuscles endowed with amœboid movements which are described in my first works under the name of bodies No. 2, and he admits that the plasmodia of Marchiafava and Celli only represent the first stage in the development of these elements. The figures given in that treatise do not leave any doubt about the identity of the elements observed at Pavia and those described by me; the hyaline bodies possessed of amœboid movements and the crescent-shaped or oval bodies are exactly represented.

Golgi emphasises the rose-shaped form. The parasitic element undergoes segmentation regularly, while the pigmented granules collect towards the central part; these segments detach themselves, assume the appearance of rounded corpuscles, and becoming free, are changed into amœboid spherical bodies. The rose-shaped bodies consequently would represent one of the methods of the multiplication of parasitic elements.

Golgi has seen in most of the patients a direct relation between the number of the parasites and the intensity of the fever.

Blood taken from the spleen in the different stages of the attacks of fever has enabled him to ascertain that the number of parasites was much larger in the splenic blood than in the peripheral blood.

In a paper which appeared in the 'Archives italiennes des

sciences médicales' in 1889 under the title of "The Development of the Parasites of Paludism in Tertian Fever" and in a more recent work published in the 'Archives italiennes de biologie,' t. xiv, fasc. 1, 2, Golgi showed the differences which, according to him, exist between the parasites of tertian fever and those of quartan fever. These differences could be summed up much as follows: the parasite of tertian fever accomplishes its evolution in two days, that of quartan fever in three days.

The amœboid bodies of tertian fever have much quicker movements than those of quartan fever.

The parasites of tertian fever cause the decoloration of the red blood-corpuscles, which they attack easily and rapidly, whilst in quartan fever the red blood-corpuscles invaded by the parasites keep their characteristic coloration until their destruction is almost completed.

In quartan fever the corpuscles of the affected blood have a great tendency to lessen, whilst in tertian fever the affected corpuscles have often a larger diameter than healthy ones.

In tertian fever the protoplasm of the parasites is very transparent, the contours are very slightly differentiated; in quartan fever the protoplasm appears less delicate, the contours of the parasites being more apparent.

In quartan fever the pigment presents itself under the shape of granules or bundles, larger than in the tertian; the colour of the pigment may also be a little different.

Lastly, and that is what constitutes the principal difference, the segmentation of the rose-shaped elements is not made in the same way in the tertian as in the quartan. In the tertian the number of rounded corpuscles which come from the segmentation of pigmented elements is larger than in the quartan. Fig. 6, taken from Golgi, shows this difference well; the number of segments would be about twice as large in the tertian as in the quartan.

In the quotidian fever, now the parasite of the tertian, now that of the quartan is found; which Golgi explains by admitting that the quotidian does not represent a particular type, but only a complicated form of the tertian or the quartan, double tertian or triple quartan. This hypothesis can only be admitted with difficulty by clinical observers, especially by those who have practised in hot countries, where the quotidian is much the most common of the intermittent fevers.

According to Golgi the crescent-shaped bodies are met with in the fevers of an irregular type; for my part I have very often met with them in regular intermittent fever.

Golgi succeeded in finding flagella, and he observed that these elements only showed themselves in the blood at the time of the febrile attacks and for a few hours before those attacks.

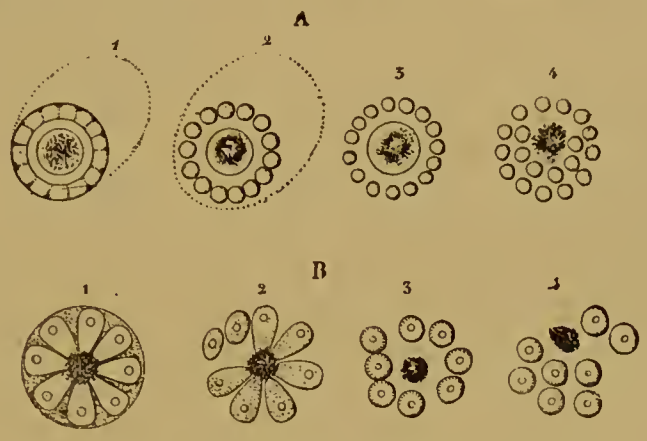


FIG. 6.—A. 1, 2, 3, 4. Segmentation of a pigmented element in tertian fever. The outline of a blood-corpuscle may still be seen in figures 1 and 2. In figure 4 the separation of the corpuscles resulting from segmentation is complete. B. 1, 2, 3, 4. Segmentation of a pigmented element in a case of quartan fever. In figure 4 the separation of corpuscles resulting from segmentation is complete.

We shall see later on that a certain number of Italian observers, following Golgi, have admitted the existence of several species of parasites of paludism.

It is to be noticed that several authors who defend the theory of Golgi are much more confident than himself; Golgi, whilst admitting several varieties of parasites, has never, to my knowledge, asserted that these parasites belong to absolutely different species, without relation to each other. It even appears, from the following paragraph in the last work by Golgi ('Archives italiennes de biologie,' 1890), that he admits the possibility of the passage of the parasite from one form to another.

In 1884 Councilman and Abbot had expressed doubts concerning the parasitic nature of the elements described by me; their investigations had been made on the cadavera, *i. e.* in very bad conditions so far as the examination of parasites is concerned, they being rapidly defaced after death.

However, in 1887, in a communication to the Pathological Society of Philadelphia, Councilman announced that he had succeeded in finding hæmatozoa in all the palustral patients whom he had had the opportunity of examining ('Fortschritte der Medicin,' 1888, No. 12, pls. v and vi).

In a first series of examinations of blood obtained by pricking the finger, Councilman established the existence of flagella 11 times out of 80.

In a second series the examination was made on blood extracted directly from the spleen, and the flagella were found 16 times out of 21 patients. This is a very remarkable result, which shows that the rarity of flagella in the peripheral blood should not be made a pretext for disputing the importance of these elements.

According to Councilman, the crescent-shaped bodies and the oval bodies which spring from them are only to be found in patients suffering from palustral cachexia; the segmented forms being found in the shivering stage of the attacks of intermittent fever.

Lastly, Councilman found that the action of quinine, very decided on the amœboid elements and the flagella, is much less marked on the crescent-shaped bodies, thus agreeing with my own observations ('Traité des fièvres palustres,' p. 201).

The works of W. Osler, like those of Sternberg and Councilman, are confirmatory of mine. Like them, Osler at first accepts my descriptions of the parasites of paludism with much scepticism, in particular that of flagella; the existence of such elements in the blood seems to him unlikely. However, he undertook control researches, and was not long in being convinced of the truth of my descriptions (communic. to the Pathol. Society of Philadelphia, 'The British Medical Journal,' 1887).

In 70 patients suffering from different forms of paludism Osler succeeded in finding the hæmatozoa 63 times; the negative observations are, moreover, explained by the fact that the patients had been submitted to treatment by quinine.

In the acute forms of paludism Osler principally met the small hyaline elements, possessing amœboid movements and often pigmented, described in my first works by the name of bodies No. 2. The crescent-shaped bodies were found almost always in persons suffering from palustral cachexia, or at least from recurring intermittent fever. The flagella were noticed in seven cases (six chronic and one acute); the segmented or rose-shaped figures in six cases.

The accompanying figures (Fig. 7), taken from Osler's work, leave no doubt about the identity of the parasitic elements observed by him and myself. Concerning the relation of the parasites to attacks of fever Osler has come to the same conclusions as I did; it is before and during the beginning of the attack

that the parasitic elements are found in the blood, though this rule has exceptions.

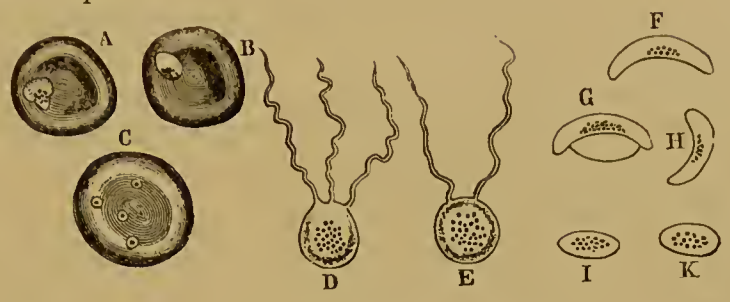


FIG. 7.—Some aspects of parasitic elements of palustral blood, from the work of W. Osler.

A, B, C. Blood-corpuscles to which pigmented spherical bodies of small size adhere. D, E. Pigmented spherical bodies with flagella. F, G, H. Crescent-shaped bodies. I, K. Oval bodies.

Quinine causes the parasitic elements to disappear more rapidly in acute than in chronic forms.

In a second communication to the Pathological Society of Philadelphia, in 1887, Osler confirms his first conclusions, and calls attention to the remarkable similarity which exists between the descriptions of authors who have studied the hæmatozoa of paludism in different parts of the world.

Osler has noted the existence of the flagella less frequently than Councilman, but he has not examined the blood from the spleen taken directly by puncture as was done by Councilman. Osler noticed that the amœboid bodies which adhere to the red blood-corpuscles can be detached and become free in the blood; this is one of the arguments on which I relied in maintaining that these parasites are only attached to the red blood-corpuscles, that they have a depression, more or less, at the point of adherence, and are not an integral portion of the red blood-corpuscles, as some authors maintain.

Maurel, who has made many investigations of the micro-organisms of the air, of the water and the soil of marshy countries, at first doubted the existence of my hæmatozoon, which he had not succeeded in finding. At the end of his 'Microscopical Researches upon the Etiology of Paludism' (Paris, 1887) he declares that he is now convinced of its existence.

In a paper read before the New York Society of Pathology, in 1888, James is said to have discovered the existence of the hæmatozoa in 34 out of 35 examinations of patients suffering from palustral fever.

James made experiments in vain for parasitic elements

analogous to those of palustral patients in the blood of a great number of patients not infected with paludism; therefore he insists upon the importance of searching for hæmatozoa from a diagnostic point of view.

He always met crescent-shaped bodies in the chronic forms of paludism, and the segmented bodies during the febrile paroxysm, and gives the following propositions as proved.

1st. Parasitic elements, which have been described as hæmatozoa of paludism, are uniformly found in the blood of palustral patients.

2nd. The crescent-shaped bodies are only met in the chronic forms of paludism.

3rd. The segmented forms are observed only before and during the paroxysms.

4th. Under the action of large doses of quinine the parasitic elements disappear rapidly from the blood, with the exception of the crescent-shaped bodies.

We therefore see that Councilman, Osler, and James agree in attributing the crescent-shaped bodies specially to the palustral cachexia. As a general rule this agrees with my own observation, but I think that James, in particular, has formulated his view too absolutely.

Vandyke Carter discovered the existence of hæmatozoa in the blood of a great many palustral patients in India. I regret not having succeeded in procuring his original work.

Evans, surgeon to the Hospital at Mandalay, found the small hyaline elements, generally pigmented, in the blood of palustral patients; these bodies live either in a free state or in a state of parasitism on the red corpuscles (communic. to the Clinical Society of London, 1888).

Soulié succeeded in showing the presence of parasites in the blood of palustral patients at Algiers, notably the bodies provided with flagella. Concerning these elements Soulié writes as follows:

"It is impossible, when you have once seen them distinctly, not to be convinced of their existence and of their animated and parasitic nature. It is a curious sight to watch those long arms moving with such vigour round the sphere which supports them, capable of drawing in all directions and giving all manner of forms to one or more blood-corpuscles, situated in their neighbourhood. Sometimes one of the flagella detaches itself, and continues its march in the shape of a corkscrew in the serum, turning aside the blood-corpuscles which it meets in its

passage; it assumes the shape of a spirillum or of a spirocheta. After a few hours the movements grow slower, and finish by stopping at a temperature of 15° to 20° C. Like the crescent-shaped corpuscles, they do not stain well with aniline colours" ('Comptes rendus de la Société de Biologie,' 1888, p. 168).

Soulié adds, it is true, that the examination of the blood has often been negative.

It is difficult to understand the meaning of these words *negative examination* in relation to the study of the parasites of paludism.

The result of the examination depends to a large extent on the method of making the investigations, and on the time given to them. It has very often happened that I found parasitic elements, sometimes in great numbers, in preparations of blood the examination of which had been pronounced negative.

The hæmatozoa are easily concealed in the middle of red blood-corpuscles, especially at the beginning of the examination of the preparations, when the red blood-corpuscles are piled together; it is therefore necessary that the examination should be extended, and also resumed several times.

Special stress should be laid on the state of the patient and the treatment he has undergone. We have seen that it is a little before and at the beginning of the attacks that there were more chances of finding the parasites of paludism in peripheral blood.

In a new work ('Bulletin méd. de l'Algérie,' April 1st, 1890) Soulié says that in thirty patients suffering from paludism whom he examined during the months of October and November, 1889, the hæmatozoa were found fourteen times; and he adds that many patients were only examined once after being treated with quinine, which explains the rather larger number of cases in which the examination of the blood proved negative.

In Russia, Metschnikoff, Sacharoff, and Bartoschewitsch have succeeded in discovering the hæmatozoon of paludism: moreover Danilewsky and Metschnikoff have shown the existence of a similar parasite in the blood of various animals, and specially of some birds; this question will be referred to in the next chapter.

Sacharoff found the hæmatozoon in almost all the patients he had examined. He describes the five following forms (communic. à la Société de Médecine de Tiflis):

1st. Rounded or irregular-shaped corpuscles, with contours not well defined, possessing amœboid movements, enclosed in red

blood-corpuscles; the outline of these elements may be brought out by a concentrated solution of methyl blue.

2nd. The same elements containing (principally in pernicious attacks) numerous granules of pigment; the methyl blue stains these bodies entirely.

3rd. The same corpuscles, free in the blood and pigmented, showing sometimes the rose-shaped segmentation; the corpuscles resulting from the segmentation may enter the red blood-corpuscles and give rise to the forms No. 1.

4th. Crescent or oval forms, pigmented; Sacharoff also remarks that this form is particularly frequent in palustral cachexia, and that it resists quinine treatment more than the others.

5th. Hæmatozoa with flagella endowed with rapid movements.

In 1889 Sacharoff published a pamphlet in Russian with the title 'Paludism in the Transcaucasian Railway,' which is interesting principally on account of the micro-photographs appended to the text. Several of these photographs give these crescent-shaped bodies perfectly, and even the spherical bodies adherent to red blood-corpuscles.

The treatise of Khenzinsky entitled 'Contribution to the Study of the Micro-organisms of Paludism' (Odessa, 1889) deserves mention here; a plate representing different aspects of the hæmatozoa of paludism is added to this work.

Enrique Morado and Tomas Coronado found the hæmatozoon of paludism with its different forms at Havana, both the crescent-shaped bodies and the spherical bodies and flagella ('Cronica medico-quirurgica de la Habana,' October, 1889).

In a work published in 1890 in the same journal Coronado first describes the alterations which take place in normal blood after its coming out of the vessels, alterations which he says are very important to Havana on account of the high temperature of the atmosphere; and he shows conclusively that these alterations must not be confused with those which are produced by the presence of hæmatozoa. He afterwards describes the hæmatozoa of paludism.

In seventy-one patients suffering from palustral fever whom he examined, the spherical bodies were met thirty-six times, the crescent-shaped bodies twenty-nine times, the flagella eleven times; the last were always associated with spherical bodies.

Coronado shows mobile corpuscles free in the serum, which would be embryonic forms of the hæmatozoa. The parasitic nature of these corpuscles does not seem well proved. Mobile corpuscles similar to those described by Coronado are often seen in the

blood of patients suffering from affections other than paludism, and even in that of healthy people (see Chap. III).

Coronado concludes from his investigations that several kinds of hæmatozoa do not exist causing the different clinical varieties of paludism, but one simple polymorphic hæmatozoon.

The hæmatozoon of paludism has also been found in Mauritius by Elie Anderson, and at Hong-Kong by J. M. Atkinson.

Pietro Canalis published several interesting works on the hæmatozoa of paludism, dating since 1889.

In sixty-three patients suffering from palustral fever, who were examined with great care and often at very short intervals in the military hospital at Rome, the hæmatozoa of paludism were discovered in every case, but were never seen in the blood of patients suffering from affections other than paludism.

P. Canalis admits with Golgi that the parasites of paludism present a different evolution in the tertian and quartan fevers; he also tries to show that there exists a third variety, to which he gives the name of *half-moon-shaped bodies,* which is the most characteristic form of the evolution of these parasites. This last variety is met with in lengthened attacks of quotidian fevers or subintrants, being able in the continued forms to rapidly produce cachexia in certain pernicious fevers and in the irregular fevers.

According to Canalis, the cycle of development of this third variety may be divided into four phases: the amœboid bodies, half-moon or oval bodies, rounded bodies and flagella, and segmented bodies. The semi-lunar bodies are developed in the red blood-corpuscles at the expense of the amœboid bodies; they transform themselves into oval bodies, then into spherical bodies from which flagella emerge. The semi-lunar forms usually only appear in the blood after repeated attacks from the fifteenth to the thirtieth day after a first attack. Canalis found these elements only once in the blood on the seventh day of the disease.

Among these phases of evolution there is only one characteristic body—the crescent-shaped body. Canalis confesses that in the first phase (amœboid bodies) the third variety which he wishes to be admitted is not to be distinguished from the other two; the flagella also are not peculiar to this variety; lastly, the author, who admits that the crescent-shaped bodies, after being transformed into spherical bodies, may undergo segmentation or sporulation, does not say how the segmentation differs from that which is observed in tertian and quartan fevers.

It should be noticed that Canalis has not seen this segmenta-

tion take place in the course of a microscopic observation, and it is by induction that he has been led to admit it.

The crescent-shaped bodies remain, which surely are very characteristic. Are these bodies always found in certain clinical forms of paludism, exclusive of others? That is a question which we shall examine further on.

Feletti and Grassi ('Sur les parasites du paludisme,' Catane, 1889, and 'Riforma medica,' March, 1890) have succeeded in finding the hæmatozoa of paludism at Catania, and they do not hesitate to admit that the elements which I have described are really parasites—a fact all the more interesting because Professor Grassi was at first little favorable to this opinion. Feletti and Grassi said that, by modifying the methods of research hitherto used, they had noticed the existence of a nucleus inside the spherical bodies; the name of *amibules* is proposed by them to be given to the smallest of these bodies, and the name of *amibæ* to the others. The nucleus of the amœboid bodies is of great size, and most often eccentric; it resembles that which is found in many Rhizopods. A nucleolus is found in the nucleus. Feletti and Grassi do not describe the alteration of the method of observing which they have used.

The semi-lunar bodies would also seem to contain a nucleus with a nucleolus.

According to Feletti and Grassi, two species at least of hæmatozoa of paludism should be distinguished; the first giving birth to regular fevers, and the second to irregular ones. The parasites of the irregular forms are characterised by the crescent shape, as Golgi and Canalis had already mentioned. Feletti and Grassi noticed a very marked difference between the two species of parasites in all cases of fever studied at Catania since September, 1889, the crescent-shaped bodies never having been met by them in the tertian or quartan fevers.

Feletti and Grassi must have seen at Catania, as may be seen everywhere, fevers which change their type, and after having been continued or quotidian assume the quartan type; it should be admitted that in these cases, which are very frequent, the two varieties of parasites co-exist in the blood.

According to these authors, the flagella only represent one phase of the alteration of the hæmatozoon. They acknowledge, however, that flagella may be found in the blood of certain patients only a few minutes after the blood is taken from the vessels.

The researches of E. Antolisei and Angelini are, on most

points, confirmative of those of Golgi and Canalis ('Riforma medica,' January, 1890, and 'Archivio Italiano di Clinica Medica,' 1890).

The hæmatozoon of the quartan fever is, according to these observers, the one least characterised among the parasites of paludism, and the one whose evolutions are most regular and consequently easiest to study.

On the first day of the intermission, pigmented spherical bodies are found in the blood of patients suffering from quartan fever; on the second day these elements, having grown larger, are found in the blood-corpuscles or free in the plasma, but the free elements are rarer than in the tertian. On the day of the attack segmented forms appear in the blood six, eight, or ten hours before the beginning of an attack. During the febrile attack the examination of the blood reveals principally amœboid bodies without pigment, and segmented bodies become more and more scarce; Antolisei has not witnessed the change of the spores into amœboid bodies as a result of segmentation.

Sporulation would seem to be the determining cause of the attack of fever, which, according to Antolisei, is severe in proportion to the number of forms in process of segmentation.

In no case of quartan fever has Antolisei met any crescent-shaped bodies or flagella.

If there exist in the blood two generations of parasites, the one being one day older than the other, a double quartan fever is the result; three generations may produce a triple quartan, *i. e.* a fever with the symptoms of a quotidian; but it is rare, according to Antolisei, for the quotidian to be due to such transformation of the quartan.

In certain *sub*-continued fevers the same parasitic elements may be met as in the quartan.

The parasitic forms which are met in the blood of patients suffering from tertian fever are complex and much more difficult to understand, in the opinion of Antolisei, than those of the quartan fever. In many cases, writes this authority, elements have been found which were not expected, and which did not seem to have any relations with the febrile cycle in which the observation is made; in a certain number of cases of tertian fever it has been impossible to find segmented bodies in spite of frequent examination of the blood.

In the first few hours which follow an attack of tertian fever, amœboid bodies with or without pigment, and free or enclosed within the red corpuscles, may be generally observed. On the

day of the apyrexia the pigmented bodies appear more and more large and numerous, being found in largest numbers in the blood eight or ten hours before the attack. The flagella have often been discovered in the blood of patients suffering from tertian fever.

The number of spores is larger in the segmented bodies of the tertian than in those of the quartan fever, as has been shown by Golgi.

Antolisei admits that most quotidian fevers are produced by the hæmatozoa of the tertian type, but he does not consider that the observation of the facts will allow any opinion to be formulated as to the existence of two generations of parasites, which would come to maturity after an interval of twenty-four hours.

The principal characteristics of the hæmatozoa of irregular fevers seem to be the following:—At the beginning of the infection induced by this variety of parasites there are often only amœboid bodies to be found in the blood, at least in peripheral blood; after a variable time the crescent-shaped bodies appear; the appearance of these elements cannot always be waited for; on account of the severity of the fever, administration of quinine is necessary. The patients may have several recurrences of fever without the crescent-shaped bodies being observed; these, however, show themselves at last, and are characteristic of this variety of parasites (Antolisei and Angelini).

When only amœboid movements are observed in the blood, it is impossible to say whether it is a tertian, or quartan, or irregular fever.

The crescent-shaped bodies come from amœboid bodies; the sporulation is made as with the other varieties of rounded corpuscles (Canalis). From these spores the amœbæ proceed which in turn produce a new generation of parasites.

The amœbæ, at a certain point of their development, instead of following the evolution common to the other forms and reproducing themselves with the rounded form, assume the semi-lunar form. There is no direct observation which shows the passage of one amœba, with or without pigment, into the semi-lunar form, but there are many reasons for believing that this is their mode of development (Antolisei and Angelini).

The semi-lunar bodies take the oval form, then the rounded form, and from this rounded form flagella often proceed. Antolisei and Angelini have not seen the flagella in the act of liberating themselves.

The other processes which are observed in the semi-lunar forms are the following :

1st. The budding, which may take place on the crescent-shaped, oval, or rounded forms.

2nd. Disintegration (death) ; the protoplasm is broken up into irregular hyaline fragments with a simple contour.

3rd. The sporulation ; this takes place as in the quartan fever, the pigment accumulates in the centre ; soon the spherical body is segmented and gives rise to rounded corpuscles with a double outline, eight, ten, or twelve in number.

These bodies in process of sporulation are not very common in peripheral blood, the internal organs appear to be the seat they prefer.

When the blood of a patient suffering from irregular palustral fever only shows spherical bodies, it is certain that after a variable time, should the patient have a relapse, the crescent-shaped bodies will be found (Antolisei and Angelini).

Quinine causes the amœboid bodies to disappear from the blood, but not the crescent-shaped bodies, which persist for a variable time.

The flagella do not appear to represent a necessary phase of the crescent-shaped bodies, but only an accidental phase.

In another work ('Riforma medica,' April, 1890) Antolisei writes concerning the variety of the hæmatozoa characterised as crescent-shaped bodies, "The biology and morphology of this entity vary with the intensity of the infection it sets up, with the season in which the infection takes place, and with the individual conditions of the patients who suffer from it."

The differential characters attributed by Antolisei and Angelini to the three species of hæmatozoa recognised by them are, as we see, wanting in precision.

C. Terni and G. Giardina ('Rivista d' Igiene e Sanita Pubblica,' May 16th, 1890) have examined the blood of eighty-five patients in the military hospital at Rome during the months of October, November, and December, 1889. In most of the irregular fevers and of the palustral cachexias they found the crescent-shaped bodies, which confirms the theories of Golgi and Canalis.

Terni and Giardina have observed the flagella twenty-five times in eighty-five cases, and they found, as I did, that the flagella are more likely to be found in the blood of individuals in danger of an attack, and also that they are always associated with the spherical bodies.

A. Bignani has studied the distribution of the parasitic elements

in the different organs of patients who have died from pernicious attacks ('Accad. med. di Roma,' anno XVI, t. v, ser. 2) ; he has come to the following conclusions :—The parasites are always found in much larger numbers in the small arteries and the capillaries than in the vessels of average or large size. The adult forms of the parasites and the bodies in process of segmentation have a great tendency to accumulate in some capillary network, especially in that of the brain, the lungs, the spleen, the medulla of the bones, the liver, and the intestines; in some cases of pernicious fever with bilious symptoms, the capillary network of the intestines was richer in parasites than all other organs. The crescent-shaped and oval bodies are more abundant in the spleen and the medulla of the bones than anywhere else.

The parasites accumulate where the circulation is sluggish, as in the brain capillaries, and they cause, according to Bignani, the endothelial lesions which increase the difficulty of circulation still more. In the veins, the parasites (amœboid forms) are often adherent to the walls like leucocytes. The perniciousness, as Bignani rightly observes, always coincides with a very great abundance of parasites; but these parasites, although in very large numbers in the viscera, may be scarce enough in the blood taken from the finger.

The search for the parasites of paludism in cadavera is difficult because these parasites are rapidly deformed and are confused with melaniferous leucocytes ; this confusion has been made by all the authors who previously to me had studied the anatomic lesions of paludism. Bignani made his post-mortems only a few hours after death, which explains why he has been able to find the parasites with their characteristic appearance.

Bignani recommends the following plan for the study of the hæmatozoa in the tissues taken from the cadavera :

1st. As a means of fixing, absolute alcohol and solution of sublimate of 1 per cent., to which he adds 0·75 per cent. of chloride of sodium, and from 0·50 to 1 per cent. of acetic acid ; the preparations remain in this liquid from a quarter of an hour to a few hours, according to their size.

2nd. For the staining of these sections : the aqueous solution of safranin, the solution of methyl blue with one per 10,000 of potash, vesuvin in aqueous solution, Bismarck brown and Grübler's red magenta. These last two colouring substances are those which have given the best results.

The German authors at first received the *Bacillus malariæ* of

Klebs and Tommasi Crudeli with much favour, ignoring my hæmatozoon; but the recent works by Paltauf, Kahler, Plehn, Bamberger, and of Quincke corroborate mine.

Paltauf has found the hæmatozoon of paludism ten times out of ten, and Kahler five times out of five ('Société de Médecine de Vienne,' December 20th, 1889).

Bamberger has established the presence of these parasites in all palustral patients whom he has examined, and he has never found similar organisms in individuals suffering from diseases other than paludism ('Société de Médecine de Vienne,' May 2nd, 1890).

Plehn ('Société de Médecine de Berlin,' March 5th, 1890) has observed the hæmatozoa of paludism in the blood of several patients who had intermittent fever in Germany, and principally in the blood of workmen who had contracted the fever in the neighbourhood of Potsdam. Plehn, who has ascertained that these hæmatozoa were never met with except in paludism, and disappeared under quinine treatment, has no doubt that they are the pathogenic cause of paludism.

Quincke (Kiel, 1890) has had the opportunity of examining eight patients suffering from palustral fever; six of these patients had worked in digging the canal from the North Sea to the Baltic, the other two cases came from the Lower Elbe and Kiel. In one case only was the fever quotidian; in the other cases it had a tertian type. In the eight patients the examination of the blood showed the existence of the hæmatozoa of paludism.

Quincke had not observed the constant relations which, according to Golgi, would exist between the nature of the parasitic elements in the blood and the febrile type. He points out that pseudo-vacuolated alterations of the red blood-corpuscles, which have nothing in common with the parasites of paludism, are often observed in the blood of palustral patients, and are also seen in large numbers of diseases, and even in the blood of healthy persons.

The works of Plehn and Quincke are interesting, although they are founded on a small number of facts. It was useful to ascertain that intermittent fever, which was contracted in the neighbourhood of Potsdam or Kiel, was accompanied with the presence of the same parasites in the blood as the fevers of Algeria and the hot countries.

Pfeiffer has also observed the hæmatozoa of paludism ('Les Protozoaires pathogènes,' Jena, 1890).

As to the numerous works recapitulated above, all of them

(except for a few differences on secondary points) agree with my observations, only a small number can be set against them with different conclusions.

Only a single work confirmatory of the opinions expressed by Klebs and Tommasi Crudeli on the existence of a *Bacillus malariæ* has been published since 1882, that of Schiavuzzi.

On April 4th, 1886, Tommasi Crudeli announced to the Medical Academy of Rome that B. Schiavuzzi had succeeded in obtaining a pure culture of a bacillus collected in the air of the marshes in the neighbourhood of Pola in Istria, and that this bacillus was identical with the one which had been previously described by Klebs and himself.

A new communication was made on that subject to the Medical Academy of Rome at the sitting of December 5th, 1886; lastly, Prof. Ferdinand Cohn, who had followed the researches of Schiavuzzi at Pola, published the result, in 1886, in his paper ('Beiträge zur Biologie des Pflanzen,' 1888).

The bacillus isolated by Schiavuzzi is found in the earth of palustral districts under the shape of oval spores, mobile, refracting light strongly; in the body of animals inoculated, and in the cultivation fluids, it would appear to be developed in long filaments, first homogeneous, afterwards transversely segmented.

It is somewhat surprising to find in the treatise of Schiavuzzi, as the proof of his assertion that this bacillus is the agent of paludism, only four experiments on rabbits which had been inoculated with the cultivation fluid of the bacillus found there (Pola). Moreover these experiments do not prove much. The thermometric tracing from the rabbits inoculated by Schiavuzzi differ very little from those of healthy rabbits; the temperature of animals, and of rabbits in particular, undergoes variations of temperature at night, consequently the oscillations of some tenths of a degree cannot be considered as showing a diseased state. In one of these observations a well-marked rise, which also was not repeated, may be explained by local accidents, even the puncture of inoculation. As Golgi says, Schiavuzzi, Tommasi Crudeli, and Cohn must have had a very extraordinary imagination to see authentic examples of intermittent fever in the rabbits in these facts (Golgi, 'Intorno al Preteso *Bacillus malariæ* di Klebs, Tommasi Crudeli, e Schiavuzzi,' Torino, 1889).

The post-mortem changes found in the rabbits under experiment are not more characteristic than the thermometric tracings.

The treatise by Schiavuzzi, far from confirming the opinions

held by Klebs and Tommasi Crudeli, on the contrary shows the weakness of the foundation for the belief in the *Bacillus malariæ*.

Golgi has tried to verify the assertions of Schiavuzzi, and has made experiments on rabbits with cultures of the bacillus prepared by Schiavuzzi himself.

The conclusion arrived at from these experiments is that the injections of the bacillus of Schiavuzzi have never produced intermittent fever in rabbits; after inoculation an observer can scarcely notice the slight elevation of temperature, which is not repeated on the following days, and which has been also noticed after the inoculation of cultivated liquids of non-pathogenic organisms.

Golgi has carefully examined the blood of rabbits inoculated with the culture fluid of the bacillus of Schiavuzzi. That examination only showed him a few of those commonplace alterations of the red blood-corpuscles which take place even in normal blood after it comes out of the vessels; he has never met any elements similar to the parasitic elements of palustral patients.

Golgi comes to the conclusion that the bacillus of Klebs, Tommasi Crudeli, and Schiavuzzi has nothing to do with paludism.

Another Italian author, as far back as 1887, in a review of the parasites of paludism, recapitulated the history of the bacillus described by Klebs and Tommasi Crudeli as follows: "From the moment of its discovery, the *Bacillus malariæ* has been continually losing its ground to such an extent that to-day it is completely abandoned" (U. Arcangeli, 'Rivista Clinica,' No. 1, 1887).

The place of the *Bacillus malariæ* seems to be among the vaunted parasites of paludism which have no longer anything but historic interest.

In 1886 Von Sehlen published a work on the etiology of paludism, in which he announces that he has found micrococci about 1 μ in diameter in the blood of patients suffering from intermittent fever, who were examined during the cold stage. By cultivating the blood taken from these patients in gelatine he obtained colonies of micrococci, whilst other cultivations made with blood taken during the intermission did not produce anything. The earth of marshy localities seems to have yielded colonies of micrococci similar to those of palustral blood (Sehlen, "Ueber die Aetiologie der Malaria," 'Arch. de Virchow,' May, 1886, p. 319).

The attempts made by different observers to reproduce these experiments have only given negative results. Palustral blood does not contain any micrococci, that name would not describe the embryonic forms of the hæmatozoa of paludism; the smallest of these elements, it is true, resemble by their dimensions the micrococci described by Sehlen, and it might be supposed that he had noticed these embryo forms and mistaken them for micrococci were it not for the question of cultivation.

Up to the present time the attempts at the cultivation of the hæmatozoon of paludism have only given negative results. For my part I have made numerous attempts in that direction without the smallest success (Chap. I, p. 29), and other observers have not been more fortunate than I.

Schwalb ('Réunion des médecins allemands à Magdebourg,' September, 1884, and 'Virchow's Arch.,' September, 1886, p. 486), having succeeded in setting up lesions similar to those of palustral melanæmia in rabbits by giving repeated doses of sulphur or oxysulphide of carbon (COS) to these animals, has come to the conclusion that paludism is a poisoning by oxysulphide of carbon.

I mention this chemical theory of paludism for completeness' sake, but I consider it is useless to discuss it. Intermittent fever has not been observed, so far as I know, in workmen exposed to the vapours of sulphide of carbon, and the existence of oxysulphide of carbon in the countries in which paludism prevails has still to be demonstrated.

The hæmatozoon of paludism is difficult to observe, especially in our climate, and in subjects already under treatment, and also when its different appearances are unfamiliar; it is not surprising, therefore, that investigations undertaken under these conditions have been sometimes negative. A large number of observers, after having at first denied the existence of the hæmatozoon of paludism, have become convinced of the reality of this parasite after new researches.

I think I may conclude, from this review of works subsequent to mine, that the existence of the parasites described by me in palustral blood is well established. These parasites have been found in the most distant parts of the globe, and, as Osler has observed, there is a remarkable coincidence between the descriptions which have been given in Europe, Africa, Asia, and America.

How are these new parasites to be classified? Are they really the pathogenic cause of paludism? These questions will be examined in the following chapters.

CHAPTER III.

The hæmatozoon which I have discovered in palustral blood is a sporozoon—Similar hæmatozoa exist in different animals, and principally in birds.

The parasitic nature of the elements described in the first chapter is no longer disputed at the present day; however, I think it would be well to say a few words about the investigations of Mosso and Maragliano, which aimed at proving that altered blood-corpuscles might take the appearance of some of the parasitic elements of palustral blood.

Mosso injected the blood of a dog into the peritoneal cavity of a bird, and for three or four days after the injection he noticed some changes of the red blood-corpuscles, which he tried to compare to the changes in palustral blood.

Observers who undertook to confirm these researches have, after studying the parasites of the palustral blood, come to conclusions diametrically opposed to those of Mosso.

A. Cattaneo and Monti injected the blood of a dog eighteen times into the peritoneum of birds (fowls and pigeons), after Mosso's plan, and examined the contents of the peritoneum at different times varying between the first and fifteenth day after the operation.

In this experiment the blood injected is separated during the first few days into a liquid part and a coagulum; in proportion to the length of time since the injection, the liquid part grows less and the coagulum becomes firmer.

Red corpuscles (of bird and dog) more or less altered are found in the liquid part and in the coagulum; also normal or granular white corpuscles, globuliferous or pigmented cells similar to those which have been described by Bizzozero as found in the medulla of the bones, which seem to be derived from the peritoneal endothelium. These bodies of the changed blood must not be confused with the parasitic bodies of palustral blood.

Plates produced in Cattaneo and Monti's work show the

different appearances which the changed red and white corpuscles of Mosso's experiment take; it is sufficient to glance at these plates to be convinced that the hæmatozoa of paludism have nothing in common with these changes of the blood.

Marchiafava and Celli, who have repeated the experiment of Mosso, have arrived at the same conclusions as Cattaneo and Monti. This fact deserves the more notice, because at the beginning of their researches these authors declared that my parasites were nothing but the normal elements of the blood more or less changed.

Maragliano has studied the changes which are seen in human blood when subjected to drying, heat, and different reagents.

According to Maragliano, in a preparation of normal blood surrounded with paraffin, some changes of red blood-corpuscles may be found which have a close relation to some of the alterations described in palustral blood, specially the clear spaces, non-pigmented, on which Marchiafava and Celli have specially insisted. Some plates which accompany the treatise of Maragliano show the alterations of the red blood-corpuscles observed.

It appears evident, after examination of these figures, that Maragliano has observed neither the pigmented spherical elements nor the crescent-shaped bodies nor the flagella of the palustral blood; none of the bodies represented by him contain pigment, none show even vaguely the appearance of the flagella. The only doubtful point is that concerning the small clear spaces non-pigmented. It is certain that, under the influence of heat and drying, clear spaces are often made in the red blood-corpuscles, and it is possible for these to be confused with the blood-corpuscles to which some small hyaline spherical bodies, not yet pigmented, adhere.

This source of error can be avoided by examining fresh blood at the ordinary temperature, and in any case it should not be used as a proof in regard to the other parasitic elements of the palustral blood.

Cattaneo and Monti, who have repeated the investigations of Maragliano, conclude that the alterations described by him have no relation to those of palustral blood. Such is also the conclusion of Dr. Tomas Coronado of Havana, who has studied both the alterations just described and those of palustral blood, comparing them one with another.

For my part, I have often been in a favorable position to examine the blood under the conditions stated by Maragliano, and I have never seen any of the elements which I consider

characteristic of paludism when the blood was taken from a patient suffering from paludism.

In a recent discussion at the Congress of the Italian Society of Internal Medicine, Maragliano admitted the existence of the hæmatozoa of paludism, whilst maintaining that the plasmodia (*i. e.* the spherical bodies deprived of pigment) might be confused with the corpuscular changes ('Semaine médicale,' 1890, p. 394). Brought down to these limits, the criticism of Maragliano seems to me quite just.

The changes which heat produces on the red corpuscles of the blood must also be put out of the question. It is known that when a preparation of normal blood is heated to 57° C., distinct changes of the red blood-corpuscles may be seen taking place. Projections of little sarcoid balls, which are endowed with the Brownian movement, appear on their edges.

Talamon again called attention last year to these alterations of the red blood-corpuscles, and particularly to what he called the flagellar disfiguration ('Société Médicale des Hôpitaux,' February 26th, 1890, and 'Journal de la médecine moderne,' March 6th, 1890).

Talamon brings about these changes by placing the preparation of fresh blood 8 or 10 centimetres distant from a very hot coke fire, ten to twelve seconds being sufficient to produce the changes; the slide placed on the back of the hand at that instant gives a fairly severe sensation of burning.

This experimental process is bad for two reasons: first, if the preparation is heated too much all the blood-corpuscles are destroyed; secondly, the temperature at which the changes are produced cannot be ascertained. By using the hot stage it is easy to notice that a temperature of 56° to 57° C. at the minimum is necessary for the alterations in the red blood-corpuscles to take place. As soon as the temperature reaches that degree, little sarcoid balls are formed on the circumference of the red blood-corpuscules; these sarcoid balls are often transformed into prolongations of variable length, which are endowed with a movement more or less rapid but little varied: the sarcoid balls which leave the red blood-corpuscles are endowed with Brownian movement.

These facts have been very well studied by MM. Schultze and Ranvier. Talamon made his observations with a very strong power (objective 12 in the immersion of Verrick), therefore the phenomena have been described by him in much brighter colours than by Schultze and Ranvier; an enlarged representation of a

phenomenon which is common, or at least can be produced at will, is found in his description.

The differences which exist between the flagella of paludism, and the sarcoid projections of the normal blood-corpuscles submitted to the action of heat, are numerous.

1st. The flagella of the hæmatozoon of paludism may be observed at the ordinary temperature of the laboratory; I have often observed them at a temperature not even 15° C. The sarcoidal protrusions on the red blood-corpuscles are only developed when the blood is heated from 56° to 57° C.

2nd. The flagellæ of the hæmatozoa have never been seen except in patients suffering from paludism; they are always joined in the blood of these patients with other parasitic elements—the pigmented spherical bodies from which they appeared to spring; the flagella never spring from red blood-corpuscles, as is always the case with sarcoidal protrusions, whose formation is brought about by strongly heating the blood.

3rd. The flagella of paludism differ from the sarcoidal protrusions in their shape and dimensions, being always more uniform than those of the prolongations; also by the rapidity and variety of their movements. None of the observers who have watched the flagella move in all directions, roll up, then unroll, giving the most varied movements to the blood-corpuscles (which at times they appear to seek to penetrate), will admit that these movements may be mistaken for those of the sarcoidal protuberances produced by heat. The flagella sometimes move so quickly that they give a transitory movement to the spherical body to which they are attached. When they have become free they retain the same rapidity and the same variety of movements.

Hayem ("De la contractilité des globules rouges et des pseudo-parasites du sang dans l'anémie extrême," 'Soc. Méd. des Hôpitaux,' February 21st, 1890) has called attention to some alterations in the shape of the red blood-corpuscles which are found in pernicious anæmia; these alterations have been classified by him under the four following types:

1st Type.—Certain red corpuscles, sometimes of great size, which have the capacity of altering their shape on the spot (amœboid contractility).

2nd Type.—Certain red corpuscles which show prolongations in the shape of a finger of a glove, mobile or motionless; the movements of these projections are most often simple oscillations; sometimes a very sharp tentacular prolongation takes place.

3rd Type.—Oscillatory movement of the very small corpuscles which remain suspended in the plasma.

4th Type.—Bodies out of focus in the preparation (pseudo-parasites). Most generally these latter elements present the appearance of small knotty sticks, narrow and of a variable length.

"These pseudo-parasites possess a continuous oscillatory movement round their vertical axis, and in addition an inflexion movement following their facets. The result of this double movement and of their irregularity of contour is that each of them, considered individually, changes its shape constantly, a peculiarity which alone would be sufficient to distinguish these mobile bodies from the parasites with which they might be confounded.

"Such a body, which has at a given instant the appearance of a small stick, suddenly assumes that of a small rounded mass carrying a sort of flagellum. At other times the small stick, resembling a bacterium, takes a curve and assumes the shape of a V or of a small triangle. In other cases the element assumes the shape of a diplococcus.

"Whatever their form may be, all these small bodies move about rapidly in the preparation" ('Bulletin de la Soc. Méd. des Hôpitaux,' 1890, p. 119).

The different characteristics of the pseudo-parasites of the blood, and of the flagella of the palustral blood, are easy to trace; the flagella do not develop themselves on the sides of the blood-corpuscles like the pseudo-parasites of Hayem; they do not resemble those knotty prolongations of very unequal length which have the appearance of bacteria or of diplococci. Lastly, the very complicated movements of the flagella cannot be compared to those of these débris of red corpuscles, which, possessing the Brownian movement, are also carried about by the currents which always occur in the plasma of fresh blood—currents which are due to the differences of temperature and to the evaporation which takes place at the edges of the cover-slip.

The movements of the red corpuscles described by Hayem, with the exception of those of the first type, do not seem to be those of living bodies. They persist for a few days in preparations made aseptically, and may be excited at will by suddenly raising the temperature of the blood, which evidently alters the vitality of the blood-corpuscles (Browicz, 'Neuvième congrès de médecine interne,' Vienna, 1890).

A. Edington ("Report on the Morphology and Development of

tho Blood," in 'Brit. Med. Journ.', May 31st, 1890) has pointed out the existence of elements to which he gives the name of albocytes, which are found in normal blood. Thoy are colourless corpuscles, spherical, about the size of a third of the diameter of a red blood-corpuscle, which would seem to be formed in the interior of a special white corpuscle or matricyte. The albocytes, at first colourless, increase in size little by little, become loaded with hæmoglobin, then become biconcave, and thus reach the state of adult red corpuscles.

Talamon considers that the albocytes of Edington are no other than the hæmatoblasts of Hayem ('Médecine moderne,' 1890, p. 728).

At the Congress of Berlin, 1890, Kollmann, of Leipsic, again called attention to the pseudo-organisms of the normal human blood. When normal human blood gathered with antiseptic precautions is examined, a number of little bodies, says Kollmann, can be seen resembling micrococci or bacilli; these corpuscles, the largest of which measure 0·5 μ in diameter, are endowed with very quick movements. Examination by staining reagents shows that these are artificial products resulting from blood-corpuscles or leucocytes; the cultivations on gelatine are neutral.

These pseudo microbes of the blood have been mistaken, as Kollmann says, more than once for real micro-organisms.

The confusion of these elements, or blood-corpuscles having undergone alterations with the hæmatozoa, could only be possible in the first phase of the evolution of the parasites, *i. e.* at the time when they present themselves under the aspect of small non-pigmented elements making clear spots in the blood-corpuscles. We must confess that certain altered blood-corpuscles have, especially in dried blood, a great analogy with red blood-corpuscles invaded by hæmatozoa in the first stage of their development.

Celli and Guarnieri have admitted that the vacuoles artificially produced in dried blood-corpuscles have been more than once described as parasitic bodies; the confusion is all the more easily understood because on the stained preparations the colouring matter, *e. g.* methyl blue, may be accumulated in the vacuoles as if it had an affinity to a parasitic element.

E. Antolisei notices that the blood coming from persons free from paludism, sometimes presents alterations which remind one much of the first phases in the dovelopment of the hæmatozoa of paludism ('Gazzetta degli Ospitali,' 1889, No. 77). When only

these non-pigmented forms are found in the blood of a patient paludism must not be too hurriedly diagnosed.

Several observers, deceived by these resemblances, have thought that they had found alterations identical with those which characterise paludism, in the blood of patients suffering from other affections. This confusion, I say, is only possible in the first phase of the hæmatozoa, and it is difficult to make when examining fresh blood which has not been submitted to the action of heat, nor to that of reagents capable of altering the shape of the blood-corpuscles; it was in order to avoid these sources of error that in my first researches I always examined the blood when fresh and pure, without the addition of any reagent.

Kœnig, of Berlin, shows the following method of distinguishing the amœboid bodies from the pseudo-vacuoles:—the diaphragm of the microscope is taken away suddenly, leaving the mirror in its place, with the result that the amœboid bodies disappear, while the vacuoles remain and are still more easily distinguished (Tito Gualdi, Congress of Berlin, 'Semaine médicale,' 1890, p. 305).

What is the nature of the parasite of palustral blood? What place should be assigned to it in the scale of beings?

This polymorphic parasite belongs evidently to a species other than the schizophytes, among which all the pathogenic microbes known up to the present time have been included; most authors admit that it should be classified among the sporozoa, but this opinion has found some few opponents.

According to Feletti and Grassi the hæmatozoa of paludism should be placed among the Rhizopods ('Riforma medica,' March, 1890), and they should be divided into two different species.

1st. *Hæmameba,* with three varieties:

a. *H. præcox,* which produces the quotidian fever, with attacks tending to repeat each other at shorter intervals;

b. *H. vivax* (simple and double tertian);

c. *H. malariæ* (simple double or treble quartan).

2nd. *Laverania,*[1] producing irregular fevers which in a few days change their character: continued, subcontinued, quotidian, tertian, &c.

Antolisei has attempted to show that the hæmatozoon of paludism had some relation with the *monadines* of Cienkowski, or the *proteomixita* of Lankester ('Riforma medica,' April, 1890).

A certain number of sporozoa are now known, which evidently belong to species akin to the hæmatozoa of paludism.

[1] I first described the hæmamiba as a crescent-shaped body, I do not see therefore why my name should be given to one of these species more than another.

Balbiani has divided the sporozoa into, 1st, gregarinæ; 2nd, oviform psorospermiæ or coccidia; 3rd, tubuliform psorospermiæ or sarcosporidæ; 4th, myxosporidæ; 5th, microsporidæ ('Leçon sur les sporozoaires,' Paris, 1884).

The polymorphism of coccidia, their parasitic state in the living cells, the complicated phenomena which are present at their development, occur in the life-history of the parasites of paludism.

It is indeed among the coccidia that the hæmatozoa of paludism should be classfied according to Metschnikoff, whose authority in such matters is so important.

According to Kruse, the hæmatozoon of paludism should be considered as a hæmogregarina and not as a coccidia.

Besides the coccidia, Giard has mentioned among the sporozoa having some affinity with the parasites of paludism, the *microsporon* of the silkworm, and the *Lithocystis Schneideri*, a constant parasite of the interior of the sea-urchin. This latter parasite has a plasmodial form and polysporous cysts; crescent-shaped bodies are formed in variable numbers in each spore, and produce the amœbæ which are transformed into flagella.

Eimer discovered a coccidium in 1870 in the intestine of a mouse, which was studied by Schneider afterwards, who proposed to call it *Eimeria falciforme*. According to Eimer, this parasite is seen under several aspects: first, a cystic form enclosed in the epithelial cells of the intestines; second, falciform corpuscles enclosed in the epithelial cells or free in the intestines: these latter possess a rather rapid movement, and the bend of the crescent becoming emphasised, the sudden straightening of the crescent afterwards takes place; third, amœboid bodies which, after having wandered for several days on the surface of the intestines, appear to penetrate into the epithelial cells and thus re-assume the primitive phase.

A coccidium is found in the intestines of the salamander, which has great analogy with the *Eimeria falciforme* of the mouse. This coccidium is developed in the nucleus of the epithelial cells of the intestines, under the appearance of a rounded granular body which segments itself and gives rise to crescent-shaped bodies arranged in bundles. These latter elements, when free, are animated with movements identical with those of the *Eimeria falciforme*: the bend is exaggerated, then the crescent straightens suddenly. In May, 1889, I noticed the presence of these parasites in the intestines of several salamanders in the laboratory of M. Metschnikoff at the Pasteur Institute. According to Metschnikoff, these parasites assume the flagellated form at a certain phase of their development. J. Steinhaus has given a good

description of these coccidia under the name of *Karyophagus salamandræ* ('Arch. de Virchow,' 1889, t. cxv).

It is not much more surprising to see parasites developed in or upon the corpuscles of the blood than in the epithelial cells of the intestine, as is the case with the *Eimeria falciforme*. Nevertheless this comparison would have doubtless appeared a little strange if parasites, which are still more akin to those of paludism, had not been found in the blood of different animals.

As far back as 1843, Gruby pointed out the presence of an organism with flagella in the blood of a frog, which was called by him *Trypanosoma sanguinis*.

In 1880, Griffith Evans described a disease which rages in India among horses, mules, and camels, and which is called *surra*. This disease, which has the character of a remittent fever, is caused by hæmatozoa which have been described under the name of *spirilla* (by Evans), then under the name of *Spirochæta Evansii* by Steel. Steel and Evans have been successful in transmitting this disease to dogs, horses, and mules.

Lewis observed hæmatozoa in the rats of India, which he thinks are identical with those of the *surra* disease, while Crookshank found these parasites twenty-five times out of one hundred in the blood of the European rat. It is a polymorphic organism, which is seen at times under a globular form, at others under the form of an organism with flagella, and again under the form of crescent-shaped bodies.

Gaule has described a hæmatozoon of the *Rana esculenta* under the name of *cytozoon* ('Arch. f. Physiol.,' 1880–81, and 'Revue d'hygiène,' 1885, p. 686). This cytozoon is found in the red blood-corpuscles in the shape of an elongated body with a nucleus or in a free state in the plasma; it then possesses very rapid movements. The body of the cytozoon is vermiform, and very thin at the extremities, its length on the average being equal to the half of the long axis of a red blood-corpuscle. Cytozoa of the largest size have been found in the blood of the triton.

These parasites of the blood of the frog have been described by Ray Lankester, Wallerstein, and Grassi under the name of *Drepanidium ranarum*, and by Kruse under that of *Hæmogregarina* of frogs.

At the same time as drepanidium, amœboid bodies enclosed in red blood-corpuscles are often found in the blood of the frog, which seem to be only one phase of the development of the drepanidium; these amœboid bodies sometimes contain certain kinds of bacilli, which are multiplied there, and are not met in a free state in the

serum. The real significance of these latter parasites in the blood of a frog is still rather obscure (Gabritchewsky, 'Annales de l'Institut Pasteur,' 1890, p. 440).

The existence of the hæmatozoa in fishes was demonstrated in 1841, for the first time, by Valentin.

In 1883, Mitrophanow described flagellated infusoria in the blood of a carp and roach; these parasites, at one phase of their development, are seen in the state of amœboid bodies without flagella.

Chalachnikow has very often observed hæmatozoa in fishes coming from the provinces of Kherson and Kharkov, the Dneiper and the lakes around Tobolsk; these hæmatozoa have great analogy with the trypanosma of the frog and rat.

Organisms provided with flagella may be observed frequently in the blood of the tortoise (*Emys lutaria*) and of the frog (*Rana esculenta*), and are also found in the lymph, the urine, and even in the bile.

These parasites, which correspond to the *Hexamitus* of Dujardin, possess six flagella, four anterior and two posterier, and make a way for themselves with much rapidity through the blood-corpuscles, by pushing them aside or driving them before them.

The hexamitus also lives in a free state in the intestinal duct of tritons, frogs, lizards, and tortoises. The alterations in the structure in the intestinal wall in inanition favour the entrance of this parasite into the blood; the intestinal mucous membrane becomes more permeable for the young forms of the hexamitus, which afterwards spread into the whole vascular and lymphatic system.

In examining the blood of lizards (*Lacerta viridis, Lacerta ogilis*) taken at Kharkov and its neighbourhood, Danilewsky and Chalachnikow have frequently found that a large number of red blood-corpuscles were invaded by parasitic elements. These hæmatozoa are nearly always enclosed in the blood-corpuscles, though some that are free and move slowly in the serum amongst the blood-corpuscles may be met at times.

This parasite in the blood of the lizard, or hæmocytozoon, is oftenest seen under the appearance of a little worm, whose extremities are more or less thin; its dimensions are variable, from 10 to 15 μ in length, and each parasite contains one nucleus. The invaded blood-corpuscles increase in size and become discoloured.

The hæmocytozoon sometimes possesses a rudimentary movement, consisting of a flexion in the direction of the bend, followed

by a straightening; elevation of the temperature (30° to 38° C.) augments the intensity of that movement, cold having the opposite effect.

The free hæmocytozoa have the appearance of little worms endowed with movements similar to those above described; some small constrictions may also be distinguished.

Little protoplasmic elements, which have scarcely a quarter of the volume of a leucocyte, may also be observed in the blood of lizards; these probably represent the hæmatozoa in the first phase of their development.

The frequency of the hæmatozoa varies very much according to the habitat of the animals. Out of five lizards taken from a garden at Kharkov, in August and September, there was one at least whose blood contained these parasites, while in the lizards taken at 15 kilometres from the town the hæmatozoa were much scarcer.

The hæmatozoon of the lizard probably enters through the digestive tracts, but nothing is proved on this point.

The blood of the marsh-tortoise frequently contains parasites free or enclosed in red blood-corpuscles; these were observed for the first time by Danilewsky in 1884.

Plate IV, fig. A, reproduces some of the appearances of the hæmatozoa of the tortoise according to Danilewsky's observations.

The parasites enclosed in the red blood-corpuscles or cytozoa are first seen under the appearance of a rounded colourless spot, sometimes oblong, which enables them to be distinguished easily from the substance of the blood-corpuscles: the cytozoon is situated at the side of the nucleus; it contains a few shining granules, but no pigment (1—5, fig. A, Pl. IV).

At a more advanced stage of its development the cytozoon is seen inside the red blood-corpuscle under the shape of a transparent, colourless, immobile little worm (6, 7, 8, fig. A, Pl. IV).

This little worm grows, takes a greyish hue, and a nucleus makes its appearance towards the middle of the worm; one of the extremities becomes curved so much that the parasite, which is folded upon itself, may have a length twice the diameter of the blood-corpuscle which contains it.

The structure of the little worm is extremely simple; it is a cylindrical body rather thin at its extremities, representing a single cell with one nucleus.

At its state of complete development the parasite becomes mobile and escapes from the blood-corpuscle, which it drags along for some time afterwards (9—12, fig. A, Pl. IV).

The elements 9, 10, 11, are interesting from the point of view of the interpretation of the very fine line which very often joins the crescent at its two ends in the crescent-shaped bodies of palustral blood; this line represents the edge of the blood-corpuscle altered and become very transparent. On the blood-corpuscle of the tortoise the presence of the nucleus is very characteristic.

The little worm after becoming free moves with large helicoid circular undulations; later, transverse constrictions which change their place during the movements of progression, and which may be compared to contractions, are seen.

Danilewsky has found *gregarine cytocysts* in the medulla of the bone of tortoises (15, 16, fig. A, Pl. IV). Inside the red corpuscles, which are pale and distended, oval bodies with a mammillated surface may be seen; these are muriform, and soon are segmented more completely and give birth to embryos (fig. A, 17, 18, Pl. IV).

According to Danilewsky, the adult parasite is encysted in a red corpuscle, and an intra-cellular metamorphosis of the gregarina is produced, similar to that of *Monosporea* (A. Schneider) in cytoplasma; the protoplasm is afterwards divided into mobile embryos.

The cytocysts of the hæmatozoa of the tortoise are interesting to compare with the segmented elements or rose-shaped elements of the palustral blood.

The hæmatozoa of the tortoise have a great analogy with those of the lizard.

The hæmatozoa of birds are still more akin than the preceding to those of paludism.

Danilewsky found hæmatozoa in the blood of several species of birds, which he has described under the following names:—*Pseudovermicules, pseudovacuoles, polimitus sanguinis avium, pseudospirilla, trypanosoma.*

The first four of these forms appear to correspond to the different phases of a polymorphic parasite, which has a very great analogy to the hæmatozoa of paludism.

The *pseudovacuoles* or *cytozoa* (1—4, Pl. IV, fig. B) are seen under the appearance of clear spots of variable shape and dimensions inside the red blood-corpuscles; the smallest of these elements are from 2 to 4 μ in diameter, the largest reach the size of the blood-corpuscles. Several cytozoa are often found in the same blood-corpuscle.

The hæmocytozoon of birds contains black granules of pigment

in variable number, which seem to be the product of a transformation of the hæmoglobin like the pigment of the parasites of paludism.

It should be noticed that in cold-blooded animals (frogs, lizards, tortoises) the hæmatozoa do not give rise to the formation of pigment as is the case in the hot-blooded animals (Danilewsky).

The pseudovacuoles or hæmocytozoa appear to be the young and temporary forms of the hæmatozoa of birds.

The granules of pigment enclosed in the cytozoa are sometimes endowed with a very quick movement similar to that which I have described in certain elements of palustral blood.

The *pseudovermicules* have an elongated form 14 μ to 17 μ in length; the substance of the parasite has a greyish colour; in the centre a nucleus is always found; the body of the vermicule is very thin at its extremities, one of which is generally more rounded than the other. These elements are mobile; the movements are slow, being quickened by heat; the pseudovermicule usually advances in a curved line or in a larger spiral, transverse constrictions being made during these movements (5, fig. B, Pl. IV).

The *polimitus* presents the most interesting form of the hæmatozoa of birds; it was described in 1884 by Danilewsky, and has been observed by several others, especially by Metschnikoff.

The polimitus is developed in the red blood-corpuscles; its form is generally spherical; in its interior flagella are in motion which give a movement to the polimitus and alter its form; after a certain time the capsule opens and the flagella escape, showing energetic movements.

The excapsulated polimitus (which proceeded from the blood-corpuscle at first enclosing it) measures on an average 6 μ, sometimes 12 μ, and even 15 μ in diameter (8, 9, fig. B).

The flagella, which have variable lengths, are independent of each other in their movements; one will often stop while the others continue to move.

The free end of the flagella is usually a little swollen, but that is not an invariable characteristic. The excapsulated polimitus shows oscillatory movements which are given to it by the flagella; sometimes it is segmented.

Danilewsky found the polimitus in the blood of the magpie, the jay, and the owl; he made observations on birds who had been recently caught, and also on those who had been captive for some time.

The polimitus of birds is always developed in the red blood-corpuscles, and it is only exceptionally to be met in a free state in the serum. It may be ascertained by collecting blood in a pipette which contains a solution of osmic acid, or else by drying the blood rapidly; under these conditions no free polimitus is found in the preparations. The cooling to which the blood is submitted when taken from the vessels favours the excapsulation; by heating the preparation to 40° C. the excapsulation may be prevented. No free polimitus is observed at that temperature, whilst in the same preparation cooled to 20° C. many may be seen (Danilewsky).

The polimitus is composed of a capsule and fluid contents, in which are found black granules (melanin) often possessing very quick movements. The flagella move first inside the polimitus, then liberate themselves from the interior, move about for some time before severing their attachment to the polimitus, and at last become free; they constitute then the pseudospirilla.

The pseudospirilla are endowed with very rapid movements, which may last for an hour or even longer.

Swelling sometimes takes place on the pseudospirilla of birds as on the flagella of palustral blood, which is explained by the protoplasmic nature of those elements.

Danilewsky has not succeeded in cultivating the small pseudospirilla of the blood of birds, also he has not observed their division, and thinks that they cannot multiply in a free state.

Beside the polimitus and the pseudospirilla, organisms are met with sometimes in the blood of birds which are similar to the parasites observed in the blood of the rat and of the hamster (*cricetus*), and which have been described under the name of *Herpetomonas Lewisii*. Danilewsky found these organisms for the first time in the blood of several birds (owl, jay) in 1885, and gave them the name of *trypanosoma sanguinis avium*. In 1861, Eberth noticed the existence of a trypanosoma in the gullet of birds.

The *trypanosoma sanguinis avium* has a cylindrical shape, the posterior end is thinner than the anterior; the body is a greyish colour, half transparent, homogeneous, and of a soft consistence. The anterior extremity is extended into a flagellum of variable length which becomes thinner and thinner, a vibrating membrane makes a hyaline border. The vibrations of the flagellum and those of the membrane correspond in rapidity, extent, and direction.

The trypanosoma has a spirilliform movement, the flagellum being directed forwards.

In the interior of the trypanosoma a greyish homogeneous nucleus may be found, having a nucleolus.

The trypanosoma is multiplied by longitudinal division.

According to Danilewsky these hæmatozoa are found in birds which are fed by their parents after having been hatched, and not in those which find their food themselves. It seems proved, in the case of the trypanosoma at least, that this parasite is developed in the digestive canal and especially in the crop, and that the young are infected by their parents.

Generally the presence of the hæmatozoa does not cause any morbid disturbance in the birds. In more than 300 birds examined by Danilewsky containing hæmatozoa, death only occurred in four or five ; in these cases an extraordinary number of parasites were present in the blood ; the liver and the spleen were enlarged, and the melanæmia was very pronounced.

Danilewsky proposes the two following hypotheses in order to explain the habitual harmlessness of the hæmatozoa of birds: there is perhaps in birds a tolerance transmitted by heredity; perhaps also the temperature of the blood of birds is too high for the parasitic elements to be set free.

In a recent work ('Annales de l'Institut Pasteur,' December, 1890) Danilewsky says that he has found rose-shaped bodies, similar to those which are seen in palustral blood, in the blood of certain birds ; these bodies, resulting from the segmentation of the endocorpuscular parasities, give rise to eight, ten, and often twenty spores, which become free. These spores, even when not separated, present a nucleus, and are easily stained by methyl blue or by safranin.

The free spores are seen under the appearance of oval corpuscles, very small, with well-defined and thick contours, having a great resemblance to the spores of the microsporidæ.

The birds in whose blood these rose-shaped bodies are met with are often diseased, the temperature rises from 1° to 1·5°, the bird no longer eats but grows thin, sometimes it is attacked by convulsions and dies ; generally the illness ends by recovery in from four to six days.

These facts supplied Danilewsky with new arguments to prove that these parasites in the blood of birds are the same as the parasites of paludism.

The differences which exist between the hæmatozoa of palustral blood and those of the blood of birds may, according to him, be explained by the difference of the surroundings in which the parasites live.

Besides the hæmatozoa described above, Danilewsky has found *leucocytozoa* in the blood of certain birds (owl); these are parasites which, instead of penetrating into the blood-corpuscles, enter the leucocytes and are developed there. "One part of these germs evidently perishes in the struggle against the activity of the phagocytes, whilst the other part keeps the vital capacity and consequently the power of subsequent development. Very probably the same struggle takes place during the malarial infection of man, especially in the spleen and medulla of the bones" ('Annales de l'Institut Pasteur,' 1890, p. 427).

The leucocytozoa of the owl have been met with principally in the medulla of the bones; they appear to represent only one of the phases in the development of the *polimitus avium*. Danilewsky has often noticed the excapsulation of the polimitus and the energetic movements of the flagella in the spring of the year.

The same parasites which Danilewsky describes in the blood of the jay, the magpie, and the owl were found in Sicily by B. Grassi and Feletti in the blood of several species of birds, and principally in that of the sparrow and domestic pigeon. As Grassi and Feletti point out ('Communication à l'Académie des Sciences naturelles de Catane,' March 23rd, 1890), it is interesting to notice the presence of the hæmatozoon in species so common as the sparrow and the pigeon. The birds in whose blood Grassi and Feletti found hæmatozoa came from parts of Sicily in which paludism is endemic.

Up to the present I have sought in vain for the hæmatozoa in the blood of sparrows and pigeons which I have been able to procure in Paris.

Besides the trypanosoma, which has nothing to do with the parasites of paludism, Grassi and Feletti have observed in the blood of birds—

1st. A form akin to the crescent-shaped bodies of palustral blood.

2nd. A form of amœba akin to the amœboid bodies of palustral blood (my spherical bodies), to which Grassi and Feletti propose to give the name of *hæmamœbæ*.

Usually the amœbæ occupy the extremities of the red blood-corpuscles, and the semi-lunar bodies the sides.

The crescent-shaped bodies of birds possess a nucleus easily discerned; on reaching a certain phase of their development they take the spherical form and shoot out flagella.

In February and the first half of March, at Catania, the

sparrows infected with parasites were in proportion of 20 per cent. After that time the number of infected birds went on increasing, and at the end of April all the birds examined were infected. Most had only semi-lunar bodies; very few had hæmamœbæ at the same time. In previous researches Grassi and Feletti noticed, on the contrary, that amœbæ always existed at the same time as the crescent-shaped bodies.

In May and June the hatching took place. No parasites were found in the embryos or in the young still without feathers; some were sometimes found in the young ones which were still in the nest, but already capable of flying; much oftener still in the young ones which had already left the nest.

Grassi and Feletti consider that the disease is not hereditary, and that it is not transmitted by the parents which feed their young.

In their opinion the infection is produced in the surrounding media; it seems always to begin with the semi-lunar bodies without hæmamœbæ. Grassi and Feletti show the co-existence of the hæmamœbæ and the semi-lunar bodies, but this does not prove the identity of these parasites; the semi-lunar bodies exist in almost all birds, and it is not surprising that they are associated with other parasites. Grassi and Feletti do not hold that the hæmamœbæ and the semi-lunar bodies represent two forms of a polymorphic parasite, but the arguments which they advance against this opinion do not seem to me convincing.

The semi-lunar bodies multiply in the blood of the bird. If birds whose blood contains numerous adult semi-lunar bodies are systematically observed, after eight days the existence of very small semi-lunar bodies may be noticed, which grow larger little by little, and become full grown; the multiplication appears to be by division. It should be noticed in passing that nothing similar is seen in palustral blood; the semi-lunar or crescent-shaped bodies have always very approximately the same dimensions, and nothing shows that they can be multiplied by division.

Kruse has observed these hæmatozoa in the blood of the rook and the crow.

During the summer of 1889, in Paris, I succeeded in finding the parasites described by Danilewsky in the blood of the jay. A summary of the observations made repeatedly during the months of May, June, and July, 1889, on one of these birds follows.

A large number of red blood-corpuscles were altered and contained pigmented elements; there were often five or six altered

blood-corpuscles at the same time in the microscopic field (oc. 1 and obj. 9 of Verrick).

The altered blood-corpuscles presented clear spaces of variable dimensions, which could easily be distinguished by their transparency from the substance of the blood-corpuscles, which was, however, of a paler tint than that of normal red blood-corpuscles.

The hyaline elements, which appear as if enclosed in the blood-corpuscles, had a rounded, or more often elongated shape, in the direction of the long axis of the blood-corpuscle.

With but very few exceptions these elements were pigmented; some were curved, and extended nearly the complete circle of the nucleus. In the smallest only one granule of pigment could be found, in the others the number and position of the granules of pigment were very variable.

The granules of pigment enclosed in the largest elements were sometimes endowed with a very rapid movement.

The blood-corpuscles which contained the parasites grew paler and paler, so that a time came when only the nucleus of the blood-corpuscle could be discerned at the side of the parasite; at last the nucleus itself disappeared, and the parasite was found free in the blood. The liberated parasites were rare exceptions compared with the parasites enclosed in the blood-corpuscles.

Several times I saw pigmented elements breaking down; numerous mobile and short pseudospirilla escaped from them, which were difficult to observe, and which seemed to me very different from the flagella of palustral blood.

The spherical elements, containing mobile pigmented granules, were sometimes endowed with a quick oscillatory movement, similar to the movement of the analogous elements in palustral patients.

The jay which was the subject of this observation did not show any apparent disease even when the parasitic elements were very numerous in the blood; it recovered spontaneously. The examination of the blood made several times from August, 1889, to April, 1890, did not reveal the existence of any of the parasitic elements above described.

On April 19th the bird died by accident. The examination of the blood taken from the heart showed the existence of large-sized nematoids, but no endocorpuscular parasite was found. The examination of the spleen was also negative.

Plate III, fig. B, represents some of the parasitic elements observed in this bird; the dry blood has been treated with eosine and methyl blue.

The hæmatozoa of birds are evidently near akin to those of paludism, but the identity of the two species is not proved. By the side of the analogies important differences are noticeable: the pseudovermicules, mobile and presenting constrictions, do not seem to me comparable to the crescent-shaped bodies of palustral blood. The pigmented cytozoa have certainly a great similarity to the pigmented spherical bodies of palustral blood, which adhere to blood-corpuscles; it must, however, be noticed that in the blood of birds the cytozoa are almost always enclosed in the red blood-corpuscles, while the spherical elements are often free in palustral blood. The amœboid movements of these elements are more pronounced in palustral blood than in the blood of birds. Finally, the pseudospirilla which escape from the cytozoa of birds seem to me very different from the flagella of palustral blood.

Because of the analogies which exist between the hæmatozoa of birds and those of palustral blood, it was interesting to know if it were possible to inoculate these latter parasites into birds. In June, 1889, I injected a few drops of palustral blood rich in parasitic elements into the brain of a young jay whose blood was normal. After this operation I did not notice any alteration in the blood of the bird; the examination of the blood made several times during the months of July, August, and October was always negative. In December, 1890, I repeated the experiment; a few drops of palustral blood containing crescent-shaped bodies were injected into the veins of a jay without any result.

Before coming to any conclusion on this subject it will be necessary to multiply these investigations and to experiment on different species of birds; it is possible that certain hæmatozoa of birds belonging to palustral districts are identical with those of paludism, but that has not yet been proved.

To sum up: the parasites of palustral blood are not now as isolated as they seemed to be when I gave my first description of them; they are found to belong to a group the importance of which increases every day. Perhaps there may be occasion to create a special division in the class of sporozoa to contain, along with the coccidia, the hæmatozoa of paludism and the analogous hæmatozoa which have been discovered in different animals. I leave to naturalists the task of solving this question.

CHAPTER IV.

The hæmatozoon which I have described is the pathogenic cause of paludism—The parasitic elements of palustral blood represent the different stages of the evolution of the same polymorphic hæmatozoon—Relation of these different stages to the febrile types.

The hæmatozoon which I have described is found in palustral patients in Europe, Asia, Africa, and America, with the same characteristics; this is a great presumption in favour of its pathogenic *rôle*, especially if it be added that this parasite has never been found except in paludism.

This latter proposition does not admit of any exception; the presence of a single one of the parasitic elements previously described is pathognomonic of paludism, and allows the diagnosis to be made as certainly as the presence of the echinococcus or débris of echinococci in a fluid allows us to diagnose a hydatid cyst.

In Algeria I very often made a histological examination of the blood of anæmic patients who were free from paludism—of dysenteric patients especially; I have never noticed in these cases the presence of hæmatozoa. This result has been confirmed by all the observers who have tested my researches.

Before the presence of the hæmatozoa had been noticed in palustral blood, melanæmia was considered as the most characteristic lesion of paludism; but nobody could explain why this lesion took place in paludism and not in other febrile diseases.

At present we know that melanæmia is the consequence of the development of the hæmatozoa, and it seems logical to conclude from it that the agents of melanæmia are also those of paludism.

Under the influence of quinine treatment the hæmatozoa disappear at the same time as the fever disappears, which is an

[1] Thus the histological examination of the blood is very useful in all cases where the diagnosis of paludism offers difficulties; it allows the separation of diseases which appear with almost identical clinical forms, though they may be as different in nature as typhoid fever and palustral continued fever with typhoid state; sun-stroke, and certain pernicious attacks, &c. In our climates these grave forms of paludism are rarely met, nevertheless the question of the palustral nature of such accidents arises rather frequently.

important proof of the cause and effect relation which exists between these parasites and the phenomena of paludism. The crescent-shaped bodies resist quinine treatment better than the other elements. Why wonder at this? Numerous facts of the same kind could be brought forward in the history of parasites, which are often much more difficult to destroy under one particular form than under any other. In this particular case the resistance of certain elements even gives a good explanation of the recurrence which is so common in intermittent fever.

It has sometimes been brought forward that as paludism is not a contagious disease, its parasitic nature was doubtful. The diseases produced by parasites which live on the surface of the body are easily transmissible; it is also the same with diseases which, like typhoid fever or cholera, cause the elimination of products containing pathogenic microbes. It can be easily understood that it would be different in the case of diseases which are due to the presence of parasites in the blood or in the tissues, and in which there is no elimination of the parasitic elements into the external media.

Persons suffering from trichiniasis or filariosis are not dangerous to their surroundings; they do not communicate their disease any more than do palustral patients.

Moreover it is possible to inoculate paludism from man to man. As far back as 1881 I was able, from my knowledge of the hæmatozoa of paludism, to give the conditions of success for this experiment.

Gerhardt injected palustral blood (about one gramme) into the connective tissue of patients with chronic affections other than paludism, and he says he twice succeeded in setting up intermittent fever ('Zeitsch. f. klin. Med.,' Bd. vii); these results are weakened by other facts in which injections of blood into the connective tissue have given only negative results. It is probable that, in the two cases in which Gerhardt succeeded in inoculating fever, the blood injected into the connective tissues had entered small vessels.[1]

Mariotti and Ciarocchi have inoculated paludism in four patients under treatment in the hospitals of Rome for chronic affections non-palustral ('Lo Sperimentale,' 1884). These observers always failed when they made subcutaneous injections of

[1] As far back as 1880, Doehmann had tried to inoculate paludism from man to man with serous fluid of herpetic vesicles of a palustral patient. The observations of Doehmann are by no means conclusive (V. J. Chassin, 'Sur l'inoculation de la fièvre intermittente,' Thèse de Paris, 1885).

palustral blood; on the contrary, they noticed that intra-venous injections were very efficacious.

Marchiafava and Celli also succeeded in transmitting paludism by an intra-venous injection of palustral blood, while subcutaneous injections only gave them negative results; they have seen hæmatozoa appear in the blood of persons inoculated by intra-venous injection, at the same time as regular and well-characterised attacks of intermittent fever took place, which yielded to quinine.

Marchiafava and Celli operated in the following manner:—A Pravaz syringe was used to make the intra-venous injections; it was sterilised every time after having been enclosed in a glass tube closed with wadding, the syringe being taken from the tube only at the moment of using it; the operator's hands were washed in a solution of sublimate, and then, with the same solution, he washed the skin of the fold of the elbow of the palustral patient from whom the blood was to be taken, and also that of the patient in whom the injection was to be made. The point of the cannula was driven into one of the veins at the bend of the elbow of the palustral patient, a small quantity of blood was aspirated, then immediately injected into one of the veins of the bend of the elbow of the subject who lent himself to the experiment; the quantity of blood thus transferred was at most one gramme.

I summarise the Observations 1 and 3 (Marchiafava and Celli, "Nuove ricerche sulla Infezione Malarica," 'Annali di Agricoltura,' 1885).

Obs. 1.—Young man of 17, suffering from transverse myelitis, free from paludism. A first experiment was made of two subcutaneous injections in this young man with blood taken from a palustral patient; these injections did not produce any effect.

On August 21st and 26th, 1884, intra-venous injections were made with palustral blood containing many parasitic elements, and particularly flagella; on the day following the last injection an attack of fever resulted, which was repeated on the following day; the patient suffered from well-marked quotidian fever, which yielded to sulphate of quinine, but which reappeared several times. The spleen became enlarged,—in short, the examination of the blood revealed the existence of the parasitic elements which characterise paludism.

Obs. 3.—Man aged 32, suffering from cerebro-spinal sclerosis, free from paludism.

On September 6th subcutaneous injection of palustral blood was made, which had no effect.

On September 13th he received an intra-venous injection of one gramme of blood taken from a patient suffering from palustral cachexia with irregular attacks of fever; on September 20th (seven days after the injection) he had an attack of fever which was repeated on the following days. The temperature chart published with this observation is exactly that of the quotidian intermittent fever; at the same time the spleen was enlarged, and the examination of the blood revealed the hæmatozoa of paludism. The fever yielded easily to sulphate of quinine.

T. Gualdi and Antolisei communicated two cases of palustral fever to the Royal Academy of Medicine of Rome in 1889; the fever was induced experimentally in two healthy individuals by the intra-venous injection of palustral blood.

Antolisei, Gualdi, and Angelini published in 1889 ('Riforma medica,' September and November, 1889) four other cases of experimental paludism. It is needful to dwell shortly on the examination of these facts, which are interesting not only from the point of view of the transmission of paludism from man to man, but also because they give important data as to the duration of the incubation of paludism, and also for the discussion of the theory which allows the existence of several species of hæmatozoa of paludism.

It is important to know if, by inoculating blood of the tertian or quartan type, these types could be reproduced in the individual inoculated, and it was specially in order to solve this question that Gualdi and Antolisei made the experiments which I will here summarise.

First fact.—Intra-venous injection into a neurasthenic patient, who has never had palustral fever, of three cubic centimetres of blood taken from a patient with quartan fever five hours before the attack. Ten days after the injection the temperature rose slowly to 40·8° C.; in three days the patient had, in fact, a continued fever, the spleen enlarged; on the following days the fever reappeared without regular type, the blood contained amœboid bodies.

The patient had several relapses of fever in September, 1889 (the intra-venous injection had been made in May, 1889); the examination of the blood revealed semi-lunar bodies as well as amœboid bodies (Gualdi and Antolisei, "Une quarte expérimentale," 'Riforma medica,' November, 1889).

Therefore in this patient, who was inoculated with blood of the quartan fever, a fever was induced which was at first continuous, then irregular, with amœboid bodies but without crescent-

shaped bodies, and when the relapse occurred four months after the injection, crescent-shaped bodies were found.

Second fact.—Patient of 42, suffering from traumatic hemiplegia. For ten years he had had no fever; on May 17th an injection was made of palustral blood taken from a patient with quartan fever five hours and a half before the attack; twelve days afterwards an irregular fever appeared, with enlargement of the spleen. Examination of the blood revealed pigmented spherical bodies; in the case of the patient who had supplied the blood many forms in endogenous multiplication could be found.

The incubation lasted ten days in one case, twelve in the other.

In neither was the febrile type reproduced in the subjects experimented upon.

Third fact.—Intra-venous injection made with the blood from a tertian fever patient. The blood was taken at the beginning of an attack and injected on July 17th into a man of twenty-four, suffering from cerebellar tumour. On July 27th an attack of fever resulted, which returned on the 29th; on the 27th the examination of the blood did not show anything abnormal. During the second attack pigmented spherical bodies were found, with mobile pigmented granules.

The attacks came at shorter intervals, attacks on the 2nd and 3rd August with hypertrophy of the spleen.

This fever was arrested by quinine, the parasitic forms disappearing rapidly from the blood.

Fourth fact.—Patient of 52, suffering from diffuse cerebro-spinal sclerosis. On July 17th an injection was made, as with the previous patient, with blood from the same subject with tertian fever.

On July 27th an attack of fever; apyrexia on 28th and 29th; slight attack on the 30th (the fever would consequently be of a quartan type).

On August 2nd an attack of fever; new attacks on August 3rd and 4th (quotidian type); on the 5th no fever; on the 6th last attack; on August 14th and 15th subcutaneous injections of quinine.

The examination of the blood of this patient from August 2nd to 7th, spherical bodies with or without pigment; no segmented forms were found in this or the first case.

In the last two patients the incubation lasted ten days, and the fever produced was irregular.

Fifth fact.—The blood was taken on October 7th, 1889, from a patient with quartan fever of first invasion, in whose blood bodies in process of segmentation were very abundant.

Two cubic centimetres of blood taken from the basilic vein were injected into the same vein in a subject suffering from softening of the brain who had never had fever. On October 19th the patient, into whom palustral blood had been injected, had an attack of fever, the blood containing spherical bodies with or without pigment.

On October 20th and 21st apyrexia occurred, and the spherical bodies increased in number and size, and on the 22nd many of the elements were in process of segmentation.

On October 22nd, attack of fever, the temperature rising to 38·9° C.; on the 25th another attack.

In this case quartan fever was produced with the blood of a patient himself suffering from quartan fever, and the parasitic elements observed in the blood of the two patients showed a great resemblance; but it is also open to question whether, had the patient been examined later, at the period of relapse, crescent-shaped bodies would not have been found, as was the case in the subject of the first observation.

Sixth fact.—A man of 45, suffering from paralytic dementia. On September 25th two cubic centimetres of blood were injected into his veins; this blood contained only crescent-shaped bodies.

On October 3rd a slight attack of fever resulted, but nothing abnormal was found in the examination of the blood.

On October 4th 0·75 gramme of sulphate of quinine was given by mistake; during the night of October 4th a very severe attack of fever occurred; on the morning of October 5th the temperature was 40·5° C.

In the examination of the blood amœboid bodies were seen.

New attacks of fever came on the 5th during the day; on October 6th, 7th, 8th, 9th, there was slight rise of temperature.

During the night of October 9th the patient had a rather severe attack of fever; on the 10th two attacks; on the 11th and 12th slight attacks; on the 13th an examination was made of the blood, showing, besides amœboid bodies, a small number of semi-lunar bodies. Apyrexia from October 14th to 19th.

On October 21st a slight attack of fever; on the 22nd semi-lunar bodies and flagella were found; on October 23rd the last attack, which was slight.

In this case the incubation lasted thirteen days.

The fever was irregular, but its development was stopped by the administration of a dose of sulphate of quinine.

I shall return to these facts later on when speaking of the plurality of the parasites of paludism, and of the duration of the incubation of palustral fever; for the present I only point out that paludism can be transmitted at will from man to man by intra-venous inoculation, and that the parasites of paludism can be seen appearing in the blood of the inoculated subject as soon as the fever declares itself.

To sum up: 1st. The hæmatozoa have been found in the palustral patients of all countries with the same characteristics, and there is a remarkable agreement between the already numerous descriptions which have been given of it.

2nd. These hæmatozoa have never been found in persons who were not suffering from paludism.

3rd. The development of the hæmatozoon is intimately connected with the production of melanæmia, which is the most characteristic lesion of paludism.

4th. Quinine causes the hæmatozoa to disappear from the blood at the same time as it cures the palustral fever.

5th. It has been possible to transmit paludism from man to man by injecting a small quantity of blood, taken from the veins of a palustral patient and containing hæmatozoa, into the veins of a subject free from paludism.

The conclusion that the hæmatozoa are the pathogenic agents of paludism appears to me to be indisputable.

From the point of view of general pathology, this unexpected fact, that a sporozoon is the cause of one of the most important diseases among those which lately were classed in the group of infectious diseases, deserves to be emphasised as a new proof of the diversity of the pathogenic agents, and of the risks which might be run in generalising too rapidly and drawing inferences from the nature of some of these agents as to the nature of others.

Is paludism the only disease produced in man by the presence of parasites belonging to the class of sporozoa? We are still ignorant about the real nature of a great many pathogenic agencies, and it is very probable that some of these agencies are of the same nature as palustral fever.

It is very likely that yellow fever, which is an iufectious disease, endemic like paludism, may have a parasite similar to that of paludism for its pathogenic cause.

Goitre, which is a type of endemic disease, might also be caused by a protozoon, which should be carefully looked for in

the hypertrophied thyroid, its seat of election, as the spleen is the seat of election of the hæmatozoa of paludism.

We see from the researches of Darier, confirmed by those of Malassez and of Wickham, that Paget's disease of the mamma is due to sporozoa of the order of Coccidia or Psorospermiæ.[1]

The cutaneous psorospermosis must be placed along with Paget's disease, the vegetating follicular psorospermosis, and probably the *molluscum contagiosum* of Bateman.

According to Sacharoff, the parasite of relapsing fever is near akin to the hæmatozoa of paludism ('Communication à la Société de Médecine de Tiflis,' 1888). This parasite, which it is easy to see in the blood after the defervescence of the fever, seems to be twenty times the diameter of a red blood-corpuscle in length; made up of an amœboid protoplasmic mass, containing granulations and almost always a nucleus; it emits prolongations which, when free, take a spiral form; these prolongations appear to be no other than the elements which are described by Obermeyer under the name of spirilla.

Sacharoff notices that these hæmatozoa of recurrent fever have a great analogy to those of paludism, and proposes to give them the name of *hæmatozoa of relapsing fever.*

Danilewsky admits with Sacharoff that the spirilla of relapsing fever have a great analogy to the pseudospirilla of the blood of birds, and he gives as a proof of that opinion the fact that the spirilla of relapsing fever cannot be cultivated in artificial media any more than the pseudospirilla of birds.

Loesch ('Archives de Virchow,' t. lxv), Grassi, Perroncito, Sonsino, Kartulis (même recueil, 1886, t. cv, p. 521), have described some amœbæ of the large intestine which may play an important part in the etiology of the dysentery of hot countries, and in the pathogenesis of abscess of the liver.

Is the hæmatozoon of paludism unique? Is there a single polymorphic parasite, or are there several species of parasites giving rise to different clinical manifestations of paludism?

From the beginning of my researches I put this question to myself. The clinical manifestations of paludism are very varied, and, on the other hand, the parasites of paludism are seen

[1] Darier, 'Société de Biologie,' April 13th, 1889, and 'Commun. au Congrès International de Dermatologie de Paris,' August 8th, 1889. L. Wickham, "Anat. path. et nature de la maladie de Paget du mamelon" ('Arch. de méd. expér. et d'anat. pathol.,' 1890, p. 46). Malassez, "Sur les nouvelles psorospermoses chez l'homme" (même recueil, 1890, p. 302). L. Wickham, 'Contrib. à l'étude des psorospermoses cutanées,' Paris, 1890.

in the blood under several forms; it was therefore natural to ask if such and such form of parasite did not correspond to such and such clinical variety ('Traité des fièvres palustres,' p. 196).

In order to solve this problem I increased the number of my observations, and since 1884 the results given by the analysis of 432 cases of paludism have been published by me.

I have only promulgated the two following general rules concerning the relations which exist between the febrile type and the parasites observed in the blood:

1st. Often only the elements described in my first publication under the name of bodies No. 2, and in my subsequent publications under the name of spherical bodies, are found in the blood of patients suffering from palustral fever of first invasion (continued or quotidian); and sometimes all the parasites observed in these fevers belong to the first degree of development of these elements (spherical bodies of very small volume, non-pigmented or containing only one or two granules of pigment).

2nd. The crescent-shaped bodies are usually found in the blood of patients suffering from relapses of fever or palustral cachexia.

Even these rules admit of exceptions; for instance, the crescent-shaped bodies have been met at times in the blood of patients attacked with a fever of first invasion.

In 400 observations analysed from the point of view of the existence of crescent-shaped bodies, these elements have been found 107 times in the following manner ('Traité des fièvres palustres,' p. 196):

Intermittent fever, first invasion	10 times.
Intermittent fever, recurrent	50 ,,
Pernicious attack	2 ,,
Palustral cachexia	45 ,,
Total	107 times.

I have also studied the relations which exist between the parasitic elements of the blood and the febrile paroxysms, and I have shown that it is specially before and at the beginning of the attacks of fever that the most characteristic parasitic elements are found in the blood in the greatest number.

I arrived, in 1884, at the conclusion that the different forms in which the hæmatozoa of paludism present themselves belong to one and the same polymorphic parasite; since then I have always upheld this opinion.

For the last few years several Italian observers have tried to

prove that the hæmatozoa of paludism belonged to several species, and that there was a constant relation between such and such species of parasite and such and such clinical manifestations of paludism.

I have shown in the preceding chapter the differential characters which have been ascribed by Golgi, Canalis, and Antolisei to the parasites of the tertian and quartan types, and we have seen that the most important of these characteristics was supplied by the mode of segmentation of the elements.

In the theory of Golgi, quotidian fever would be now a tertian, now a double quartan; consequently sometimes the parasites of the tertian, sometimes those of the quartan type would be found in the blood of patients suffering from quotidian fever.

Golgi and Canalis have admitted more recently a third variety of parasites of irregular fever, characterised by the crescent-shaped bodies.

The hæmatozoa of paludism would therefore be of three kinds:

1st. Hæmatozoa of the tertian;

2nd. Hæmatozoa of the quartan;

3rd. Hæmatozoa of the irregular fevers.

Gualdi and Antolisei and Angelini have published investigations which confirm those of Golgi and Canalis; these researches have already been summarised (Chap. II, p. 68).

Terni and Giardina, who have specially studied the irregular palustral fevers, agree with the foregoing observers that these fevers are produced by a hæmatozoon which differs from the hæmatozoon of the tertian and of the quartan types, and which is characterised by the crescent-shaped bodies.

Under this title of *irregular palustral fevers* must be comprised the continued and subintrant[1] fevers, the irregular and intermittent fevers with long intervals of apyrexia, and also the palustral cachexia; these constitute, it must be confessed, not a very homogeneous group.

Feletti and Grassi admit the existence of two varieties of parasites, as has been already remarked.

1st. The *hæmamibæ* (corresponding to my spherical bodies), these being the parasites of the regular fevers.

2nd. The *Laverania* (characterised by crescent-shaped bodies), these being the parasites of the irregular fevers.

Feletti and Grassi affirm that at Catania the palustral fevers were always from the beginning of the attack very exactly classified

[1] [An example of a subintrant fever is a double quartan or a double tertian.—TRANS.]

in these two divisions of the regular and irregular fevers, and that the same varieties of parasites always corresponded to the same variety of fever. I was somewhat surprised at this assertion, to prove which Feletti aud Grassi have not so far given any definite facts.

When one has studied paludism in hot countries, and repeatedly seen its different manifestations succeed each other in the same subject, it is difficult to understand how these manifestations can be so easily grouped under the two titles of regular and irregular fevers.

The theory of the plurality of the hæmatozoa of paludism raises numerous objections.

The unity of paludism, from a clinical and anatomico-pathological point of view, is indisputable. Such or such forms in such or such conditions are oftener met; the tertian and the quartan types, *e. g.*, are much more common in our climates than in hot countries, but it cannot be said that here there is a home for tertians, here a home for quartans or for irregular fevers; it is in the same endemic centres that fevers of different types are contracted, and these types vary in a regular manner with the season and with the climate.

The pathological anatomy also shows the unity of paludism; melanæmia and hypersplenia are lesions common to all palustral fevers.

Lastly, the same treatment can be applied to all the types of fever.

It is a well-known fact that the fever often changes its type in the same patient; it is rare, especially in hot countries, for a fever to begin with the tertian or quartan type; more generally it is first continued or quotidian, and at the time of a relapse is transformed into tertian or quartan. The type of fever may even modify itself when patients have left the palustral countries in conditions which exclude the idea of a new infection. If these facts are to be explained on the hypothesis of the plurality of parasites, it will be necessary to admit that the different species of hæmatozoa must generally co-exist in the same patient, and are in turn predominant.

According to Golgi, the quotidian intermittent fever may be at times a double tertian, at times a treble quartan, which is very convenient for the theory he defends, but very unlikely. Quotidian fever is the most common clinical form in the principal homes of paludism, and doctors who have practised in hot countries will have difficulty in admitting that it springs from

the tertian or quartan type, that is, from types comparatively rare in these countries.

The morphological characters ascribed to the three species (Golgi, Canalis, Gualdi, and Antolisei), or to the two species (Grassi and Feletti) of hæmatozoa of paludism, are insufficient to allow each of these species being recognised in the different phases of its evolution.

The hæmatozoa of the tertian and of the quartan and of irregular fevers show themselves in the blood first under the aspect of small amœboid elements, which have the same appearance in the three species of paludism; the segmentation and sporulation are also made in an almost similar manner, the difference being that in the quartan the number of spores is generally smaller than in the tertian. The segmented bodies, as Antolisei admits, are often absent, especially in the tertian, which deprives that characteristic of much of its importance.

The crescent-shaped bodies are, it is true, very characteristic; and were it proved that they are always present in the irregular fevers and never in the regular fevers, we might admit the two varieties described by Grassi and Feletti. But the relations which exist between the appearance of crescent-shaped bodies in the blood and such or such types of paludism are far from being so simple. The exceptions to the rule, if there be any rule, are very numerous.

The supporters of Golgi's theories are obliged to make many concessions. Thus it is that Gualdi and Antolisei are obliged to acknowledge that the type of fever does not depend only on the variety of parasites, but also on individual conditions, so that the same variety of parasites may produce different febrile attacks.

The same observers admit that the hæmatozoa of the irregular fevers may be evolved in certain cases *without passing through the phase of crescent-shaped bodies.* Now, as this phase is the only characteristic one, it does not appear what there is in these cases to distinguish this variety of hæmatozoa. The admission that the hæmatozoa of irregular fevers may or may not pass through the phase of crescent-shaped bodies approaches very closely to the opinion of those authors who, agreeing with me, hold that the parasite is unique, but that its development is variable.

If the three species of hæmatozoa were distinctly separated, and always in exact relation to the febrile type, by injecting blood taken from a patient suffering from tertian or quartan

fever into a subject free from paludism, the tertian or the quartan type ought always to be produced in the inoculated patient. Gualdi, Antolisei, and Angelini have tried to supply this experimental proof of the plurality of the hæmatozoa of paludism. It has been noticed (p. 77) that these observers have six times injected blood coming from palustral patients into the veins of subjects free from paludism, for the purpose of ascertaining whether they could reproduce the type of fever of the patient supplying the blood in the inoculated person.

In one case only this result (which should be the rule if the theory of the plurality of the hæmatozoon of paludism were true) was obtained. One person inoculated with blood of quartan fever had two attacks of the quartan type; in the other cases the results were either unfavorable to Golgi's theory, or at least proved very little. For instance, the intra-venous injection of quartan blood caused in one case a fever, first continued, then irregular, and after a relapse the appearance of crescent-shaped bodies was observed. The blood of a patient with quartan fever producing an irregular fever, and giving rise to crescent-shaped bodies, is, it seems to me, the exact opposite of Golgi's theory.

In order to explain these facts Antolisei suggests the hypothesis that the germs of the different varieties of paludism may co-exist in the same patient; the forms belonging to the evolving cycle of the hæmatozoon which is in activity, if I may thus speak, being only visible in certain patients ('Riforma medica,' April, 1890). If in the experiment just mentioned the blood of quartan fever produced an irregular fever, it was because the patient suffering from the quartan type of fever had in his blood—1st, the parasite of the quartan type; 2nd, the parasites of the irregular fevers in a latent state.

In certain patients suffering from irregular fevers, crescent-shaped bodies are found in the blood taken directly from the spleen, whilst the blood obtained by pricking the finger contains none ('Riforma medica,' March, 1890); Gualdi and Antolisei give this fact as a fresh proof of the relation which exists between the irregular fevers and crescent-shaped bodies. Before coming to any conclusion it would be necessary to examine the blood obtained by puncturing the spleen in patients with tertian or quartan fevers; perhaps crescent-shaped bodies would sometimes be found there.

Terni and Giardina admit that the crescent-shaped bodies are absent in certain cases of irregular fevers, and that the parasites

of the regular and irregular fevers are sometimes combined in the same individual; they advance the hypothesis that this combination is frequent in the fevers of hot countries.

"In Algeria," say Terni and Giardina, "the cases in which all the varieties of hæmatozoa of paludism are associated perhaps predominate; this would be in keeping with the gravity of the infection and the frequency of remittent and quotidian fevers in tropical countries. These cases, which are rare in Rome, are still more so in Northern Italy" ('Rivista d' igiene e sanita pubblica,' May 16th, 1890).

It thus appears that the upholders of the plurality of the hæmatozoon of paludism are obliged to heap up hypotheses in order to meet the objections which facts are constantly bringing to bear against their theories.

With the purpose of testing the assertions of the writers who have assumed the existence of several species of hæmatozoa of paludism, I have selected from among my observations, either already or not yet published, those which seem to me to present most interest from the special point of view of the relations which exist between the parasitic forms and the febrile types, and I have grouped them in five series, as follows:

1st. Palustral fevers by first invasion: continued, regular quotidian, or with subintrant attacks. 2nd. Quotidian intermittent fevers (relapses). 3rd. Tertian fevers. 4th. Quartan fevers. 5th. Patients observed on several occasions, often at long intervals, and who have presented fevers of different types.

1st. *Palustral fevers of first invasion.*—In my 'Traité des fièvres palustres' I have published a certain number of observations which show that in palustral fevers of first invasion, either spherical bodies or crescent-shaped bodies may be met with in the blood. The following table shows some of these facts.

Obs. 23.[1]—Clinical form: Quotidian fever of first invasion ('Traité des fièvres palustres,' p. 255). Result of examination of blood: Crescent-shaped bodies, spherical bodies, flagella.

Obs. 24.—Clinical form: Quotidian fever of first invasion (op. cit., p. 256). Result of examination of blood: Spherical bodies, flagella; no crescent-shaped bodies.

Obs. 31.—Clinical form: Continued fever at the beginning, afterwards quotidian, of first invasion (op. cit., p. 266). Result of examination of blood: Spherical bodies of very small volume in

[1] In order to avoid confusion between the observations of my 'Traité des fièvres palustres' and the observations given in this work I have used Roman figures to designate the new observations.

great numbers, often three or four of these elements adhere to the same blood-corpuscle ; no crescent-shaped bodies.

Obs. 32.—Clinical form : Continued fever at the beginning, afterwards quotidian, of first invasion (op. cit., p. 268). Result of examination of blood : Small spherical bodies in great numbers, either free or adherent to the blood-corpuscles ; no crescent-shaped bodies.

Obs. 35.—Clinical form : Palustral continued fever with typhoid state ; eight days of invasion (op. cit., p. 296). Result of examination of blood :—First examination : spherical bodies of average or small size (the latter are very numerous) ; no crescent-shaped bodies. Second examination : after the subsidence of the fever, spherical bodies, crescent-shaped bodies (rare).

Obs. 36.—Clinical form : Quotidian fever of first invasion ; grave attacks with typhoid state (pernicious phenomena). Result of examination of blood : Spherical bodies of small volume in great numbers ; no crescent-shaped bodies. Relapse : Regular quotidian fever (op. cit., p. 295). Result of examination of blood : Spherical bodies, flagella ; no crescent-shaped bodies.

Obs. 42.—Clinical form : Quotidian fever of first invasion, pernicious phenomena (op. cit., p. 318). Result of examination of blood : Spherical bodies of small size in great numbers, either free or adherent to the blood-corpuscles ; no crescent-shaped bodies.

Obs. 43.—Clinical form : Quotidian fever, acute cachexia (op. cit., p. 328). Result of examination of blood : Crescent-shaped bodies, spherical bodies, flagella.

The new observations which are found at the end of this volume, and concern palustral fevers of first invasion, are summarised in the following table on the special point now under consideration :

Obs. 1.—Clinical form : Palustral continued fever of first invasion. Result of examination of blood : Spherical bodies ; no crescent-shaped bodies.

Obs. 2.—Palustral fever of first invasion. Result of examination of blood : Spherical bodies of very small volume ; no crescent-shaped bodies.

Obs. 3.—Clinical form : Palustral fever of first invasion. Result of examination of blood : Spherical bodies of very small volume ; no crescent-shaped bodies.

Obs. 4.—Clinical form : Palustral continued fever or quotidian intermittent fever with subintrant attacks. Result of examination of blood : Spherical bodies ; no crescent-shaped bodies.

Obs. 5.—Clinical form: Palustral continued fever of first invasion. Result of examination of blood: Spherical bodies of very small size; no crescent-shaped bodies.

Obs. 6.—Clinical form: Quotidian intermittent fever of first invasion. Result of examination of blood: Spherical bodies, flagella; no crescent-shaped bodies.

Obs. 7.—Clinical form: Palustral fever of first invasion. Result of examination of blood: Spherical bodies, flagella; no crescent-shaped bodies.

Obs. 8.—Clinical form: Quotidian fever of first invasion. Result of examination of blood: Spherical bodies, flagella; no crescent-shaped bodies.

Obs. 9.—Clinical form: Quotidian fever of first invasion. Result of examination of blood: Crescent-shaped bodies, spherical bodies.

Obs. 10.—Clinical form: Quotidian fever of first invasion. Result of examination of blood: Crescent-shaped bodies, spherical bodies.

Obs. 11.—Clinical form: Palustral fever of first invasion; continued or quotidian form with subintrant attacks. Result of examination of blood: Crescent-shaped bodies; no spherical bodies.

Obs. 12 and 13.—Clinical form: Quotidian fever of first invasion. Result of examination of blood: Crescent-shaped bodies; no spherical bodies.

These facts prove that the authors who wished to formulate absolute rules concerning the parasitic forms which are met with in the blood of patients suffering from palustral fever of first invasion, and who asserted that no crescent-shaped bodies were found in these cases (James), or, on the contrary, that the crescent-shaped bodies characterise the palustral continued fevers and the quotidian fevers with subintrant attacks (Canalis), have too hastily drawn a general conclusion from insufficient facts.

Spherical bodies of small volume, and often in very great numbers, are usually observed in recent fevers (summer or autumn), but spherical bodies of average size and flagella, spherical bodies with crescent-shaped bodies, and even crescent-shaped bodies alone may be seen (Obs. 11, 12, and 13). In my 'Traité des fièvres palustres' I point out that the crescent-shaped bodies have been observed ten times in patients suffering from fevers of first invasion, twice in patients from pernicious attacks, and ninety-five times in patients from palustral cachexia or recurrent fever (op. cit., p. 196).

2nd. *Quotidian intermittent fever* (relapses).—(A) Observations already published in my 'Traité des fièvres palustres.'

Obs. 14.—Clinical form : Quotidian intermittent fever (relapse) (op. cit., p. 245). Result of examination of blood : Crescent-shaped bodies, spherical bodies, flagella.

Obs. 18.—Clinical form : Quotidian intermittent fever (relapse) (op. cit., p. 249). Result of examination of blood : Spherical bodies, flagella ; no crescent-shaped bodies.

Obs. 21 and 25.—Clinical form : Quotidian intermittent fever (relapse) (op. cit., pp. 252—257). Result of examination of blood : Spherical bodies, flagella ; no crescent-shaped bodies.

Obs. 26.—Clinical form : Quotidian intermittent fever (relapse) (op. cit., p. 258). Result of the examination of the blood : Spherical bodies of average or small size, flagella ; no crescent-shaped bodies.

Obs. 29.—Clinical form : Quotidian intermittent fever (relapse) (op. cit., p. 263). Result of the examination of the blood : Crescent-shaped bodies in great numbers ; spherical bodies.

Obs. 40.—Quotidian intermittent fever (relapse), pernicious accidents (op. cit., p. 313). Result of the examination of the blood : Spherical bodies of average or small size ; no crescent-shaped bodies.

Obs. 44, 45, 46.—Clinical form : Quotidian intermittent fever, rapid cachexia (op. cit., pp. 330–31). Result of the examination of blood : Crescent-shaped bodies, spherical bodies, flagella.

(B) *New observations.*

Obs. 14.—Clinical form : Quotidian intermittent fever (relapse). Result of examination of the blood : Spherical bodies ; no crescent-shaped bodies.

Obs. 15.—Clinical form : Quotidian intermittent fever (relapse). Result of the examination of the blood : Spherical bodies, segmented bodies ; no crescent-shaped bodies.

Obs. 16.—The same.

Obs. 18, 19, 20, 21.—Clinical form : Quotidian intermittent fever (relapse). Result of the examination of the blood : Spherical bodies, flagella ; no crescent-shaped bodies.

Obs. 22.—Clinical form : Quotidian intermittent fever (relapse). Result of the examination of the blood : Crescent-shaped bodies, spherical bodies, flagella.

Obs. 23.—Clinical form : Quotidian intermittent fever, rapid cachexia. Result of the examination of the blood : Crescent-shaped bodies, spherical bodies.

Obs. 24.—Clinical form: Quotidian intermittent fever (relapse). Result of the examination of the blood: Crescent-shaped bodies, spherical bodies, flagella.

In the blood of palustral patients suffering from relapses of quotidian intermittent fever we may therefore find, 1st, spherical bodies of small or average size, without flagella or crescent-shaped bodies; 2nd, spherical bodies and flagella without crescent-shaped bodies; 3rd, crescent-shaped bodies and spherical bodies with or without flagella; 4th, spherical bodies and segmented bodies,—that is to say, all the varieties of shapes of the hæmatozoa.

I might have multiplied the observations of quotidian fever in which I have noticed only spherical bodies with or without flagella, and which show that the crescent-shaped bodies are very often absent from the quotidian fevers. Golgi and Canalis admit, it is true, that the quotidians are the double tertian or triple quartan, and this is an ingenious theory, since, thanks to it, all the quotidian fevers—that is to say, most of the fevers observed in hot countries—would be lost sight of. I have already said that this hypothesis seems to me inadmissible. The quotidian type is the most common febrile type in hot countries; and when a fever reappears several times always with the same type, as in the Obs. 14, I do not at all see the grounds for saying that it is a double tertian or triple quartan. We shall see, besides, that the crescent-shaped bodies have been noticed in patients suffering from well-marked tertian or quartan fevers, which completely ruins the theory of the two or three species of hæmatozoa.

3rd. *Tertian fevers.*—(A) Observations published in my 'Traité des fièvres palustres.'

Obs. 19. Clinical form: Tertian intermittent fever (relapse) (op. cit., p. 250). Result of the examination of blood: Spherical bodies, flagella; no crescent-shaped bodies.

Obs. 20.—Clinical form: Tertian intermittent fever (relapse) (op. cit., p. 251). Result of the examination of blood: Spherical bodies, flagella; no crescent-shaped bodies.

Obs. 27.—Tertian intermittent fever (relapse) (op. cit., p. 259). Result of the examination of the blood: Crescent-shaped bodies, spherical bodies, flagella.

Obs. 28.—Clinical form: Tertian intermittent fever (relapse) (op. cit., p. 261). Result of the examination of the blood: Spherical bodies, flagella; no crescent-shaped bodies.

Obs. 30.—Clinical form: Tertian intermittent fever (relapse)

(op. cit., p. 265). Result of the examination of the blood: Spherical bodies of medium or small size, flagella; no crescent-shaped bodies.

(B) *New observations.*

Obs. 25.—Clinical form: Tertian intermittent fever (relapse). Result of the examination of the blood: Spherical bodies, flagella; no crescent-shaped bodies.

Obs. 26.—Clinical form: Tertian intermittent fever (relapse). Result of the examination of the blood: Spherical bodies, flagella; no crescent-shaped bodies.

Obs. 27.—Clinical form: Tertian intermittent fever (relapse). Result of the examination of the blood: Crescent-shaped bodies; no spherical bodies.

Obs. 29.—Clinical form: Tertian intermittent fever (relapse). Result of the examination of the blood: Crescent-shaped bodies, spherical bodies, flagella.

Obs. 30.—Clinical form: Tertian intermittent fever, sixth relapse (tertian type). Result of the examination of the blood: Crescent-shaped bodies; no spherical bodies. Seventh relapse (tertian type). Result of the examination of the blood: Spherical bodies, flagella; no crescent-shaped bodies.

Obs. 31 and 32.—Clinical form: Tertian intermittent fever (relapse). Result of the examination of the blood: Crescent-shaped bodies, spherical bodies, flagella.

Spherical bodies, with or without flagella or crescent-shaped bodies, may, therefore, be met with in the blood of patients suffering from tertian intermittent fever. The crescent-shaped bodies have been found alone several times (Obs. 27 and 30). This latter observation is particularly interesting. During the sixth relapse of fever of tertian type I found only crescent-shaped bodies in the blood; at the seventh relapse, again with the tertian type, the blood contained spherical bodies and flagella without crescent-shaped bodies. In the fifth series of facts further examples of the co-existence of crescent-shaped bodies with tertian fever will be found. Obs. 46 especially deserves notice, and we shall return to it.

4th. *Quartan fevers.*—The observations of quartan fever which are found at the end of this volume are summed up exactly as follows, from the point of view of the relation which exists between the clinical form and the parasites:

Obs. 33.—Clinical form: Quartan fever (relapse). Result of the examination of the blood: No crescent-shaped bodies; spherical bodies.

Obs. 34 and 35.—Clinical form: Quartan fever (relapse). Result of the examination of the blood: Spherical bodies, segmented bodies; no crescent-shaped bodies.

Obs. 36.—Clinical form: Quartan fever (relapse). Result of the examination of the blood: Crescent-shaped bodies, spherical bodies, flagella.

Obs. 37.—Clinical form: Quartan fever (relapse). Result of the examination of the blood: Here again it must be noticed that the crescent-shaped bodies have been found in the blood, either isolated or joined together. In Obs. 37 the crescent-shaped bodies have been found to the exclusion of other parasitic elements. The segmented bodies have been noticed in Obs. 34 and 35.

I have never observed quartan fever but as a relapse, and all authors agree that this fever seldom begins with the quartan type. If there existed a special parasite for the quartan, it seems evident the quartan fever would be produced from the beginning of the attack.

5th. *Palustral fevers with variable type; patients observed at long intervals.*—Observations of this series may be summed up in the following table:

Obs. 33.—Clinical form: Tertian fever (relapse). Result of the examination of the blood: Crescent-shaped bodies, spherical bodies, flagella. New relapse of fever with quotidian and afterwards tertian type. Result of the examination of the blood: Crescent-shaped bodies, spherical bodies, flagella.

Obs. 39.—Clinical form: Intermittent quotidian fever. Result of the examination of the blood: Crescent-shaped bodies, spherical bodies, flagella. Relapse (pernicious phenomena). Result of the examination of the blood: Spherical bodies.

Obs. 40.—Clinical form: Tertian fever. Result of the examination of the blood: Spherical bodies, flagella. Relapse (quotidian attacks). Result of the examination of the blood: Crescent-shaped bodies.

Obs. 41.—Clinical form: Tertian, afterwards quotidian fever. Result of the examination of the blood: Crescent-shaped bodies, spherical bodies.

Obs. 42.—Clinical form: Quotidian fever. Result of the examination of the blood: Crescent-shaped bodies, spherical bodies. Relapse (tertian type). Result of the examination of the blood: Spherical bodies; no crescent-shaped bodies.

Obs. 43.—Clinical form: Palustral continued fever. Result of examination of the blood: Spherical bodies of small size; no

crescent-shaped bodies. Relapse (with the tertian, afterwards quotidian type). Result of the examination of the blood: Spherical bodies; no crescent-shaped bodies.

Obs. 44.—Clinical form: Quotidian fever. Result of the examination of the blood: Spherical bodies; no crescent-shaped bodies. Relapse of fever. Result of the examination of the blood: Spherical bodies, flagella; no crescent-shaped bodies.

Obs. 45.—Clinical form: Quotidian (relapse). Result of the examination of the blood: Crescent-shaped bodies, spherical bodies. Relapse (with the tertian type, and new relapse, quotidian attack). Result of the examination of the blood: Both relapses, spherical bodies; no crescent-shaped bodies.

Obs. 46.—Clinical form: Quotidian (relapse). Result of the examination of the blood: Spherical bodies, segmented bodies; no crescent-shaped bodies. Relapse (of fever, tertian type). Result of the examination of the blood: Crescent-shaped bodies; no spherical bodies Second relapse. Result of the examination of the blood: Spherical bodies; no crescent-shaped bodies.

Obs. 47.—Clinical form: Irregular fever (relapse). Result of the examination of the blood: Spherical bodies, segmented bodies; no crescent-shaped bodies.

It has been known for a long time that the type of fever is often modified in the same patient; it was interesting to know if the nature of the parasitic elements of the blood was modified at the same time as the type of the fever. Some of the observations of this fifth series would be favorable to this opinion, principally Obs. 40 and 42. In these two cases relapses with tertian type were accompanied with the presence of spherical bodies in the blood, and relapses with the quotidian type by the presence of crescent-shaped bodies. But Obs. 46 shows that the inverse ratio may be met; here it is the tertian fever which is marked by the presence of crescent-shaped bodies, and the quotidian fever with that of spherical bodies.

In Obs. 38 and 43 we see that the type of fever changes without the nature of the parasitic elements of the blood being modified.

Obs. 47 relates to an irregular fever, the type of which I have not been able to ascertain. Now in this case the presence of the crescent-shaped elements has never been noticed; this is contrary to what ought to have taken place in these circumstances if these elements were the parasites of the irregular fevers.

All these facts tend to prove that there exists no direct and

constant relation between the forms under which the hæmatozoa are seen in the blood, and the clinical manifestations of paludism; all we can say is that certain parasitic forms are oftener found in certain patients,—the crescent-shaped bodies, *e. g.*, in the relapsed fevers and in the cachectics, as I demonstrated long ago.

That several species of hæmatozoa of paludism exist does not receive more support from zoological theories than from clinical observation; but all the zoological theories which we possess at present concerning these parasites are very incomplete.

Is it, then, so difficult to understand that the same sporozoon may take different shapes?

I have quoted already (Chap. III) several examples of sporozoa which are seen under very different aspects,—*Lithocystis Schneideri, Eimeria falciforme, Depranidium ranarum;* and it would be easy to multiply examples.

In the laboratory of M. Metschnikoff, at the Pasteur Institute, I examined some parasites of the *Apus* which are fixed in the mobile gills; these parasites evolve by producing now amœboid, now crescent-shaped bodies; M. Metschnikoff, in showing me these facts, added that probably it was the same process that occurred with the hæmatozoa of paludism. The type of the fever is very probably much more likely to be determined by individual conditions than by the variety of the parasitic elements of the blood; we shall return to this point in the following chapter.

CHAPTER V.

In what form is the hæmatozoon of paludism found in the exterior media, and how is the infection produced?—Meteoric and telluric conditions which favour the development of paludism—Predisposing individual causes—Influence of race and age—Congenital paludism—Incubation—Pathology of the phenomena of paludism.

It might have been hoped that, as the different appearances which are taken in the blood by the parasites of paludism were known, it would be easy to find them in the surrounding media.

From the beginning of my investigations I endeavoured to find the forms under which the hæmatozoon of paludism existed in water or in earth; I have examined numerous samples of the water or soil of localities in Algeria where palustral disease prevails, and I have several times noticed the presence of organisms which have some analogy with the hæmatozoa of paludism in the stagnant water of the fever localities; chiefly amœboid bodies having one or several flagella similar to the spherical bodies of palustral blood,—with this difference, that the arrangement of the flagella was more regular in the Protozoa found in water. These organisms were not pigmented, but as the hæmatozoa of paludism probably borrow their pigment from the red blood-corpuscles, it was not to be expected that they would be found pigmented in the exterior media.

Maurel, who has met with these amœboid bodies or analogous organisms in an ordinary vegetable infusion, has pointed out the analogies which exist between them and the parasites of the palustral blood (Maurel, 'Recherches microscopiques sur l'étiologie du paludisme,' Paris, 1887, pp. 202—204).

Grassi and Feletti have noticed the existence of very small amœbæ with pseudopodia without contractile vacuoles in the soil of palustral countries; this amœba is encysted rather easily, and in that state may probably be carried by the atmospheric air, and it has been found in the nasal cavities of healthy young pigeons which had been placed for two nights in a palustral

locality, at a height of six feet from the ground. Nine days after, these pigeons had crescent-shaped bodies in their blood.

Grassi and Feletti compare this amœba with those described by Maurel, and seem disposed to believe that it is under this form that the parasite of paludism is found in the exterior medium.

The morphological resemblances are far from being complete, and the identification of these organisms with the hæmatozoa of paludism seems to me very rash. If the hæmatozoon of paludism lived in water and in the soil under forms identical with those which it possesses in the blood, there seems no reason why it should be difficult to cultivate it in the exterior medium by putting a few drops of the blood of a palustral patient in a little water or sterilised earth, a culture of the parasitic elements being then obtained; these attempts at cultivation have, so far, given only negative results.

It seems to me probable that the hæmatozoon of paludism exists in the palustral media in the state of a parasite on some animal or plant.

According to James, parasites which have a certain analogy to the hæmatozoon of paludism may be found in the vegetable kingdom; they are amœbæ provided with flagella at one phase of their development, and contain chlorophyll. This same fact has been pointed out to me by M. Certes.

We saw (Chap. III) that parasites near akin to the hæmatozoon of paludism are found in the blood of birds, and it is possible that the hæmatozoon of paludism itself exists in the blood of certain animal species.

Mosquitoes are always abundant in palustral countries, and it has been found that the drainage of the ground, which suppresses the fever, also drives away mosquitoes (Lamborn, 'La destruction des moustiques,' analysis in 'Revue scientifique,' 1890, p. 498). Possibly these insects play a part in the propagation of paludism as in that of filariosis.

For a long time the mode of propagation of filariosis was unknown. The filariæ, because of their size and the comparatively elevated group to which they belong, are, however, easier to study than the hæmatozoa of paludism; it is now known that the filariæ of man undergo one phase of their development in the bodies of mosquitoes. The mosquitoes, by sucking the blood of patients suffering from filariosis, absorb embryo filariæ, which develop themselves in the body of these insects. When the mosquitoes die and fall into the water, the filariæ escape and the

infection takes place through drinking water. Out of 140 female mosquitoes examined by Lewis, twenty were literally filled with filariæ.

Findlay, of Havana, thinks that mosquitoes are the principal agents of dissemination of yellow fever, and Hammond is of the same opinion.

The fact that it is difficult to find a form under which the hæmatozoon of paludism is met in the exterior world is not surprising when we know that it is a question of sporozoa; the history of the development of these entities is yet to be written (Balbiani).

Do the parasites get into the system with the water that is drunk or with the inspired air?

It seems to be a common opinion in the present day that air is seldom the vehicle of pathogenic agents, and that it is water which in most cases should be blamed. So far as paludism is concerned, both modes of infection seem possible; but while the infection through the air is generally admitted, so much so that the words *mal' aria* (bad air) have become synonymous with palustral fever, the infection through water is disputed by some authors.

Persons who have contracted paludism have almost always made use of the water of palustral localities, at the same time breathing the air, consequently it is difficult to say which has been the mode of infection.

Numerous facts tend to prove that the infection may take place through drinking water.

1st. It has been found repeatedly that in the same localities, among persons living under the same conditions, but drinking water from different sources, some were severely attacked by palustral fever while others escaped. (See principally my 'Traité des fièvres palustres,' pp. 458—464.)

2nd. In certain localities which were formerly insalubrious it has been sufficient to place pure water at the disposal of the inhabitants, instead of the stagnant water which was formerly used, for palustral fevers to disappear.

3rd. In some localities, otherwise very healthy, people may contract fever, whose drinking-water comes from unhealthy localities, and the persons most exposed to infection in these conditions are those who consumed most water.

4th. Travellers passing through unhealthy countries often succeed in escaping fevers by only drinking water that has been boiled, while people who do not take that precaution suffer severely.

It has been objected that the infusoria and the amœbæ are destroyed by the digestive apparatus.

The protecting action of the *normal* digestive juices is indisputable, but it often happens that this action, for some cause or other, takes place under unfavorable conditions, and loses much of its efficacy. The properties of the digestive juices may explain why a great number of persons escape from fever, whilst others, living in apparently identical conditions, are severely attacked.

In the case of the first, the digestive juices whose secretion was normal destroyed the parasites brought by the water; whilst in the others, alterations of the digestive apparatus and weaker activity of the digestive juices enabled the parasites to multiply and penetrate the system.

Bouchard and Legendre have laid stress on the predisposition to infectious diseases, and particularly to typhoid fever, which is the consequence of the alteration of the digestive apparatus, and principally of the dilatation of the stomach (Bouchard, 'Leçons sur les auto-intoxications dans les maladies,' 1887, and 'Thérapeutique des maladies infectieuses,' 1889, p. 91).

The following fact seems to me sufficiently convincing concerning the infection through water: Palustral fever is rarely contracted inside the town of Constantine, particularly at the Casbah, which is the highest point. During the summer of 1882 I received into my service several Government workmen employed in the Commissariat department, inside the Casbah; these men were suffering from palustral fever for the first time, and they asserted that for a long time they had not been out of Constantine. Having been employed at the oven, they had suffered much from heat, which outside reaches from 35° C. to 40° C. in the shade, and in the room adjoining the oven was over 50° C.; on account of this these workmen drank from six to seven litres of plain water every day between meals. It was natural that the digestive juices being diluted by the great quantities of water, taken without food, whilst the secretion was almost nil, were no protection to the system.

If the form under which the parasite of paludism is found in the exterior world and its method of penetrating the system are not yet understood, at least the causes which favour its development and its penetration into the blood are known; the study of these causes is most important, as it is the basis of prophylaxis.

Paludism is essentially an *endemic* disease; it is possible to

trace the regions in which it prevails, in the same way as naturalists show the regions in which such and such a plant is found and in which such and such an animal species has its habitat.

Paludism may appear in localities which for centuries have been free from it; in the Mauritius and the Isle of Bourbon, palustral fevers, formerly almost unknown, have greatly increased since 1867.

Fortunately it is more usual to see it decrease; the list is long of localities, of whole countries, which have been made healthy through cultivation of the soil.

In the eighteenth century palustral fevers were very common and very severe in Holland (Pringle). The immense works executed in order to protect the coast against invasion of the sea have considerably reduced the field of the palustral endemic.

We know by the writings of Morton, Willis, and Sydenham that palustral fevers were formerly prevalent in London, but the drainage of a marsh caused the disappearance of the fever.

Graves points out the happy results of the drainage of the ground in Ireland, and shows that in many places it has put an end to the palustral endemic ('Clinique,' t. i, traduction française, p. 3).

At Strasburg in 1832 not only intermittent fevers were still prevalent, but severe palustral fevers, complicated with pernicious phenomena; the dyking of the Ille and the Rhine, and the destruction of marshes have greatly reduced the fever.

In the Bresse, the Sologne, the Landes, and the Morbihan palustral fever is much less serious than formerly.

In Algeria paludism has almost completely disappeared from some localities where it raged at the beginning of the conquest; in all places the regular cultivation of the soil has caused it to recede.

The damp uncultivated marshy localities are those which offer to paludism a favorable medium. The existence of marshes, properly speaking, is not necessary; and, on the other hand, all marshes do not cause fever even in hot countries. At Tahiti, in Australia, and in New Caledonia palustral fevers are rare, in spite of the existence of marshes having all the objective characters of fever marshes, as Boudin has rightly remarked. Pommay has pointed out the innocuousness of marshes in the high plateaus of South Oranes (South Algeria) ('Revue d'hygiène,' 1884, t. vi, p. 184).

If the marsh, properly speaking, is not necessary, there must

at least be *humid soil.* Palustral fevers are not generated on ships at sea far from land; while in tropical countries, where ground has been dried for some time, the fevers disappear, though rain, especially when it does not last long, brings back the fever-giving qualities to the soil. The small rains which take place towards the end of the summer in hot countries, and which are soon dried up by the sun, are known to be very dangerous; the abundant rains which last a long time do not produce such ill effects, especially if at the same time the temperature falls.

The influence of heat is shown by the distribution of paludism on the surface of the earth. Palustral infection, unknown in cold countries, increases in intensity in proportion as one advances towards the equatorial regions; in the temperate and warm zones it only prevails in the hot season: it reappears every year with the same regularity, as is the case with certain animal and vegetable species.

At Rome the first case of reappearance of fever is observed every year almost exactly on the same day at the beginning of July (Mayer L. Colin, 'Traité des fièvres intermittentes,' 1870).

It is the same in Algeria; at Constantine for three consecutive years I saw the first cases of reappearance of palustral fever take place towards the end of June, and the last during November; from December to the following June I only observed relapsed fevers. From July to October the cases of fever are rapidly multiplied, which explains and justifies the expression of endemo-epidemic, often employed by authors who have written on Algerian fevers.

Thus during the winter the germ of paludism is in abeyance; like some animals it has its hibernating period, and, like them, it awakens at the beginning of summer.

The influence of altitude, of which there is no doubt, is explained by the lowering of the temperature to a large extent, and also by the fact that on high ground the waters having an easier fall, the soil naturally drains itself. Experience taught this happy influence of altitude long ago to the populations of palustral countries; the Arabs and the inhabitants of the Roman Campagna always retreat from the plains towards the mountains during the fever season.

The altitude which is sufficient to protect from fever is not very great, and this fact is extremely important for the prophylaxis of paludism. I mentioned before that in the interior of the town of Constantine fever is very rare; about one hundred yards below, however, near the gates of the city, on the banks of

the Rummel, paludism is both frequent and dangerous. It is the same at Bona; the upper town is spared, while in the lower part attacks of paludism often occur. It would be easy to multiply such examples. In a palustral country persons living in the upper storeys of a house are less exposed than those who live on the ground-floor. The germs of paludism, it would appear, rise with some difficulty into the atmosphere.

The winds which blow over a marshy district may carry the germs along, but not to a great distance. On the shores most infected with paludism the sailors escape as long as they remain in their ships; the sea air it is known is very pure, and the atmospheric dust soon disappears in the great mass of sea water.

Predisposing individual causes.—The influence of age and sex is small; if it is a fact that adult men are more frequent victims to paludism than women, young and very old people, this may be explained by the influence of their occupations, about which we shall speak later on.

Children are often attacked by paludism; according to Brun they are attacked in Egypt in a larger proportion than adults.

Men of all *races* are subject to paludism, but in a variable degree; the blacks, for instance, offer a much greater resistance than the Caucasians, a resistance which, however, does not go as far as conferring immunity, as was thought by Boudin. Palustral cachexia is not uncommon among the negroes, principally at Gaboon, Ceylon, and the Antilles, though very numerous facts show that when blacks and whites are transplanted into a palustral district the whites are attacked in a much larger proportion by paludism and present much graver forms of the disease than do the blacks, consequently negroes are valuable auxiliaries in a palustral country.

In the Mexican war the negroes who were brought from the Soudan were very useful in Terres Chaudes, owing to the remarkable immunity which they enjoyed, not only from the palustral fevers, but also from yellow fever.[1]

The Indians and the creoles are not spared; during the Mexican war a company of volunteer creoles was levied in the Antilles for

[1] Consult on this question: Graves, 'Clinique médicale,' trad. franç. de Jaccoud, 3me édit., t. i, p. 483. Boudin, "Acclimatement des races humaines," 'Rec. de mém. de méd. mil.,' 3me série, ts. xii, xiii, and xv. Laveran, article "Antagonisme" du 'Dictionn. encyclop. des sc. méd. Dutroulau, 'Traité des maladies des Européens dans les pays chauds,' 2me édit., Paris, 1868, p. 147. Corre, "De l'influence de la race dans les mal. infect.," 'Gaz. hebdom.,' 1869.

the Terres Chaudes, which was wasted rapidly under the influence of palustral fevers.

In Algeria I have often noticed paludism among the natives, but nearly always in forms milder and less acute than among the Europeans; the Arab has evidently a greater tolerance, either personal or hereditary, for the agent of paludism than has the European.

The most unhealthy occupations in palustral countries are those which bring man most often and most directly in contact with the soil. The workmen employed in drying up marshes, in digging harbours or ditches, navvies, gardeners, agricultural and harvest labourers, afford the largest number of victims to paludism.

Paludism is essentially a disease of the country, as typhoid fever is a disease of towns. In the central parts of Rome people are exempt from the fever which rages with violence in the Campagnia and even up to the gates of Rome (L. Collin, *op. cit.*). All weakening causes, for instance, fatigue, mental or physical strain, anæmia resulting from privation or previous disease, predispose to paludism.

It was long ago noticed that the parasites are developed by preference in weakened constitutions whose vitality is already lowered, just as mosses and lichens invade the trunks of sickly trees. It seems, says Pasteur, that life repels the life which wishes to graft itself on it; it is when an individual grows weak that it becomes an easy prey to the parasites which besiege it.

The results of the experiments made by Charrin and Roger, also by Canalis and Morpurgo, to determine the part of fatigue and fasting in the etiology of infectious diseases, agree entirely with the results of observation.

Rats which have been fatigued fall easy victims to an attenuated anthrax virus, which has no power on them in their normal state (Charrin and Roger, "La fatigue et les maladies microbiennes," in 'Semaine médicale,' 1890, p. 29).

In researches which were recently published by Canalis and Morpurgo (Rome, 1890) it is shown that by starving animals they can be made liable to diseases which they resist in their normal state; pigeons and hens deprived of food lose their immunity from anthrax. During the time of fasting the number of leucocytes in the blood is diminished (Canalis and Morpurgo), which might perhaps explain the disappearance of the exemption.

A first attack of paludism confers no immunity; on the contrary, individuals who have once had palustral fever are more

liable to contract it. It may be said that relapses are the rule; these relapses, however, do not imply a new infection, the agent of paludism being able to remain in a latent state for a long time.

Paludism can be inoculated by intra-venous injection, as we have seen, but it is not propagated by contagion from man to man.

"*Congenital paludism.*—A certain number of scientific observations exist which tend to prove that paludism may be congenital; these observations were made by Sue and Hawelka (Bouchut), by Playfair and by Duchek (Griesinger), by Bohn and by Bureau (Leroux, 'Revue de médecine,' 1882, pp. 569—575).

"Playfair reports the obervation of a woman who, during her first pregnancy, was repeatedly attacked every fortnight with remittent fever; the child at its birth showed so hypertrophied a spleen that its edge reached the umbilicus; the child had no fever till the age of two, but was pale and sickly. Duchek has observed a case exactly similar; the child died shortly after its birth, and presented a pigmented splenic tumour and pigment in the blood of the vena porta" (Griesinger, 'Traité des maladies infectieuses,' 2me édit., trad. franç., 1877, p. 20).

The observations of Chiarleoni show that the germ of paludism may attack the fœtus, and it often kills it when the mother is not submitted to quinine treatment. The children born at full time from mothers who have suffered during their pregnancy from attacks of palustral fever, but who have been treated by quinine, on the contrary, most generally show a normal development and the signs of good health ("Le paludisme et la fonction de la génération chez la femme," in 'Ann. univers. di Medicina,' April, 1886).

It was believed until recently that the placenta formed a perfect filter which prevented the microbes passing from the mother to the fœtus, and the existence of congenital paludism might appear in opposition to the parasitic nature of the disease (Leroux, 'Revue de médecine, 1882, p. 661).

Straus and Chamberland have shown that the microbes of symptomatic anthrax, of fowl-cholera, and of experimental septicæmia, passed from the mother to the fœtus ('Société de Biologie,' Nov. 11th, 1881), and that the anthrax bacillus itself is not always stopped by the placenta ('Société de Biologie,' Dec. 16th, 1882), contrary to the opinion of Davaine.

It can be understood that the hæmatozoa of paludism, which in their first phase of development are in the state of amœboid corpuscles, very small, free or intimately adherent to the blood-cor-

puscles, may be able to pass through the placenta. The transmission of paludism from the mother to the fœtus may easily be reconciled with the ideas concerning the parasitic nature of disease which exist at the present day.

In order to dispel all doubts concerning congenital paludism it would be interesting to examine the blood of the newly born child of a mother suffering from paludism, and thus to ascertain the existence of the hæmatozoon.

Guarnieri and Bignami experimented twice for hæmatozoa in the blood of fœtuses of three and six months respectively from cachectic mothers; in both these cases the examination was negative. No conclusions can be drawn from these negative facts; new researches are necessary.

Incubation.—A few authors have expressed the opinion that the invasion of paludism might be very rapid; the case has been often quoted of travellers attacked suddenly with pernicious symptoms while crossing a marshy district. In order for this fact to prove anything, it would be necessary to show, 1st, that the travellers had not already been for some time under the influence of paludism; 2nd, that the phenomena observed were really due to paludism, and not to other causes—as, for instance, heat apoplexy. Up to the present time this proof has not been forthcoming. I myself hold that there always exists a period of incubation, whose minimum duration may be from six to ten days.

"I have seen," says Maillot, "a large number of soldiers fall ill, who only left camps near the marshes ten or twelve days previously" ('Traité des fièvres,' p. 263).

I have already pointed out the following fact which I had occasion to observe:—A body of French troops landed at Bona in the summer, and marched by stages from Bona to Constantine, traversing localities well known to be unhealthy; on the march no case of paludism occurred. However, only a few days after the arrival at Constantine, where the men were located in very healthy barracks, symptoms of paludism appeared in a large number of the men; certain patients were seized a month or more after their arrival, whilst others were attacked seven or eight days after crossing the marshy districts.

Sorel has reported similar facts: "The encampment of Takitount, which is at an altitude of 1051 metres, and situated outside the ordinary zone of paludism, received on August 8th, 1881, a reinforcement of eighteen soldiers, who having landed at Bougie on August 3rd, started on the 6th. On the 18th twelve men of that detachment fell ill, and were admitted to the

hospital at Setif on the 19th. On August 21st and 24th two new patients of the same detachment were also sent into hospital, and in all the symptoms of paludism were unmistakably present."

As Sorel remarks, "it is evident that these men had contracted the germs on the road from Bougie to Takitount (one of the stations is very unhealthy), which would give from seven to nine days as the duration of the incubation in most cases" ('Archives de méd. militaire,' 1884, t. iii, p. 293).

In recent years paludism has been inoculated several times from man to man, as already has been mentioned (Chap. IV, p. 75); these facts of the experiments concerning paludism are interesting from the point of view of the incubation of paludism.

It is shown by the experiments of Mariotti and Ciarocchi, Celli and Marchiafava, Gualdi, and Antolisei and Angelini, that when palustral blood containing hæmatozoa is injected into the blood of a man free from paludism, the fever appears in the inoculated subject on an average ten days after the injection. These experiments were made in conditions very favorable to the infection, since the hæmatozoa were introduced directly into the blood.

The duration of the incubation given by the experimental process agrees exactly, as we see, with the data of observation.

The period of incubation may be very long; it should rather be called the *latent period;* it is not rare to meet people who never had fever in Algeria, but who shortly after their return to France suffered from very characteristic symptoms (Maillot, op. cit., p. 263).

Dutroulau ('Traité des maladies des Européens dans les pays chauds,' 2me édit., Paris, 1868, p. 233), after having given several examples of prolonged incubation of paludism, adds, "I might multiply greatly these examples, which all have the same signification, namely, a variable period of latency of the miasma before the onset of the fever. How far can this period extend? Up to the present time it is impossible to determine this."

The hæmatozoa of paludism may remain latent in subjects who have never had any symptoms of paludism, as well as in those who have been attacked once or several times.

Verneuil and De Brun have shown that this period of latency may be very long. De Brun gives the case of a man of fifty-one who had a relapse of African fever seventeen years after his return to France, and nineteen years after his last attack of fever; the surroundings in which this patient lived rendered a fresh infection impossible.

Any morbid cause, however—for example, a traumatism—may on occasions be the cause of the return of attacks; the traumatisms affecting the spleen more especially provoke fever (De Brun, "Les causes individuelles au somatiques de l'impaludisme," in 'La médecine moderne,' May 8th, 1890).

A period of latency as long as that shown by De Brun seems *a priori* very extraordinary. In order that the case quoted by this author should be unassailable, it would be necessary for the presence of the hæmatozoa of paludism to have been noticed in the blood at the time of the relapse; the appearance of attacks of fever more or less regular is not sufficient to characterise paludism. A nervous fever may at times be observed, which almost exactly resembles intermittent fever; this I have observed frequently in old palustral patients. This nervous fever, which is observed in anæmic and neurotic patients, is not much influenced by quinine; it disappears after a few days without any treatment being necessary.

How do the hæmatozoa when once introduced into the blood produce the phenomena of paludism?

The phenomena of paludism, it seems to me, may be attributed in great measure, 1st, to the alterations of the blood produced by the hæmatozoa; 2nd, to circulatory disturbances, and the irritation which the presence of these parasites causes in the tissues, and principally in the nerve-centres.

The hæmatozoa live at the expense of the normal elements of the blood. The invaded red blood-corpuscles grow paler and paler in proportion as the parasites develop, and even their contours at last disappear. It may be said that no anæmia, except the anæmia resulting from hæmorrhage, can be better explained than palustral anæmia.

The pigment, which is so abundant in the small vessels of all the organs in subjects who have died from pernicious attacks, also shows that the hæmatozoa are extremely destructive to the red blood-corpuscles.

Moreover anæmia is the most constant symptom of paludism. All the authors who have described palustral phenomena have insisted on the rapidity with which anæmia takes place. A few grave attacks are sufficient to make a patient unrecognisable, so marked does the anæmia become. Certain patients become anæmic and fall into cachexia without having any fever. Anæmia constitutes with them the principal and, so to speak, solitary symptom of the infection.

Frerichs, who had been struck with the abundance of the

pigment in the capillaries of tho brain of subjects who had died from pernicious fever, was the first to advance the theory that the thrombosis produced by the accumulation of the pigment plays an important part in certain phenomena of paludism.

This opinion has been the subject of severe criticism; it was indeed difficult to understand how these thrombi, formed of pigment, should rapidly vanish and give rise sometimes to intermittent symptoms. There were also objections on account of the action of quinine, which did not very well agree with the theory of pigmentary thrombosis.

The fact that the thrombus is formed not of inert material, as Frerichs thought, but of parasitic elements, allows of the possibility of the obstruction being removed tolerably quickly (though, after all, this is not always the case); also it explains why quinine has often great efficacy.

The paralysis and transient aphasia which are sometimes observed during the paroxysms of the fever may be satisfactorily explained by temporary obstructions limited to certain vascular areas of the brain.

The capillary hæmorrhage, which is not rare (especially in the brain) in subjects who have died from pernicious attacks, would appear to result from the same cause.

The obstruction of the capillary vessels by the hæmatozoa is not an hypothesis; it is a fact easily verified, especially by the examination of the brain-capillaries of subjects who have died from pernicious attacks with delirious or comatose symptoms.

Bignami found very extended parasitic thrombosis of the intestinal and gastric mucous membrane in certain subjects who had died from choleraic pernicious attacks.

It may be easily understood that the presence of the hæmatozoa provokes hyperæmia, vascular congestions, and inflammations. When patients recover rapidly the congested organs soon resume their normal size. In the long run the irritation produced by the presence of the parasites and by the repeated congestions accruing from it ends in chronic inflammation, whose seat of election is naturally the viscera which are more specially the habitats of the parasites.

It is thus that the spleen in old palustral patients constantly shows inflammatory alteration, interstitial splenitis, and perisplenitis. Chronic hepatitis and nephritis follow in order of frequency; I have also sometimes noticed chronic pneumonia.

The lesions of chronic inflammation once established in a viscus persist, even grow worse, after recovery from paludism.

For this reason cirrhosis of the liver or chronic nephritis continue to develope in patients who have not had any attacks of fever for a long time.

The presence of hæmatozoa in the small vessels of the cerebro-spinal centres furnishes a satisfactory explanation of the nervous symptoms, headache, pain in the back, delirium, convulsions, and coma (pernicious attacks). The initial cold of the onset is essentially a nervous phenomenon; as for the rapid elevation of temperature, the opinions now held concerning the physiology of the spinal cord shows that symptom also to be attributed to the irritation of this organ.

In filariosis accompaniments of fever identical with those of paludism may be observed, but they do not answer to a regular type.

Intermittency is very far from constituting a constant characteristic of paludism, and it is often wrong to employ the expression intermittent fever to designate this malady.

Palustral irregular continued fevers, cachexias of the first onset, intermittent fevers with variable types, &c., are often observed alongside intermittent fever with a regular type, especially in the hot countries where paludism prevails with intensity.

On the other hand, intermittency is not peculiar to the phenomena of paludism; it has been noted frequently in neuralgias which were not of palustral origin, and even in traumatic nephritis (W. Mitchell, 'Des lésions des nerfs et de leurs conséquences,' trad. de Dastre, Paris, 1874).

The hectic fever of tubercular disease is a quotidian intermittent fever, the difference being that the paroxysms occur in the evening and, unlike quotidian fever of palustral origin, resist treatment by quinine.

Certain affections of the liver may also provoke intermittent symptoms (J. Cyr, "De la périodicité de certains symptômes hépatiques," 'Arch. gén. de méd.,' May, 1883).

Verneuil and Mathon have shown that wounds of the spleen in subjects free from paludism and living far from palustral centres might give rise to periodic attacks of fever (Verneuil, 'Du paludisme considéré au point de vue chirurgical,' 1883, p. 4; Mathon, 'De la splénite traumatique,' Thèse, Paris, 1876).

"It is certain that the contusions of the spleen are sometimes followed by periodic fever, but that symptom does not belong more exclusively to palustral intoxication than does delirium to alcoholic intoxication, or the paralysis of the radial extensors to saturnine poisoning. Moreover the liver and kidneys, together with the spleen, possess the property of creating a febrile con-

dition with regular returns. Lastly, every one knows there is a specific intermittenco and a symptomatic intermittence in very varied morbid states" (Verneuil, op. cit., p. 5).

The knowledge of the fact that injuries of the spleen often produce intermittent symptoms is very important, for with palustral patients it is certainly the spleen which is the most affected of all the viscera by the presence of the parasites, and there is nothing exaggerated in comparing the invasion of this organ by the myriads of parasites to an injury.

Observers who, like Councilman and Golgi, have examined the blood of the spleen in patients with paludism, have noticed the parasitic elements in much greater abundance than in the blood taken at the periphery; thus Councilman succeeded sixteen times out of twenty-one in finding the flagella in the blood of the spleen, these bodies being much rarer in the blood obtained by the pricking of a finger.

Pathological anatomy also shows that the spleen is the hotbed, if I may so say, of the parasites of paludism. Whether death occurs after acute symptoms or as the result of cachexia, it is always the spleen which shows the most characteristic lesions in palustral patients.

In the individuals who succumb rapidly to pernicious attacks the spleen is found to be softened and often reduced to a jelly; the softening is such that the splenic pulp is fluid to the touch. The increase of volume is sometimes small, but the spleen always presents a characteristic brownish hue due to the abundance of the pigmented parasitic elements. When making the histological examination of the splenic pulp a few hours after death parasitic elements are again found, and specially the crescent-shaped bodies; but these hæmatozoa soon lose their shape, and are easily confounded with melaniferous leucocytes.

In palustral cachexia the splenic hypertrophy is constant and often enormous.

What is difficult to explain is not the intermittency, but the regularity of the intermittency; the existence of different regular types of palustral fevers makes the question still more complicated.

The first idea which comes to one's mind is that the hæmatozoa which are developed in the spleen and in the medulla of the bones migrate at times into the general circulation, and there give rise to the febrile paroxysms, or else that successive generations of these parasites are produced.

Filariosis and recurrent fever offer very curious examples of

parasites which are only seen intermittently in the general circulation.

During the day the filariæ retire into the deeper vessels; it is only towards six or seven o'clock in the evening that the parasites appear in the small subcutaneous vessels, with a military punctuality, as Cobbold remarks.

In patients suffering from relapsing fever the spirilla in the blood obtained by pricking a finger will be observed only during the febrile paroxysms; in the intervals of apyrexia the spirilla are only found in the spleen, and they are generally enclosed in the cells of this organ (Metschnikoff).

It is a little before and at the beginning of the febrile paroxysms that the hæmatozoa are seen in great numbers in the blood of the peripheral capillaries.

When these parasites are found in abundance in a patient who has not had any attack for a long time, one may infer with certainty that a relapse is imminent.

It is therefore reasonable to suppose that a direct relation exists between the febrile paroxysms of paludism and the multiplication of hæmatozoa in the blood, but the appearance and disappearance of the parasites in the general circulation do not correspond sufficiently exactly with the paroxysms and the intervals of apyrexia to explain the intermittence.

The hæmatozoa do not disappear from the general circulation after each attack, very far from it; I have often met them in abundance and with their most characteristic forms in the intervals of apyrexia.

Some authors have admitted the existence of different parasites for the tertian, quartan, and irregular fevers; we have seen (Chap. IV, p. 128) that this hypothesis, which was advanced by Golgi, is anything but proved, and that the existence of a single polymorphic parasite was much more probable: this question will not require further comment.

Experiments show that after febrile paroxysms the hæmatozoa disappear in part from the general circulation, and that the melaniferous leucocytes which result from the destruction by the hæmatozoa are then found in considerable numbers in the blood. The absorption of the hæmatozoa by the phagocytes, which become more active during the attacks of fever, is, as I said in 1884, probably one of the causes of the intermittency.

Roux and Chamberland proposed a theory in order to explain the intermittency of recurrent fever, which might also apply to the other palustral attacks. After having remarked that during

the febrile paroxysms free spirilla are found in the blood which disappear in the intervals of apyrexia, Roux and Chamberland add, "The body of a patient acts as a medium of culture favorable at certain times and unfavorable at others. Might not the fact of the intermittence be partly explained by the presence in the tissues after each abundant culture (*i. e.* moment of the attack) of substances elaborated by the parasite, and through which by their accumulation its development is obstructed? The spirilla which are hindered in their evolution are the prey of the phagocytes, while the antiseptic matter being eliminated or destroyed in the blood, the medium of culture is again favorable, and the spirilla multiply and the attack returns at the same time that free spirilla reappear in the blood" ("Immunity against Septicæmia conferred by Soluble Substances," 'Annales de l'Institut Pasteur,' 1887, p. 572).

In his very remarkable "Essai d'une théorie de l'infection" ('Congrès de Berlin,' 1890) Professor Bouchard writes, "One thing seems certain to me; it is that the bacteria act on animals by the matters which they secrete:" and further, "The fever of the infectious diseases is toxic; it is provoked by diastases such as that studied by Roussy, by ptomaines such as the amidaleine of Brieger."[1]

The general laws which are so well formulated in this work only concern the bacteria. As I have had occasion to remark before, the hæmatozoa are too far removed from the schizophytes for it to be possible to infer the mode of action of the one from the other.

The investigations of Brousse, of Roque, and of Lemoine tend to prove that the urinary toxicity is increased in paludism after attacks of fever.

Brousse arrived at the following conclusions:

1st. The uro-toxic coefficient calculated with the formula of Bouchard, the average coefficient being 0·464, rises during the attack; and the physiological effects observed are those which are generally noticed after the injection of urine: dyspnœa, myosis, fall of temperature, exophthalmia, and, even, convulsions. 2nd. This toxicity decreases during the period of convalescence of the intermittent fevers, and is very inferior to that of the urine during the attack, and besides weaker than that of

[1] See also on this subject: Bouchard, 'Actions des produits sécrétés par les microbes pathogènes,' Paris, 1890. Roussy, 'Communic. à l'Acad. de Méd.,' Feb., 12th, 1889. Du même, "Recherches expérim. sur la pathogénie de la fièvre," Arch. de physiologie,' Paris, 1890, p. 355.

the normal urine ('Société de Méd. et de Chir. pratiques de Montpellier,' May 14th, 1890).

Roque and Lemoine are still more affirmative than Brousse; according to these observers the urinary toxicity would rise to a much larger proportion after the attacks of palustral fever, and the alteration of the kidneys and the liver increases the gravity of the attacks by hindering the elimination of the toxic products ("Recherches sur la toxicité urinaire dans l'impaludisme," 'Revue de méd.,' 1890, p. 926).

The facts quoted by Roque and Lemoine are very few in number, and the general conclusions which they draw from them do not seem sufficiently justified.

The toxicity of the urine after an attack of intermittent fever ought to be compared not only to the toxicity of normal urine, but also to the toxicity of the urine after attacks of fever of equal intensity to the palustral attacks, but depending upon other causes.

In the urine of all fever patients an increase of the normal toxicity is found, as well as new toxic properties, principally the convulsion-causing property (Bouchard, 'Leçons sur les auto-intoxications,' Paris, 1887, p. 256).

I made lately some experiments on the toxicity of the urine voided after an attack of intermittent fever, and I have not noticed the great toxicity of such urine pointed out by Roque and Lemoine; however, I can conclude nothing from this. Before giving any decided opinion on the degree of toxicity of the urine in patients with palustral fevers, it will be necessary to collect a large number of data.

Certain patients become cachectic without having had any attack of fever, which renders the secretion by the hæmatozoa of a substance analogous to pyretogenine very improbable.

We see from the researches of Nuttall and Buchner that the blood and the serum of the blood have in some cases a destructive action on the microbes, apart from all influence of the leucocytes. This action is soon exhausted; it disappears when the blood or the serum is heated to 55° C. (Buchner, 'Centralbl. f. Bacter.,' June 14th and 28th, 1889; 'Anal. in Arch. de Méd. expérimentale,' 1889, p. 872.

Fodor and Lubarsch have shown the bactericidal action of the blood of the rabbit on the anthrax bacilli. In order to explain that, in spite of this action, the rabbit remains very susceptible to anthrax, these observers suggest that it is the parenchymatous organs which allow the bacilli to escape the destroying influence

of the blood; in other words, the bacilli meeting a hurtful influence in the blood of the vessels take refuge in the spleen, the liver, and medulla of the bones, where conditions much more favorable to their development would be found.

Perhaps something similar takes place in the case of the hæmatozoa of paludism, whose seat of election is in the spleen, liver, and medulla of bones; this would explain why parasites cannot be cultivated in the blood outside the organism. The degree of irritability of the nervous system, which varies with individuals and with the date of the infection, seems to play an important part in determining the type and form of the fever. If it is a strong person who has palustral fever for the first time the nervous system reacts strongly against a morbid agent to which it is not accustomed, and a continued fever, or at least a quotidian, is observed. If the patient is already anæmic, or weakened by several attacks of fever, the nervous system having become less sensitive, a fever with long intermissions then takes place.

The nervous system gets accustomed to the presence of the hæmatozoa, and reacts less and less. Among persons who have lived for a long time in palustral countries, or who have had several attacks of paludism, the attacks of fever are generally rare and slight, though those who have newly come suffer from fever of great frequency and severity.

CHAPTER VI.

Means of defence of the organism—Spontaneous cure of paludism—Rôle of the phagocytes—Tonic treatment—Specific action of quinine—Different modes of its administration—Prophylaxis of paludism.

When morbid germs have succeeded in entering the blood the human organism is not absolutely at their mercy, as would be the case with an inert medium of culture in which these germs have been sown; the living organism continues to defend itself against their action.

This law of general pathology applies well to paludism. Patients with palustral fever, even when the properties of quinine were not known, did not all die—far from it; while to-day cures called spontaneous, that is, without the use of quinine, are not rare.

In this struggle of the organism against the hæmatozoa the leucocytes seem to play an important part.

It has been known for a long time that if a substance insoluble in the serum and finely pulverised be injected into the blood of an animal, the leucocytes seize this powder rapidly and eliminate it from the blood (Ponfick, Hoffmann, Langerhans). By mixing some frog's lymph with cinnabar powder and examining under the microscope the leucocytes may be seen attacking the coloured granulations and absorbing them. The phenomenon becomes more apparent if by the help of a hot stage the temperature of the preparation be raised.

We learn from the investigations of Metschnikoff that the leucocytes seize not only the inert dust and the dead microbes, but also in a great many cases the living pathogenic microbes, and consequently this property of the leucocytes, or *phagocytosis,* plays a very important part in the evolution of the infectious diseases and the phenomenon of immunity. The cells of the splenic pulp, the cellules of the endothelium, of the subcutaneous tissue, and of the pulmonary epithelium, take part in this work. The name of *macrophages* has been proposed by Metschnikoff to

distinguish these latter elements, which are in general much larger than the leucocytes or *microphages*.[1]

Metschnikoff thinks that the phagocytes are the principal agents of recovery in relapsing and palustral fevers; in other words, they are the principal agents of the destruction of the parasites in the blood which are the cause of these two diseases.

In relapsing fever the spirilla of Obermeyer, which are found in very large numbers in the blood at the time of the attack, disappear during the apyrexia. Metschnikoff has been able to study this disease in the case of the monkey, which is easily inoculated with the spirilla.

"At the beginning of the attack, when spirilla are found in every drop of blood taken from the peripheral vessels, the spleen is still entirely free from them.

"In a more advanced stage of the disease the number of the spirilla in the spleen is very much smaller than in that of the blood. This state of things changes radically towards the end of the attack, for at that time all the spirilla are transported into the spleen. But at the beginning of the apyrexia only a very small number of microbes are free; most of the spirilla are absorbed by the leucocytes having multiple nuclei, which are abundant in the substance of the spleen. All the contents of the microphage are often found to be filled with spirilla, which makes them a shapeless heap of filaments. I have never been able to find any spirilla inside the macrophages or in the lymphoid cells having a single nucleus, which constitute the corpuscles of Malpighi.

"In a more advanced stage of the apyrexia it was much more difficult to find the spirilla again, but I have been able to ascertain their existence within the microphages of the spleen thirty-two hours after the crisis."

To sum up, "the attack lasts as long as the spirilla are living free in the blood, and ends when these parasites become the prey of the phagocytes" (Metschnikoff, 'Annales de l'Institut Pasteur,' 1887, pp. 329, 330).

[1] Metschnikoff, "Maladies parasitaires et digestion intra-cellulaire" ('Revue scientifique,' 1886). The same, "Sur la lutte des cellules de l'organisme contre l'invasion des microbes" ('Ann. de l'Institut Pasteur, 1887, p. 321). The same, "Études sur l'immunité" (même recueil, 1889, p. 289; and 1890, pp. 67 and 193). Gamalcia, "Sur la destruction des microbes dans les organismes fébricitants" (même recueil, 1888, p. 229). Bouchard, 'Thérapeutique des maladies infectieuses,' 1889, pp. 92—95. The same, "Essai d'une théorie de l'infection" ('Congrès de Berlin,' 1890).

"In studying the internal organs of two fatal cases of malarial fever I have been able to convince myself," writes Metschnikoff (loc. cit., p. 328), "in a very marked manner of the action of the phagocytes in this disease. It is principally the macrophages of the spleen and the liver which absorb quantities of malarial parasites, often in surprisingly large numbers, which belong to the neighbouring group of Coccidia."

The description of the researches of Metschnikoff concerning the phagocytes in the parasitic disease of the Daphnia, in the septicæmia of mice, and in anthrax would take me too far. It is sufficient to say that these works seem to me quite conclusive concerning the important *rôle* which has been assigned by Metschnikoff to the phagocytes.

Wyssokowitsch ('Zeitsch. f. Hyg.,' 1886, Analyse par Netter in 'Bulletin méd.,' 1887, No. 12) has experimented on eighteen varieties of microbes, principally on the staphylococci, the streptococci, the anthrax bacillus, the bacillus of typhoid fever, the comma bacillus, the pneumococcus, and the tetragonus. Whatever may be the nature of the microbes injected into the blood of an animal, their number soon decreases. If it is microbes non-pathogenic to the animal under experiment they are not found in the blood for more than three hours after the injection; if the microbes are pathogenic their number, after having diminished, increases very much in proportion as the symptoms induced by their presence manifest themselves.

The microbes are deposited in the capillaries of the organs which have a slow circulation—the spleen, liver, medulla of bones—and they are absorbed and slowly digested by the cells of the endothelium.

The resistance of the microbes deposited in the spleen or in the medulla of bones may be long. Wyssokowitsch found that some spores of the *Bacillus subtilis* which were in the spleen were still alive after three months—a fact which is interesting in the study of latent microbism.

I explained in my first publications the destruction of the parasites during the febrile attacks by the action of the leucocytes. "It is known that under the influence of artificial heat the leucocytes acquire a very great activity; the amœboid movements are exaggerated, and if the pigmented granules are placed in contact with leucocytes it is found that they seize and absorb them very rapidly. Febrile heat certainly acts in the same way as artificial heat in this experiment; in the fever patient the activity of the leucocytes is exaggerated, and the parasitic elements become their

prey more easily than in the individual whose temperature is normal" ('Traité des fièvres palustres,' p. 479).

Since then Metschnikoff, Golgi, Gamaleia, have laid stress on the *rôle* of febrile heat in the destruction of microbes.

Golgi, in his work on 'Le Phagocytisme dans le Paludisme,' which dates from 1888, allows, as I did in 1884, that the destruction of the parasitic elements by the leucocytes plays an important part in the phenomenon of the intermission, and that the febrile process increases the activity of the white corpuscles, and consequently makes the destruction of the parasitic elements more rapid.

Gamaleia, in a treatise on 'La destruction des Microbes dans les Organismes fébricitants,' arrived at the conclusion that the febrile period of the infectious diseases accompanies the destruction of the bacteria—a conclusion which applies well to the parasites of paludism.

On the contrary, the activity of the phagocytes is lessened by cold.

It is seen from the researches of Wagner that if fowls kept in the cold can take anthrax disease, as the celebrated experiment of Pasteur proves, this is caused by the fact that in them the leucocytes lose a part of their activity. The same effect may be obtained by lowering the temperature of the fowls by means of antipyrin.

According to Alexander the number of spirochetæ in recurrent fever increases when the temperature is lowered by antipyrin ('Bresl. arztl. Zeitsch.,' 1884, No. 11).

The existence of melaniferous leucocytes, which are often numerous after attacks of intermittent fever, and specially after grave attacks, shows that the leucocytes take possession of the débris of the parasitic elements, and the pigment which they contain.

But the leucocytes do not only seize on the dead parasites, they also take possession of the living ones; this sometimes may be ascertained by direct examination of the blood. The leucocytes which are attached to the parasitic elements are in process of absorbing them.

Golgi, who has made a series of punctures in the spleen at the different stages of attacks of fever, and also during the apyrexia, observed that the phagocytic forms are much more numerous in the splenic pulp than in the blood of the general circulation, especially during the initial stage of the attacks.

Danilewsky has noticed that phagocytosis has an important

rôle in the destruction of the hæmatozoa of birds ("Contrib. à l'Étude des Phagocytes," 'Ann. de l'Institut Pasteur,' 1890, p. 432).

The organism, therefore, may triumph over the hæmatozoa when left to its own resources; it contends with all the greater advantage when it is placed in satisfactory general conditions; therefore all weakening causes hinder the cure of paludism, while a tonic treatment favours it. I have observed the same fact in the animals whose blood contains hæmatozoa. Under the influence of abundant food the hæmatozoa were seen to disappear, whilst want of food favoured their development.

Patients who have become anæmic, who are worried, badly fed, have constantly relapses of fever, quinine itself becoming, so to speak, powerless to prevent these relapses; on the contrary, under the influence of good regimen and rest alone, the state of palustral patients frequently improves; the anæmia disappears, the relapses are rarer, and recovery may be obtained without any more active treatment by the simple fact that the organism has been placed in good hygienic conditions. All tonics have, therefore, a favorable action on the disease, wine, coffee, and arsenious acid taking the first place. Arsenic taken in small doses does great service in treatment of obdurate fevers and of palustral cachexia; on the contrary, when given in strong doses, according to Boudin's method, thereby provoking gastric troubles (diarrhœa or vomiting), relapses of fever often take place, and the state of the patient becomes worse.

Hydrotherapeutics are of great value, always as a tonic treatment; it sometimes succeeds when other treatment has failed: it must be remembered, however, in having recourse to this method, that the first trial may provoke a relapse. It is necessary to act with prudence, and it is always advisable to begin by short and tepid douches before trying the cold douche; the spleen should not be douched at first, and a few doses of quinine should be prescribed at the same time as the douche. It can be easily understood that a cold douche, especially if brought to bear on the splenic region, may be followed by an attack; the vessels of the spleen being contracted, the hæmatozoa are again put in circulation.

Palustral patients who have taken the waters as baths at hot springs—Vichy, for instance—also often have relapses at the beginning of the treatment unless care is exercised.

The fact that a change of climate is extremely favorable to patients who have contracted fever in hot countries is explained

by the strengthening influence of colder climates; severe heat is very weakening; the abundant perspiration, sleepless nights, dyspepsia which is almost continuous, weakens the organism; and it is not surprising that a very rapid improvement should take place in the state of patients who are able to leave the hot countries for the temperate.

The tonic treatment, which is very efficient in the chronic forms of paludism, is evidently insufficient in the grave fevers which may rapidly cause death. Fortunately we possess a remedy really and truly specific, marvellously efficacious in paludism—quinine.

The action of quinine on patients suffering from pernicious attacks, distressed by noisy delirium or sunk in coma, must be watched in order to have a just idea of the services of quinine in the treatment of paludism. In the simple intermittent fevers one or two doses of quinine are sufficient to *cut short* the fever; this expression—cut short the fever—is very appropriate here. It can be ascertained by examining the thermometric tracings of patients suffering from intermittent fever, who have had several attacks and have taken quinine; after doing so the fever stops suddenly; the line which was so irregular during the attacks becomes suddenly horizontal. No other fever is thus cut short by quinine, which is really the specific of paludism.

Cinchona was known and much appreciated in England as far back as 1660, under the name of Peruvian bark; but the cinchona powder was very difficult to administer, especially in grave fevers; at any rate, the slowness with which the absorption of cinchona took place was very detrimental to the treatment of these fevers. Pelletier and Caventou have rendered an immense service to therapeutics by isolating quinine.

Although the febrifuge properties of quinine have been known for a long time, it has not so far been known how this medicine acts; the numerous experiments made on animals or on healthy persons in order to solve this question have really, it may be said, only obscured it the more. To attempt to demonstrate the action of quinine in paludism by experimenting on healthy men or animals is the same as studying the action of the pomade d'Helmerich on the itch by rubbing this pomade on men or animals not suffering from that disease. Experimenting on the physiological action of quinine could not possibly show how this medicine cures paludism.

In 1867 Binz published experiments which showed that paludism was produced by bacteria, and that sulphate of quinine cured

palustral fever by killing the bacteria (Binz, 'Arch. de Max Schultze,' 1867).

The conclusions of Binz did not stand criticism; the bacteria described by him had no particular characteristic. On the other hand, Vulpian and Bochefontaine showed that bacteria are very slightly sensitive to the action of quinine. According to Vulpian, in order to destroy bacteria in the blood it would be necessary to give fever patients more than 30 grms. of hydrochlorate of quinine for a dose ('Cours d'Anat. pathol., 1871).

The numerous experiments of Bochefontaine show that the vibriones are destroyed with difficulty by quinine ('Arch. de Physiol.,' 1873, 1st series, t. v, p. 390); in frogs made bacteri-hæmic by the injection of cyclamine under the skin, sulphate of quinine does not destroy the bacteria which multiply in the blood.

Quinine does not kill the algæ nor the fungi which have often been assigned as being the cause of paludism. The palmellæ also are easily developed in a solution of sulphate of quinine (Wood, 'American Journal of Medical Science,' 1868).

The penicillium can live and flourish in a concentrated solution of sulphate of quinine (Bochefontaine). In the military hospitals in Algeria the bottles which contain a solution of sulphate of quinine, at a strength of 1 in 20, are almost always covered with fungi on their inner surface if they are not frequently and carefully cleaned.

These objections, quite justifiable as to the bacteria of Binz and the palmellæ of Salisbury, have no force when it is understood that the parasites of paludism belong not to the Schizophytes nor to the Algæ, but to the Protozoa.

It has been known for a long time that the Protozoa are very susceptible to the action of quinine. It is sufficient to add a very small quantity of quinine to any infusion containing a large number of infusoria, for them to be killed in a few minutes (Bochefontaine, op. cit., 404).

On the other hand, it is well known that the hæmatozoa disappear rapidly in patients submitted to quinine treatment. One conclusion only remains, namely, that quinine cures the fever by killing the hæmatozoa.

The action of quinine on the hæmatozoa may be studied directly by mixing a drop of solution of sulphate or hydrochlorate of quinine to a drop of palustral blood; in these conditions it can be noticed that the movements of the flagella are no longer observed, and that the hæmatozoa assume their dead forms. The disap-

pearance of the parasites in the blood of patients submitted to quinine treatment is another clear proof that quinine destroys the hæmatozoa.

It may be objected that many substances have antiseptic and antiparasitic properties superior to those of quinine without being antidotes of paludism.

If parasiticides like iodine or mercury could be introduced into the blood in sufficient doses, these medicines would no doubt destroy the hæmatozoa of paludism as well, and even much better than quinine; but these agents are very strong poisons to man himself, and therefore cannot be made use of to kill the parasites living in the upper part of the digestive tube.

The particular sensibility of the hæmatozoa to quinine is, after all, nothing very surprising. Certain parasites are sensitive to the action of substances which do not act on others. The root of the pomegranate tree and the ethereal essence of male fern, so useful against tænia, have no effect on ascarides; while santonine, which is efficient against ascarides, has no influence on tænia.

Raulin has shown that in order to prevent the development of the *Aspergillus niger* in a liquid, it was sufficient for the liquid to contain $\frac{1}{1600000}$ of nitrate of silver. If the *Aspergillus niger* were a parasite capable of developing itself in the blood of man it would be sufficient to administer 40 milligrammes of nitrate of silver in order to stop its multiplication in the blood of a man weighing about 150 lbs. (Duclaux, 'Ferments et Maladies,' Paris, 1882, p. 47).

A continued observation of the blood of palustral patients submitted to quinine treatment affords the opportunity of ascertaining the effect of the treatment; the parasitic elements immediately become scarcer; the spherical bodies and the flagella disappear first, the crescent-shaped bodies resisting much longer.

This variable resistance of the parasitic elements explains the frequency of the relapses. If the hæmatozoa of paludism were all found in the blood in the same stage of development, it would be difficult to understand why quinine destroys some and not the others.

The bodies which have resisted quinine give rise to a remultiplication of parasites which it is necessary to check by repeated treatment without waiting for the relapses.

This method of treatment may be compared to the sterilisation of the liquids of cultivation by the intermittent heating to 100° C. By heating to 100° C. most of the microbes enclosed in the liquid are destroyed, but some spores resist; by heating again to

100° C. after twenty-four hours the spores which are developed, and which in their new form have become more sensible to the influence of heat, may be killed. Thus it is sufficient to heat a cultivation liquid three times to 100° C. at twenty-four hours' interval in order to bring about a complete sterilisation.

It has been seen that the phagocytes play an important part in the destruction of the hæmatozoa; the question may therefore be asked whether the efficacy of the quinine treatment is not partly due to the fact that under the influence of quinine the action of the phagocytes is exaggerated.

Some experiments by Binz seem to prove that quinine paralysed the amœboid movements of the leucocytes; Hayem and Bochefontaine have ascertained, on the contrary, that these movements were not impeded by the quinine.

Probably the phagocytes take up the hæmatozoa when these have been killed or paralysed by quinine, but the activity of the phagocytes is most likely not directly influenced by quinine treatment.

How should quinine be prescribed in paludism?—under what form and in what dose?

As a general rule it may be said that in ordinary cases of simple intermittent fever quinine should be prescribed internally by the mouth, whilst in grave forms requiring a rapid intervention recourse should be had to the hypodermic method; the latter mode of treatment must also be adopted when patients who are suffering from simple fevers do not easily stand quinine administered by the mouth, also when vomiting occurs.

The endermic method, which consisted in the absorption of the salts of quinine by the skin deprived of the epidermis, and of enemata of the sulphate of quinine, was useful at times before the hypodermic method was known, but is now out of date.

In prescribing enemata of quinine one can never be sure that the dose will not be rejected before the absorption of the medicine has taken place, and it is always impossible to gauge exactly how much has been absorbed.

The hydrochlorate of quinine should be prescribed in preference to the sulphate of quinine. It contains 81 per cent. of quinine, while the bisulphate itself only contains 59 per cent.; it is more stable, more soluble, and easier to obtain pure than the sulphate of quinine (Dujardin-Beaumetz, 'Société de Thérapeutique,' March 23rd, 1887).

According to the researches of Beurmann, of Regnauld, and of Villegean quinine should be classified as follows: 1st, from its

contents in alkaloid; 2nd, its solubility ('Bulletin gén. de Thérapeutique,' 1888, t. cxiv).

Quinine Salts classified in terms of their Alkaloid.

100 parts of	basic	hydrochlorate	of	quinine	contains	81·71	quinine.
,, ,,	neutral	,,	,,	,,	.	81·61	,,
,, ,,	basic	lactate	,,	,,	.	78·26	,,
,, ,,	,,	hydrobromate	,,	,,	.	76·60	,,
,, ,,	,,	sulphate	,,	,,	.	74·31	,,
,, ,,	,,	sulphovinate	,,	,,	.	72·16	,,
,, ,,	neutral	lactate	,,	,,	.	62·30	,,
,, ,,	,,	hydrobromate	,,	,,	.	60·67	,,
,, ,,	,,	sulphate	,,	,,	.	59·12	,,
,, ,,	,,	sulphovinate	,,	,,	.	56·25	,,

Quinine classified in order of their Solubility, after J. Regnauld and E. Villegean.

1 part of	neutral	hydrochlorate	of	quinine	is soluble in	0·66	water.
,, ,,		sulphovinate	,,	,,	.	0·70	,,
,, ,,		lactate	,,	,,	.	2·00	,,
,, ,,		sulphovinate	,,	,,	.	3·30	,,
,, ,,		hydrobromate	,,	,,	.	6·33	,,
,, ,,		sulphate	,,	,,	.	9·00	,,
,,	basic	lactate	,,	,,	.	10·29	,,
,, ,,		hydrochlorate	,,	,,	.	21·40	,,
,, ,,		hydrobromate	,,	,,	.	45·02	,,
,, ,,		sulphate	,,	,,	.	581·00	,,

The salicylate of quinine, so much praised by Antonesco ('Thèse,' Paris, 1886), is very little soluble (one part is dissolved in 1430 parts of water at 20° C.); moreover 100 parts of salicylate only contain 70·12 per cent. of quinine.

The hydrochlorate of quinine is a little more expensive than the sulphate of quinine, but it is prescribed in a smaller dose.

The hydrochlorate of quinine is, because of its solubility, the best quinine salt to be employed for hypodermic injections; the basic hydrochlorate of quinine is only dissolved in 21 times its weight of water, but the neutral hydrochlorate is much more soluble; one part of basic hydrochlorate of quinine is dissolved in 21·40 parts of water, one part of neutral hydrochlorate of quinine in 0·66 of water.[1]

[1] Quinine is considered to-day as a diacid alkali; the neutral salt is the body which results from the combination of a molecule of quinine with two molecules of monobasic acid. It is through the application of this rule that the old acid hydrochlorate of authors has become the neutral hydrochlorate, although its reaction on *turmeric* paper is strongly acid (De Beurmann and Villegean, op. cit., p. 205).

De Beurmann and Villegean recommend for the hypodermic injections the following solution:

Bihydrochlorate of quinine . .	5 grammes.
Distilled water	q. s. to make 10 cubic centimetres.

A cubic centimetre of this solution represents exactly 50 centigrammes of bihydrochlorate.

In the absence of solid bihydrochlorate, the basic hydrochlorate of commerce may be utilised by the following method: —Dissolve a certain quantity of pure hydrochloric acid with distilled water until the liquid has a specific gravity of 1·045 at +15° C. Place 5 grms. of basic hydrochlorate of quinine in a graduated burette, add 5 c.c. of the acid solution; then add distilled water to make up to 10 c.c., and filter.

The solution of bihydrochlorate of quinine is clear and of an almost syrup consistency; after some time it assumes a brownish tint, without, however, being decomposed (De Beurmann and Villegean, op. cit., and 'Tribune médicale,' Sept. 18th, 1890).

The solution of bihydrochlorate of quinine although very acid to turmeric paper, is not caustic; I have not observed any eschars or gangrene in the patients treated with this solution, but very acute pain at the time of the injection, which lasted sometimes for several hours.[1]

I have also employed the following formula, which is given in the 'Formulaire des Hôpitaux Militaires:'

Monohydrochlorate of quinine	1 gramme.
Alcohol at 60° C.	3 grammes.
Distilled water	6 „

If required a few drops of hydrochloric acid may be added in order to obtain a complete solution.

At a temperature of + 15° C., a cubic centimetre of this solution contains very nearly one decigramme of quinine.

In the injections made with this solution, as with the solution of bihydrochlorate, it is necessary, it is true, to inject a larger quantity of liquid; if 1 grm. of hydrochlorate of quinine is needed, 2 cubic centimetres of the solution is injected with the ordinary Pravaz syringe through each puncture by filling the syringe twice and five punctures being made. In these conditions the absorption of the quinine is easy and rapid.

Kobner has used the following formula ('Bulletin gén. de Thérap.,' 1890, p. 506):

[1] The addition of a little carbolic acid will prevent the pain in most cases (*Trans.*).

Hydrochlorate of quinine from . . .	0·50 to 1 gramme.
Pure glycerine	2 grammes.
Distilled water	2 ,,

Prepare without acid and inject the solution tepid.

In order to avoid the possible confusion of the hydrochlorate of quinine with the hydrochlorate of morphia—a confusion which might cause very grave accidents—Vigier and Delpech have rightly proposed to write on the prescriptions and on the labels the name of the alkaloid first, as follows:

MORPHIA (hydrochlorate)
QUININE ,,

instead of—

Hydrochlorate of morphia
,, of quinine.

That would be indeed a very useful precaution.

The following formula, given by Vinson, is very good for the hypodermic injections, and very useful, as hydrochlorate of quinine is not always to be obtained:

Sulphate of quinine	1 gramme.
Distilled water	10 grammes.
Tartaric acid	50 centigrammes.

The neutral sulphovinate of quinine is almost as soluble in water as the neutral hydrochlorate (one part of the neutral sulphovinate is dissolved at an ordinary temperature in 0·70 water), but the solutions of sulphovinate of quinine have a serious inconvenience since they decompose rather quickly, and the hypodermic injections made with the decomposed solutions cause local complications, *e.g.* acute pain, abscess, gangrenous spots (Marty, 'Société de Pharmacie de Paris,' 1887; 'Bulletin méd.,' 1887, No. 12).

I have used the sulphovinate of quinine in subcutaneous injections to compare it with hydrochlorate of quinine, and I have noticed that the local complications were much more frequent with the first than with the second.

Lactate of quinine has been praised by Vigier ('Gaz. hebdom.,' 1885, p. 83).

The crystallised lactate of quinine, as found in commerce, is not sufficiently soluble for hypodermic injections.

The hydrobromate of quinine is only soluble in 60 parts of water, but a solution of this salt, 1 in 10, may be obtained by substituting distilled water and alcohol in place of pure water, as in the following formula:

Hydrobromate of quinine	1 gramme.
Alcohol	1·50 grammes.
Water	7·50 ,,

The solution of hydrobromate of quinine often gives rise to local complications.

When making hypodermic injections of quinine, it is necessary to be very careful to plunge the point of the needle of the Pravaz syringe deeply into the subcutaneous tissue; the injections made in the thickness of the dermis almost invariably cause local complications.

The solution must be perfectly clear, and have neither crystals nor spores in suspension.

Injections should be made into the limbs and not into the trunk, in view of the local complications which may take place, and which are specially likely to occur in cachectic patients.

The injection is generally followed by acute pain. A small nucleus of induration forms at the level of the puncture; most generally that nucleus vanishes or becomes absorbed, but sometimes an abscess or dry eschar about the size of a sixpence or a shilling takes place, and slowly separates. Sometimes larger eschars or even diffuse inflammation have been observed, but these grave complications are quite exceptional, and it is not the injection itself that is to blame, but the way of making it.

Baccelli lately praised intra-venous injections of quinine ('Gazzetta degli Ospitali,' No. 12, Feb., 1890).

Baccelli injected from 40 to 60 centigrammes of hydrochlorate of quinine into a vein at the bend of the elbow, using the following solution:

Hydrochlorate of quinine	1 gramme.
Chloride of sodium	75 centigrammes.
Distilled water	10 grammes.

Twenty-four hours after the injection almost all the parasitic elements had disappeared from the blood.

To prepare Baccelli's solution neutral hydrochlorate of quinine should be used, which gives an acid solution. By mixing blood with one drop of this solution it is easy to ascertain that the blood coagulates, and that the blood-corpuscles are altered, first becoming pale and then disintegrated.

The hypodermic method allows quinine to be introduced into the general circulation as quickly as the intra-venous injection, and without any danger. I do not see, therefore, why intra-venous injections should be preferred to it, for they are more difficult to perform, and may give rise to very grave local or general complications.

The intra-venous injections seem to me only to be justifiable in the most grave pernicious attacks, when it might be feared that

the hypodermic method itself would not allow the quinine to be introduced quickly enough into the blood—as, for instance, in choleraic or pernicious attacks.

Are quinine salts toxic, and at what dose do they give rise to symptoms?

On this subject many incorrect theories have been advanced, and even to-day sulphate of quinine is blamed by the public for many mishaps which are caused by paludism alone,—for instance, most of the palustral cachectics attribute the hypertrophy of the spleen to the abuse of sulphate of quinine; this, however, is met to a much greater degree in patients who have never made use of quinine than in persons who have used and abused it.

Certain people have a special susceptibility to quinine, which, even in a small dose, causes rather alarming symptoms in them; but these are exceptional facts, and, for my part, I have never met any example of them.

Trousseau and Pidoux mention having seen a young man at the hospital of Tours who was mad for a whole day after having taken a dose of 1·25 grammes of sulphate of quinine.

The same authors quote the following case:—A patient suffering from asthma, after having taken 3 grammes of sulphate of quinine at one dose, was seized with ringing in the ears, giddiness, vertigo, and excessive vomiting. Seven hours after taking the medicine he was blind and deaf, and in delirium. These symptoms disappeared of themselves (Trousseau and Pidoux, 'Traité de Thérapeutique,' 8th édit., t. ii, p. 487).

Rizu relates that every time one of his patients took sulphate of quinine, even in a very small dose, she experienced congestion of the face, and then a real attack of orthopnœa and of urticaria ('Bulletin de la Société des Médecins et Naturalistes de Jassy,' 1887).

Floyer has quoted a similar case; a strong man could not take sulphate of quinine even in a very small dose (0·15 grm.) without having violent dyspnœa and some urticaria ('Brit. Med. Journ.,' 1886).

Kobner has seen symptoms in an infant after a hypodermic injection of 30 centigrammes of sulphate of quinine—scarlatiniform eruption, colic, bloody discharge from the anus.

Doses of sulphate of quinine six times weaker than the preceding, taken internally, produced similar results in this child ('Bulletin gén. de Thérapeutique,' 1890, p. 506).

Piskiris, of Athens, has published two cases of gastro-intestinal hæmorrhage in patients attacked with palustral anæmia follow-

ing the administration of sulphate of quinine ('Galenos,' Athens, 1890).

Sulphate of quinine sometimes gives rise to hæmoglobinuria or hæmospherinuria: the urine becomes reddish or blackish; it contains albumen and hæmoglobin, but blood-corpuscles are not found. This complication has been well studied and described by Greek physicians, and in particular by Karamitzas and by Pampoukis (Pampoukis, 'Étude sur les Fièvres palustres de la Grèce,' Paris, 1888).

Karamitzas gives the example of a student who was attacked with hæmoglobinuria as soon as he took sulphate of quinine, even in such a weak dose as 0·30 grm.

Pampoukis and Chomatianos have published several similar observations.

Sulphate of cinchona will not give rise to hæmoglobinuria according to Pampoukis, and ought to be substituted for sulphate of quinine in patients subject to this complication.

According to Tomaselli quinine might produce not only hæmoglobinuria, but also an ictero-hæmaturic fever similar to the ictero-hæmaturic fever of hot countries ('Congrès de la Société Italienne de Médecine Interne,' Rome, 1888).

Spyridon Canellis (of Athens) and Pasquale Muscato have published recent examples of hæmoglobinuria from quinine ("Analysis of the Work of Spyridon Canellis," in 'Arch. de Méd. navale,' 1888, p. 476; Pasquale Muscato, "Sur l'Hémoglobinurie paroxystique par la Quinine," 'Gaz. degli Ospitali,' 1890, Nos. 17 and 19).

For my part, I have not had occasion to observe hæmoglobinuria due to quinine, and I am unable to explain why this complication, which appears so common in Greece, is so rare in Algeria.

Lépine has studied the action of quinine upon the blood of the dog and of the sheep and pig under the microscope. In these animals quinine destroyed the blood-corpuscles largely. In the living animal the cause of the destruction of the corpuscles is the passage of the hæmoglobin and of the methæmoglobin into the plasma. In healthy subjects it is rare to observe its elimination by the kidneys (hæmoglobinuria). It is possible that quinine destroys the altered hæmatin of palustral patients more easily.

Manassein has pointed out an increase of the diameter of the blood-corpuscles—from 5 to 8 per cent. in different animals—under the influence of quinine (Lépine, 'Arch. de Méd. expér.,' 1890, p. 563).

At what dose is quinine toxic and the cause of death?

Maillot and Monnerat have prescribed up to 8 or 9 grms. of sulphate of quinine daily for pernicious fevers, and for intractable neuralgias respectively.

Guersent relates that a lady, who had taken 41 grms. of sulphate of quinine in the course of a few days, temporarily lost sight, hearing, and speech, becoming deadly cold; but all these symptoms disappeared rapidly.

There exists to my knowledge, writes Briquet, a proved case of intoxication by quinine followed by death. It was the case of an insane physician who, to cure himself of a slight fever, took the enormous dose of 220 grms. of sulphate of quinine in ten to twelve days, and who succumbed to the prostration into which he had fallen (Briquet, 'Traité thérapeutique du Quinquina,' p. 585).

Giacomini, quoted by Briquet, gives the case of a man who inadvertently swallowed 12 grms. of sulphate of quinine at one time. There were symptoms of hyposthenia of the heart and of the nervous system, but these symptoms were successfully combated by the aid of stimulants.

The following facts show that a dose of 12 grms. of sulphate of quinine could cause death in an adult. Two soldiers wishing to take medicine mistook the bottle, and in place of sulphate of soda took a solution of quinine, about 12 grms. of the salt each. Half an hour after taking the medicine both men were seized with vomiting, cramp in the stomach, pallor, dilatation of the pupils, shallow respiration, shivering, small pulse, which was also irregular, slow, and at times imperceptible. They also had ringing in the ears and tendency to syncope. In one of these patients the symptoms improved, but the other succumbed to syncope (Baills, "Deux cas d'empoisonnement par le sulfate de quinine," in 'Archives de Médecine militaire,' 1885, t. vi, p. 320).

These two facts show clearly that quinine is above all a poison to the heart. They were cardiac symptoms which predominated in both these cases, and caused death in one of them.[1]

To sum up, excepting in a few subjects in whom quinine produces the appearance of symptoms more disquieting than really dangerous, it may be said that the employment of quinine in doses which are usually necessary to cure paludism presents no danger. In Algeria—and in the gravest cases—I never exceeded the dose of 3 grms. of sulphate or of hydrochlorate of quinine daily. In ordinary forms, doses of 1 grm., 0·80 grm., and even 0·60 hydrochlorate of quinine were quite sufficient.

[1] See also Rosenbusch, "Un cas d'empoisonnement aigu par la quinine avec un exanthème scarlatiniforme" ('Wien. mediz. Presse,' April 13th, 1890).

Although quinine only rarely produces any ill effects, this possibility ought not to be lost sight of; quinine intoxication, vomiting, hyposthenia of the nervous system, may result. If these symptoms are confounded with those of paludism, the dose of quinine might be still increased, and as a consequence the symptoms of intoxication would be likewise increased.

It is specially necessary to be very prudent in administering quinine for the first time to nervous persons. It should then not be begun in large doses unless the gravity of the fever requires it.

It is often considered sufficient to cut short the fever with two or three doses of quinine, waiting for a return of the fever to recommence the treatment. I consider this method to be bad, and that the endeavour should be to prevent the relapse by the help of repeated treatment; unless this is done only a few attacks are suppressed, as the parasites stopped for a time in their development very soon increase, and all has to be gone over again.

Sydenham long ago understood the necessity of a prolonged treatment by cinchona in intermittent fever. He wrote as follows:

"Cinchona, notwithstanding its efficacy, cannot be wholly depended on to eradicate the disease. . . . The best means of preventing the relapse is to repeat the febrifuge even after the cessation of the fever" (Sydenham, in 'Encyclopédie des Sci. méd.,' p. 1).

And further on, "In case the fever returns I never fail to give the patient the same quantity as before, precisely on the eighth day after the last dose of cinchona. For the patient to be placed entirely out of danger of a relapse it is necessary to repeat the treatment three or four times."

Practice shows that two or three doses are sufficient to arrest an ordinary intermittent fever, but that it often reappears at the end of seven or eight days. After the fever is arrested the first time the treatment should be recommenced six or eight days after the last attack.

Quinine might without doubt be administered for a fortnight or three weeks, but that would present enormous inconveniences for the quinine gives rise to disagreeable nervous symptoms, especially in certain patients, such as ringing in the ears, deafness; moreover the treatment would become very expensive—a consideration which is of importance to many patients, and which ought to be remembered by doctors in hospitals.

It has not, however, been demonstrated that a continued treatment with quinine has a greater efficacy over the interrupted treatment which I speak of.

I have often pointed out that better results are obtained by giving a few fairly strong doses of quinine than in prescribing it for a lengthened time, but in small daily doses.

It is evident that if one gramme of hydrochlorate of quinine is prescribed in a single dose the blood at a given time is found much more charged with quinine, and as a consequence is much more fatal to the hæmatozoa, than if 0·30 gramme of hydrochlorate of quinine were prescribed for four days.

The type of the fever does not seem to me to require the form of the treatment to be materially modified. After having been assured, notably by the examination of the blood, that the fever is really due to paludism, the following doses, for example, would be prescribed for an adult man.

The first, second, and third days 0·80 to 1 gramme of hydrochlorate of quinine daily.

The fourth, fifth, sixth, seventh days no quinine.

The eighth, ninth, tenth days 0·60 to 0·80 gramme of hydrochlorate of quinine.

From the eleventh to fourteenth days no quinine.

On fifteenth and sixteenth days 0·60 to 0·80 gramme of hydrochlorate of quinine.

From seventeenth to twentieth days no quinine.

On twenty-first and twenty-second days 0·60 to 0·80 gramme of hydrochlorate of quinine.

If the fever reappears during the course of the treatment it is necessary to prolong it.

I certainly do not pretend to give a formula applicable to every case of paludism. The preceding formula ought to be modified very often, chiefly in the grave fevers of hot countries.

The question has been much discussed as to the right period in intermittent fever that quinine should be taken. The majority of authors admit that it ought to be administered during the apyrexia.

Quinine is better tolerated at this time than during the attack of fever; it excites vomiting less often, and the absorption of the medicine is probably more complete; on the other hand, it cannot be expected to cut short the evolution of an attack of fever of normal duration when that attack has already commenced.

Let it be ever kept in mind that in the grave and continued fevers the intermissions or even the remissions need not be waited for before administering the quinine.

There was a time when the employment of quinine was con-

sidered dangerous to patients suffering from continued fevers, and was strictly limited to the intermittent fevers. Under the influence of this theory the mortality from paludism was enormous in hot countries. Maillot deserves great credit for showing that this opinion was erroneous, and that quinine should be administered in continued as in intermittent palustral fevers. The therapeutic reform which our illustrious master was the first to describe has had the happiest results, and the opinions of Maillot on continued palustral fever and its treatment are to-day universally admitted.

In serious cases hypodermic injections (1·50 to 2 grammes daily) should be made without regard to the temperature. As soon as the fever has yielded, the treatment for simple fever given above should be followed.

Hydrochlorate of quinine should be prescribed internally in solution or in the form of tabloids. In the military hospitals of Algeria the patients swallow the solution of quinine, which is prescribed and dealt out at the time by an attendant, during the visit of the doctor and in his presence. It is an excellent plan, seeing that it too often happens that when tabloids are prescribed to be taken during the day the medicine is not taken, and a search discovers the packets of quinine thrown into some corner of the ward.

In the grave pulustral fevers accompanied by pernicious symptoms the first thing to attend to, and by far the most important of all, is to get the quinine taken; but in addition to this there is often occasion to prescribe some further aids to the special treatment.

For the patients attacked with algid fever, friction either dry or with evaporating camphor liniment should be used; hot stimulating drinks—alcohol in tea, for example—diffusible stimulants, ether, acetate of ammonia under the form of draught, or, better still, hypodermic injections of ether (2 to 4 grms. of sulphuric ether), must be prescribed. The hypodermic injections of ether also render great service in patients attacked with choleraic complications.

In the case of continued fever with typhoid state and high temperature cold baths are sometimes indicated.

For the comatose symptoms when the individual is strong and plethoric, and when signs of a severe encephalic congestion are noticed, leeches may be applied to the mastoid processes in order to prevent the consecutive congestion. Cold applications to the head, counter-irritants to the extremities, and drastic purgatives are also useful.

All authors now agree in condemning the use of ordinary bleeding in the treatment of paludism.

I have found chloral hydrate (3 to 4 grms. in a mucilaginous solution) very useful in combating delirium in delirious pernicious attacks, and in alcoholic palustral patients.

When vomiting is present, effervescing drinks, champagne, ice may be given; a hypodermic injection of hydrochlorate of morphia (1 centigramme) made over the epigastrium often succeeds in soothing the vomiting. Opium should be prescribed internally if there is excessive diarrhœa.

In bilious fever, ipecacuhana and calomel are very useful, but here, again, the first thing is to prescribe quinine.

Formerly before giving quinine it was usual to prescribe laxatives and emetics. Maillot has protested against this practice, considering that if the purgatives and emetics are not in themselves hurtful, they have the great drawback of delaying the administration of quinine (Maillot, op. cit., p. 361), and a pernicious attack may come on before quinine has been given.

None of the numerous medicines which have been patronised till now as *succedanea* of quinine deserve this title, for none of them possess efficacy comparable to that of quinine in the treatment of paludism.

Arsenious acid acts specially as a tonic, and as such it may be of service in the treatment of cachexia, but the method of Boudin is insufficient and very dangerous in the treatment of the acute symptoms.

Sulphate of cinchona is cheaper than sulphate of quinine, but much weaker in its effects; it would therefore require to be given in larger doses than the sulphate of quinine, though its toxic power is equal to that of quinine.

Sulphate of cinchonidine is more toxic than the sulphate of quinine; it is dangerous to exceed 2 grms., and in order to obtain the necessary therapeutic effects this salt must be prescribed in a dose double that of the sulphate of quinine, therefore it should not be employed (Marty, "Contrib. à l'étude du Sulfate de Cinchonidine," 'Bull. gén de Thérap.,' 1884, p. 335; E. le Juge de Segrais, "Étude sur la Cinchonidine et ses sels comme Succédanés de la Quinine," 'Arch. gén. de Med.,' 1886, t. ii, p. 420).

De Brun recently tried to revive the use of cinchonidine; according to him the sulphate of cinchonidine, besides being cheaper than that of quinine, is generally better borne by the patient. De Brun prescribes 1 to 2 grms. of sulphate of cin-

chonidine in doses of 0·50 to 1 grm.; these doses may be enough in slight cases, but would evidently be insufficient in grave ones.

Analgesin or antipyrin does not cure palustral fever, it only lessens the intensity of some symptoms, *e. g.* cephalalgia and fever; as such it may be useful in the treatment of continued palustral fevers (Antony, 'Arch. de Méd. milit.,' 1887, t. x, p. 21).

This is only a palliative treatment, and while prescribing analgesin the patient should in addition be submitted to a quinine treatment, quinine being the only real remedy, especially if the fevers are those of hot countries, and if pernicious complications are dreaded.

Eucalyptus has found favour with some in the treatment of paludism, taken in the form of the alcoholate or wine of eucalyptus. The febrifuge properties of these preparations have been doubted, and, at any rate, they are by no means comparable to those of quinine.

Prophylaxis.—The prophylaxis of paludism comprises—

1st. The study of individual measures to be taken to escape paludism when obliged to live in a country where the fever prevails.

2nd. The study of measures to be taken in order to render the localities where paludism is endemic healthy.

The prophylaxis will yet be founded on more precise data, and may very probably be simplified, when it is known exactly under what form the parasites of paludism are found in the exterior medium.

At the present time rules may be framed which, being founded on experience, are of indubitable usefulness and efficacy.

In most palustral countries there is a healthy and an unhealthy season, or endemo-epidemic period. In Algeria, for example, and in Italy, fevers are but seldom contracted from December to May; during these months paludism need not be dreaded. The traveller who is master of his time should take advantage of this season of the year to travel in palustral districts; and this is also the season which should be chosen to send troops into these countries.

Breaking up the ground, earthworks, digging ditches or ponds, draining of marshes, should not be undertaken during the endemo-epidemic season. Any work of this kind which it is impossible to delay in hot countries should as much as possible be given to natives or negroes, who enjoy a remarkable immunity from paludism.

The first advice to be given to a person who is about to travel in a palustral country is to choose his residence carefully, and to take advantage of the fortunate and remarkable influence of altitude (see Chap. V, p. 101).

The site of the house should always be chosen on a height, never in a hollow or in a damp or badly drained plain. The altitude sufficient to preserve against paludism is, after all, not very great.

In the same town very healthy districts often exist along with particularly unhealthy quarters; the highest part of the town, the most central streets, and the most inhabited give the maximum of protection. On the contrary, those dwellings which are situated in the lower parts or on the muddy banks of a river should be avoided; also those which are isolated in the country, especially if situated near marshes or irrigated land.

In all hot and unhealthy countries, as in India, it has been necessary to establish *sanitoria* on the heights, where the fever season is passed.

Those travellers and soldiers who are obliged to cross and live in palustral localities during the endemo-epidemic season should carefully choose their camps, and fix them not on the banks of rivers or in the hollows, but on the highest ground available.

Persons should avoid travelling near the foci of paludism, and especially avoid spending the night there during the endemo-epidemic season. Workmen and reapers obliged to work in unhealthy localities should return to settlements on the heights for the night; sailors will find an excellent shelter in their ships.

Drinking-water should be the object of scrupulous attention in palustral localities, and especially during the endemo-epidemic season. If it is not certain that water comes from springs situated in localities free from paludism, it must be carefully filtered or, better still, boiled.

We have seen that all debilitating causes favour the development of paludism.

Great fatigue, excesses of all kinds should be avoided, especially during the endemo-epidemic season, and strengthening food should be used. Alcoholic drinks, which are dangerous in hot countries when taken to excess, are useful in moderate doses to combat the weakening effects of heat. The same may be said of spices and condiments, the use of which is made necessary by the atony of the digestive apparatus, but when taken in excess they may become injurious.

On account of its tonic properties coffee is an excellent drink

in hot countries, therefore Eastern nations make a very great use of it; the infusions of coffee and tea have besides the advantage of being made with boiling, and therefore sterilised, water.

Persons who have already had one or two attacks of fever should redouble precautions to avoid a relapse, which is always to be feared, especially if the anæmia persists. It is advisable to take quinine wine or arsenious acid, or even to undergo a hydrotherapeutic treatment, and on the slightest malaise to return to sulphate of quinine.

It is not always possible to follow these rules. Many persons are obliged to travel through very unhealthy regions, and even to sojourn there during the fever season.

The utility of a preventive treatment of paludism is very obvious when a person is living in localities where the paludism prevails to such an extent that there is little chance of escaping it, and there is fear that the attacks will become more and more insidious and grave.

Since quinine can cure paludism and destroy the parasite which has multiplied in the blood, it might be expected that cinchona and quinine administered as a preventative might hinder the parasites from multiplying in the blood.

Numerous facts prove that cinchona and quinine which cure paludism can also prevent it.

In the English navy quinine wine and sulphate of quinine are often employed as a preventive. Each time that men are sent ashore in the tropics they are obliged to take cinchona wine in the morning when quitting the vessel and in the evening on their return.

To demonstrate the salutary effects of this practice Bryson mentions the following facts:—"Twenty sailors and one officer were to be sent ashore at Sierra Leone to work during the day; cinchona bark was administered to the sailors, the officer refused to take it, and he was the only one who took the fever. Later two boats were dispatched from the 'Hydra' to explore the river Sherbo; they were absent a fortnight; every day in conformity with instructions the men took cinchona wine, and not a single man was attacked with fever, although the region explored was one of the most unhealthy on the coast. The crew of a third boat remained for two days only in the same region and at the same period, the men had not taken cinchona, and all were attacked except the officer who commanded the boat" (van Buren, "Rapport à la Commission Sanitaire des États-Unis," in 'Essais d'Hygiène et de Thérapeutique militaires,' by Evans, Paris, 1865).

On the recommendation of Bryson sulphate of quinine has been substituted for cinchona powder in stations on the west coast of Africa. A strong alcoholic solution of sulphate of quinine is poured into several casks of wine, so that 30 grms. of wine contain about 0·25 grm. of sulphate of quinine. The reports of the doctors of the Royal British Navy are in general favorable to this new method.

Quinine and cinchona were employed as a prophylactic during the War of Secession as long as the troops were called to occupy very unhealthy stations.

The reports of American military doctors are almost all favorable to this mode of treatment.[1]

Chamberlain, Wilson, David Merrit, Maylert and Bache, Swift, Thompson, confirm the good effects of quinine in preventing palustral fever.

Warren gave to 200 men of his regiment 0·30 grm. of sulphate of quinine per day during the fever season; these 200 men furnished only four cases of paludism. The rest of the regiment, numbering about 400 men, which were not submitted to the preventative treatment supplied more than 300 cases of fever.

During the summer of 1863, in the campaign of South Carolina, Samuel Logan caused a certain number of men in his regiment to take 0·25 grm. of quinine per day, and he noticed the following results:—The men who did not take quinine were attacked in the proportion of 25 per cent., those who took it irregularly in the proportion of 39 per cent., those who took it regularly in the proportion of 19 per cent.

Jilek, of Pola, mentions the following:—"736 soldiers were lodged in the same barrack in an unhealthy locality; 500 took 0·10 grm. of sulphate of quinine each day; they were attacked in the proportion of 18 per cent., whilst those who had not taken quinine were attacked in the proportion of 28 per cent."

Hertz, of Amsterdam, has observed analogous facts.

"On the west coast of Africa the officers of the 'Penelope' made an expedition up a marshy river; all had taken the precaution of taking sulphate of quinine, with the exception of one only who a week after was seized with a violent attack of bilious intermittent fever" (Gestin, quoted by Fonssagrives, 'Hygiène navale,' p. 224).

[1] 'The Med. and Surg. History of the War of Rebellion,' 1888, vol. i, pp. 111—166.

Longuet, "La prophylaxie de la fièvre intermittente par la quinine" ('Semaine médicale,' 1891, p. 5).

Thorel has been able to pass through the most unhealthy localities of Mekong, thanks to sulphate of quinine, taken in the dose of 0·60 to 0·80 grm. each week; and those of his companions who took the same precaution likewise escaped palustral fever (Thorel, 'Thèse,' Paris, 1870).

Bizardel has given new examples of the efficacy of quinine as a prophylactic of paludism. The small doses of quinine which are advised by him cannot be expected to entirely prevent the infection, but much is gained if paludism can be prevented from manifesting itself in its gravest forms.

Bizardel repeatedly points out this fact, that even in the most unhealthy regions persons who have taken quinine in prophylactic doses have not manifested pernicious symptoms; but these are the very accidents which are to be feared by men who are isolated and beyond the immediate help of a physician (Bizardel, 'De la Quinine comme Prophylactique du Paludisme,' Thèse, Paris, 1888).

Groeser, who has experimented on the preventative treatment of paludism by quinine in Batavia—that is to say, in one of the most unhealthy regions of the world,—decides in favour of this method. The attacks of fever are much less frequent and much less grave in the sailors who on landing at this dangerous port are submitted to treatment by quinine than in those who neglect this prophylactic measure (Groeser, 'Berlin klin. Woch.,' 1888, 42, p. 845; and 1889, 53, p. 1065).

The use of quinine as a prophylactic has been equally recommended by Nicolas ('Chantiers et Terrassements en Pays paludéens,' Paris, 1888).

Arsenic has been employed in Italy as a preventative medicine of paludism. Experiments have been made repeatedly on workmen and those employed on the railway and in the army.

Tommasi Crudeli says he has obtained favorable results with this medicine ('Rapport presénté au Ministre de l'Agriculture,' Rome, March 18th, 1883).

In 1883 and 1884 interesting experiments were made in Venetia upon the men of the second company of discipline who had consented to submit themselves to it. Arsenic was taken under the form of arsenical gelatine; the dose of arsenious acid was raised progressively from 1 to 8 milligrammes, and continued at that dose unless there were gastro-intestinal symptoms, in which case the medicine was suspended. In 1883 and 1884 a hundred soldiers who had never had fever, and were placed in the same conditions, took part in the experiment. Fifty soldiers

submitted to the preventative treatment by arsenious acid gave fourteen cases of palustral fever, whilst the rest of the fifty who had not submitted to the treatment furnished nineteen cases.

The difference between these figures is insignificant, and the sources of error are too numerous (it is impossible to be certain that the conditions were strictly the same in all the individuals in the experiment) for it to be possible to draw a conclusion favorable to the preventative medication by arsenious acid from these investigations ('Journal Italienne de Méd. milit.,' 1886, 1).

Sanitary precautions.—It has been seen (Chap. V, p. 98) that paludism has disappeared almost completely from a great number of localities formerly very unhealthy. Examples of this happy transformation abound, not only in Europe, but also in countries where endemic paludism is very severe—for example, in Algeria.

Among the most efficacious measures of salubrity may be quoted the drying of the morass, drainage, and cultivation of the soil.

The drying the soil by draining it, by mechanical methods, or by cultivatton obviously modifies the media in which the parasites of paludism are developed, and the soil is rendered less susceptible to the multiplication of these agencies.[1]

The drying of a marsh ought only to be made with method and with great precautions—above all in a hot country; the season in which the palustral epidemic does not prevail, or exists only with least intensity, should be chosen, and care should be taken not to uncover a great surface of the marsh during the hot season; the marsh is, indeed, much more dangerous when it begins to dry than when it is covered with water. The example of Lancisi, causing the ditches of Fort Saint Ange to be filled to assuage the ravages of paludism is well known; in Holland the same means have been employed more than once with success.

During the drying of the marsh the workmen should not pass the night in its midst, and they should be submitted to the preventative treatment with quinine during the fever season.

Regular cultivation at all times makes the soil healthy, but certain trees and shrubs are particularly good for this purpose.

The plantations of eucalyptus which have been made during

[1] Graves, 'Clinical Medicine,' vol. i, pp. 97–98. Colin, 'Traité des fièvres intermittentes,' 1870. Laveran, 'Traité des fièvres palustres,' p. 521. Thevard, 'De l'influence des transformations agricoles de la Sologne sur la diminution des fièvres intermittentes,' Thèse, Paris, 1886.

the last twenty years in a great number of palustral countries have already rendered great service, notably in Corsica, in Algeria, and in Italy.[1]

From 1861, Ramel has considered eucalyptus to be capable of combating paludism ; the credit belongs to him of having imported the *Eucalyptus globulus* into our country.

Torelli has mentioned the following fact, which is a good example of the great influence exercised by plantations of eucalyptus :—Near Rome, outside the gate of Ostia, in a place called the Three Fountains, there is a convent which in 1868 had been abandoned for a long time on account of its insalubrity, and which bore the significant name of Tomba. Pope Pius IX gave this convent to the Trappist monks who took possession of it, but in these deplorable circumstances. For the first few years it was so unhealthy that the monks could not sleep there, being obliged to spend the night in Rome, not returning to Three Fountains till after sunrise.

The first plantations of eucalyptus were made in 1869. In 1876 the improvement was such that the Trappists could stay the night in the convent without being attacked by fever. In 1877 the number of trees exceeded 2500. A space of 988 acres was then allotted to the Trappists, with the condition that they should plant 100,000 trees in ten years. In 1879 the plantation suffered much from frost, but during the following years the Trappists planted 25,000 trees each year ; and at the end of 1881 there were already 55,000 eucalyptus trees at Three Fountains, and palustral fevers were becoming rarer.

The salubrity of the farm of Three Fountains has been disputed by Tommasi Crudeli, but his assertions are contradicted by Torelli and Baccelli and by the monks who live in the convent of Three Fountains, and who are well able to judge in the matter ('Bull. de la Soc. Nationale d'Acclimatation,' Jan., 1885).

Michon has given two very interesting and convincing examples of palustral localities being made healthy by the planting of eucalyptus ('Bull. de la Soc. Nat. d'Acclimatation,' Jan., 1885). A great property situated on the east coast of Corsica, near to Algeria and to the penitentiary of Casabianca, was uninhabitable

[1] Ramel, 'Revue maritime et commerciale,' 1861. Regulus Carlotti, 'Du mauvais air en Corse,' Ajaccio, 1869. Ortal, 'De l'Eucalyptus globulus,' Thèse, Paris, 1874. Gimbert (de Cannes), 'Gaz. hebdom.,' 1875, p. 340. Torelli, 'Rapport au Senat Italien sur l'amélioration des regions au regne la malaria,' 1880. Channing, "Étiologie et prophylaxie de la malaria," 'Gazette médicale de l'Algérie,' April 30th, 1884. De Jardin-Beaumetz, article "Eucalyptus" in 'Dictionn. de thérapeutique.'

on account of fever; even the warden himself refused to remain there during the summer. The owner had planted before the guard-house a small plantation of from 200 to 300 eucalyptus, and from 400 to 500 along a river. These plantations have flourished, and now the warden is able to live there with his family, summer as well as winter. The workmen who come down from the mountain to work in the vineyards on this same property, which was formerly so unhealthy, do not contract the fever.

On the east coast of Corsica there is a small place of the name of Solenzara, in which steel-works were established. When the works were begun to be set up all the population were in the habit of emigrating for four months—from July to October,—which showed clearly how fearful the palustral endemic was. One of the owners caused sixty acres to be planted with eucalyptus; since then the fever has disappeared from Solenzara. All the population are prosperous, and no one now thinks of emigrating during the summer.

In certain localities extremely favorable to the development of paludism the plantations have not succeeded in completely dispelling the fever.

Rivière, who has disputed the febrifuge properties of the eucalyptus plantations, giving as his argument the persistence of the fever at Aïn Mokra and at the mines of Mokta (on the Lake of Fetzara in the province of Constantine), has himself furnished the explanation of their non-success, which is after all relative, because the plantations of eucalyptus have even at Mokra produced an improvement in the sanitary condition. "We have planted the banks of the Fetzara," writes Rivière, "but the plantation was required to be kept at a certain distance from the maximum limit of water, which increases suddenly owing to the torrential overflowing of the Oued-Zid and El-Aout into the immense basin. The waters cover more than 34,580 acres, and are displaced by certain winds, but the natural escape and the loss produced by rapid evaporation cause immense miasmatic surfaces to be laid bare, thus producing, through an absolutely direct isolation and rise of temperature, morbific elements against which the recent plantations on its banks are quite futile ('Bull. de la Soc. Nat. d'Acclimatation,' January, 1885). Rivière considers that in these conditions it would be advantageous to plant bamboos first, in order to circumscribe and to reduce by degrees the central basin.

The example of Aïn Mokra cannot be quoted against the eucalyptus; it is evident that it could not be expected to make

the region completely salubrious by planting eucalyptus upon the banks of such an immense marshy surface as Rivière speaks of.

The *Eucalyptus globulus* is the best known of the eucalypti; it is that which was first introduced into Europe, and is chiefly used in the old plantations: in the new plantations the *E. globulus* has been replaced by the *E. rostrata*, mainly in Algeria. The *E. globulus* does not resist cold or great heat; it requires good ground, neither dry nor too wet, and perishes rapidly in too marshy a soil. The *E. rostrata* is more hardy (Rivière, op. cit.).

Does the eucalyptus act simply as other vegetation by draining and drying the soil? If the soil is rendered more rapidly salubrious by it than by other trees, is it only because its growth is more rapid, or must it be admitted that it has special virtues, and that it enjoys the property of destroying the parasites of paludism? This latter hypothesis is in itself not unlikely. The eucalyptus, in fact, gives out aromatic vapours which possess antiseptic properties; besides, the leaves and the branches which cover the soil contain a large proportion of eucalyptol, which may prevent the development of the germs of paludism.

The influence of sulphur mines upon paludism has been pointed out by d'Abbadie. It appears, from the facts quoted by him, that the sulphurous emanations which are produced in the neighbourhood of sulphur mines have a favorable effect in palustral countries ('Commun. à l'Académie des Sciences,' September 18th, 1882). This action of sulphurous acid is easy to understand; unfortunately it does not seem that it can be used to render localities healthy.

In speaking of the individual prophylaxis I have already said that in palustral countries it is necessary to watch carefully the drinking-water, which seems to serve as the vehicle of the germs of paludism; to the general rules for making a locality healthy the necessity for providing that locality with water of good quality must, therefore, be added.

OBSERVATIONS.

Obs. 1.—*Continued palustral fever, first attack. Hæmatozoa of paludism; spherical bodies.*

Ven., aged 24, a soldier in the fifth train of artillery, admitted to the military hospital of Constantine on August 8th, 1881.

Ven. has been in Algeria for eighteen months. He is in the barracks at Bardo; says he is ill for the first time.

Four days ago Von. had severe shivering, which has not been repeated since; at the same time he felt very severe headache, general malaise; the fever would have persisted from that moment without any very prominent remissions; very strong sensation of heat, great thirst, and anorexia. Before entering hospital the patient has taken only one emetic.

On the evening of August 8th, when he was admitted, the temperature was 40° C. (diet lemonade).

9th.—Severe fever continued; 40° C. in the morning, 41·5 C. at four in the afternoon. Headache; general malaise; no stupor; no pronounced prostration; great thirst; tongue moist, a little furred; abdomen soft, without pain; no diarrhœa. The splenic dulness measures 7 centimetres vertically by 7 in width. Diet lemonade; sulphate of quinine 0·80 grm. morning and evening.

Examination of the blood made on morning of the 9th: spherical bodies of small or average size, free or adherent to blood-corpuscles.

10th.—The fever persists; 40·1° C. morning, 39·3° C. evening. Sulphate of quinine 0·80 grm. morning and evening.

11th.—The fever is falling; 36·8° C. morning; in the evening the apyrexia persists. The general state is much improved; headache and the general malaise have disappeared (sulphate of quinine 0·80 grm. morning and 0·60 grm. evening).

12th.—The apyrexia persists. The patient only shows weakness. He begins to get up. (Half a dose of sulphate of quinine 0·60 grm.; quinine wine.)

The sulphate of quinine is continued in doses of 0·60 grm. until the 18th. No relapse of fever. Appetite returns; the patient eats one ration, then two are given; quinine wine, coffee.

Examination of blood made on September 2nd: I do not find any more trace of parasitic elements.

The patient, who feels strong enough to resume service, goes out on September 3rd, 1881.

Obs. 2.—Palustral continued fever, first attack. Hæmatozoa of paludism; spherical bodies of very small size.

Rud., aged 22, soldier in the fifth train of artillery, is admitted to the hospital of Constantine on September 18th, 1881.

Rud. arrived in Algeria on December 10th, 1880. He has been well till now; is in the Bardo barracks.

On September 16th, at 4 in the evening, headache; general malaise; sensation of heat; great thirst; no shivering.

On 17th the fever persists. The patient has not taken sulphate of quinine before entering the hospital.

18th.—The fever persists; at 1.30 in the evening the axillary temperature is 40° C. Headache; general malaise; anorexia; excessive thirst. The area of splenic dulness is 9 cm. in length by 12 cm. in breadth.

19th.—38° C. in the morning, 39° C. in the evening.

20th.—39·8° C. in the morning. The patient has not taken any sulphate of quinine since he came to the hospital.

The examination of blood made on 20th at 9 a.m. shows spherical bodies of very small size, mostly non-pigmented, and adherent to the blood-corpuscles, which look like pricked or pierced corpuscles. Melaniferous leucocytes. Sulphate of quinine 1·60 grm. on two occasions.

21st.—36·4° C. in the morning. The apyrexia persists in the evening. Sulphate of quinine 0·80 grm. in the morning and evening.

22nd.—Another attack of fever, but very slight; the temperature only rises to 38·6° C. Sulphate of quinine 0·80 grm. morning and evening. No return of fever. The sulphate of quinine is continued in doses of 0·60 grm. till 29th.

The patient leaves the hospital on October 11th.

Obs. III.—*Continued palustral fever, first attack. Hæmatozoa of paludism; spherical bodies of very small size.*

Fo., aged 22, a soldier in the third squadron of artillery, is admitted to the Constantine Hospital on September 27th, 1881.

Fo. has been in Algeria five months. On the morning of the 25th shivering; headache; bilious vomiting.

On the 26th the vomiting repeated; general malaise; headache; weakness; vertigo when standing; great thirst. The patient has not had any quinine before entering the hospital.

27th.—Very high fever, 40·2° C. in the morning, 40° C. in the evening; stupor without delirium; jaundiced hue of the skin and of sclerotic. The splenic dulness is 9 cm. by 9 cm.

28th.—38·4° C. in the morning, 40·6° C. in the evening; typhoid state very pronounced, without abdominal symptoms. Examination of the blood at 2 p.m. shows very small spherical bodies, having only sometimes 1 mm. diameter, adherent to the blood-corpuscles, non-pigmented, or only containing one or two granules of pigment; melaniferous leucocytes; no crescent-shaped bodies. Sulphate of quinine 0·80 grm., the 28th, in the evening.

29th.—39·2° C. in the morning, 39·3° C. in the evening; typhoid state. Sulphate of quinine 0·80 grm. morning and evening.

30th.—Apyrexia. The general state is more satisfactory, Sulphate of quinine 0·80 grm. morning and evening.

On October 1st the temperature rises again to 39·3° C. in the evening; but from the 2nd the subsidence is complete, and the general state improves rapidly; the icteric hue disappears; strength and appetite come back. The sulphate of quinine is continued till the 9th.

The patient leaves the hospital on the 27th.

Obs. IV.—*Continued palustral fever, first attack. Hæmatozoa of paludism; spherical bodies.*

Quin., aged 22, soldier in the eleventh squadron of artillery, is admitted to the hosptial of Constantine on October 11th, 1881.

Quin. has been in Algeria nine months; says he is ill for the first time; for a month he has not left the Bardo. On 11th he came to the hospital; four days before he had an attack of headache; lumbago; general malaise; heat without shiver; great thirst; anorexia; slight diarrhœa. The patient says he has not taken any sulphate of quinine before he entered the hospital. The patient was only admitted on 11th, and comes through urgency.

11th.—I saw the patient at 4 p.m. The fever was very high, 40° C.; very great headache and much malaise; moist tongue, furred; great thirst; anorexia; a little diarrhœa; no pain in the right iliac fossa; no pink blotches; the splenic dulness is 12 cm. in height by 11 cm. in breadth (diet, lemonade).

12th.—The fever persists; at 6 a.m. the temperature still at 38·3° C.; at 4 p.m. the thermometer in axilla registered 41·2° C. (diet, lemonade). Sulphate of quinine 0·80 grm. morning and evening.

Examination of the blood made on the 12th at 8·30 a.m.: spherical bodies, of average or small size, free or adherent to blood-corpuscles; no crescent-shaped bodies.

13th.—In the morning the fever fell to 37·3° C., in the evening another slight febrile movement was noticed; at 4 in the evening the temperature was 38·8° C. Broths; sulphate of quinine 0·80 grm. morning and evening.

14th.—37·7° in the morning, 36·9° C. in the evening. General state very satisfactory; a little appetite; half a dose of sulphate of quinine 0·80 grm. morning and evening.

The sulphate of quinine is continued in dose of 0·60 grm. until the 22nd. No relapse.

The patient went out on the 28th.

Obs. V.—*Continued palustral fever, first attack. Hæmatozoa of paludism; spherical bodies of very small size.*

Mor., aged 24, soldier in the eighth company of mounted

troops, is admitted to the Constantine Hospital on August 7th, 1882.

Mor. has been nine months in Algeria. He works in the company's garden. From August 1st general malaise; headache. On the 4th general malaise and headache increased, which obliged patient to go to bed. From that time fever seems to have persisted without complete remission. There has been no shiver; headache; great thirst; complete anorexia. The patient took before coming to the hospital 0·80 grm. of suphate of quinine.

7th.—High fever; 39·9° C. at 12 midday; same temperature at 4 p.m. Typhoid state without abdominal symptoms; very severe headache; prostration. The area of the splenic dulness is 12 cm. by 13 cm.

The examination of the blood made on the 7th at 2 p.m. showed very small spherical bodies in great numbers adherent to the blood-corpuscles. Many of these bodies are not pigmented; the others only contain one or two granules of pigment. Two or three of these bodies are often found in the same blood-corpuscle. Melaniferous leucocytes. Sulphate of quinine 1 grm. at 7 p.m.

8th.—The fever persists, but is not so strong; 38·4° C. in the morning, 38·8° C. in the evening. Sulphate of quinine 0·80 grm. morning and evening.

9th.—36·8° C. in the morning, 39° C. in the evening. Sulphate of quinine 0·80 grm.

10th.—Apyrexia, which persists on the following days. Sulphate of quinine is continued till the 18th, and resumed from the 24th to the 30th.

The patient left the hospital on September 4th, 1882.

Obs. VI.—*Quotidian intermittent fever, first attack. Hæmatozoa of paludism; spherical bodies; flagella.*

Yv., aged 23, soldier in the third zouaves, admitted to the Constantine Hospital August 4th, 1881.

Yv. has been two years in Algeria. First attack of fever July 28th last year. Headache; general malaise; great thirst; heat.

On August 3rd, for the first time, Yv. has had a very characteristic attack of fever with initial rigors, heat, and perspiration.

4th.—New attack of fever at 10 a.m.; shivering; the axillary temperature was then 41·3° C., at 4 p.m. 40° C.

Examination of the blood, made at 2.30 p.m., showed spherical bodies free or adherent to blood-corpuscles. Many of

these elements are very small; no crescent-shaped bodies. The splenic dulness is 11 cm. by 14 cm.

5th.—36·8° C. in the morning. At noon shivering; at 1 p.m. the axillary temperature is 40·4° C.; at 4 p.m. it is still 40·2° C.

Examination of blood, made on the 5th, 9 a.m, (before the onset of the attack). Numerous spherical bodies, free or adherent to blood-corpuscles; spherical bodies containing mobile pigmented granules; flagella. Sulphate of quinine 1·60 grm., in two doses.

6th.—Apyrexia morning and evening. Very pronounced anæmia; general weakness. Sulphate of quinine 1·40 grm.

On the following days the apyrexia persists. The sulphate of quinine is continued in doses of 0·60 grm. until August 14th. Examination of blood made on August 17th; I do not find any more traces of parasitic elements. The patient leaves the hospital on September 5th.

Obs. VII.—*Palustral fever, first attack. Hæmatozoa of paludism; spherical bodies; flagella.*

Cour., aged 22, soldier in the 47th of the line, admitted to the Constantine Hospital August 8th, 1881.

Cour. has been three weeks in Algeria. He says he has been ill for three days; shiverings at the commencement, headache, vomitings, general malaise, intense thirst, anorexia. The patient has not taken quinine before being admitted.

On August 8th, at 11 a.m. the axillary temperature is 39·8° C.; apyrexia at night. The splenic dulness measures 12 cm. by 11. Examination of blood made August 8th at 3 p.m. at the end of the onset of fever; spherical bodies free or adherent to blood-corpuscles; some of these elements contain mobile granules of pigment, or show at their periphery flagella accompanied with very rapid movements; melaniferous leucocytes. Sulphate of quinine 0·80 grm. at 8 p.m.

9th.—Apyrexia. The patient does not show anything more than weakness; anæmia very marked. Sulphate of quinine 1·40 grm.; the sulphate of quinine is continued in doses of 0·60 grm. daily up to August 16th. There is no relapse. The patient went out on August 26th, 1881.

Obs. VIII.—*Intermittent fever; quotidian, first attack. Hæmatozoa of paludism; spherical bodies; flagella.*

Sain., aged 23, soldier in the 3rd chasseurs of Africa, entered the Constantine Hospital on September 20th, 1881.

Sain. has been in Algeria twenty-three months. No former grave illnesses. He was ill with fever the first time on September

6th, on coming back from accompanying a convoy to the Oued-Athménia. From September 6th to 20th the patient has been attended to at the corps visit.

20th.—Fever very high; at 1 p.m. 40·8° C.; at 4 p.m. 39·4° C. Headache; thirst excessive. No abdominal symptoms. The splenic dulness measures 11 cm. by 14 cm. Profuse sweating on the evening of the 20th (diet, lemonade).

21st.—Fever has fallen; morning 36·3° C. The malaise and the headache have disappeared. Sulphate of quinine 0·80 grm. at morning and evening. New attack during the day; at 4 p.m. temperature is 40° C. Examination of blood made on the morning of September 21st (before taking sulphate of quinine); spherical bodies free or adherent to blood-corpuscles; spherical bodies containing pigmented granules, mobile or provided with flagella; free flagella; spherical bodies of very small volume containing sometimes only one or two pigmented granules, free or adherent to the blood-corpuscles.

22nd.—37° C. morning; in evening apyrexia persists. Sulphate of quinine 0·80 grm. morning and evening.

23rd.—The apyrexia persists; profound anæmia; earthy look on the face; mucous membrane pale. General weakness; tongue moist; neither diarrhœa nor constipation. A little appetite (one dose; sulphate of quinine 0·80 grm.; quinine wine).

24th.—The apyrexia persists. Sulphate of quinine is continued in doses of 0·60 grm. each day to September 30th; quinine wine, coffee. No relapse. Went out October 3rd, 1881.

Obs. IX.—*Quotidian intermittent fever, first attack. Hæmatozoa of paludism; crescent-shaped bodies; spherical bodies.*

Coi., aged 23, soldier in the 3rd zouaves, entered the hospital of Constantine July 20th, 1882.

Coi. has been eight months in Algeria. Was attacked with fever for the first time six days ago; intermittent, quotidian fever very characteristic; came on with initial shivering, returned towards 10 a.m. The patient has taken three doses of sulphate of quinine before he entered the hospital.

20th.—At 4 p.m. 39·2° C. Headache very marked; general malaise, feebleness, diarrhœa; tender spot in the region of the spleen. The area of splenic dulness measures 12 cm. by 15 cm. Sulphate of quinine 0·80 grm.

21st.—Apyrexia. Sulphate of quinine 0·80 grm. morning and evening. Examination of blood made at 2 p.m.; crescent-shaped bodies; spherical bodies of average size, some of these elements contain mobile granules of pigment; spherical bodies

of very small size, free or adherent to blood-corpuscles. Melaniferous leucocytes.

22nd.—The apyrexia persists. Anæmia very marked; the patient has vertigo whenever he attempts to raise himself; ringing in the ears. Sulphate of quinine is continued in doses of 0·80 grm., afterwards 0·60 grm., till July 28th, and resumed from August 6th to 10th. No relapse of fever. Patient went out on August 11th, 1882.

Obs. X.—*Quotidian intermittent fever, first attack. Hæmatozoa of paludism; crescent-shaped bodies; spherical bodies.*

Del., aged 24, soldier in the eighth company of mounted troops, admitted to Constantine Hospital on July 7th, 1882.

Del. arrived in Algeria in January, 1882. Was very healthy till then. First attack of fever on July 1st at 9 a.m.; regular attack with initial shivering at beginning; new attacks on following days. The patient took a dose of sulphate of quinine before entering the hospital.

July 7th.—At 4 a.m. the axillary temperature 38·8° C. (end of the attack).

8th.—New attack; the axillary temperature rises to 40° C. The area of splenic dulness measures 14 cm. by 15 cm. Apyrexia from July 9th to 10th, which might be attributed to the dose of quinine taken before admission to the hospital.

11th.—Attack of fever; at 3.30 p.m. 39·5° C.; at 6.30 p.m. 39·8° C.

12th.—Apyrexia. Sulphate of quinine 0·80 grm. morning and evening. Examination of blood on the morning of July 12th; numerous crescent-shaped bodies, sometimes three or four in the field of the microscope; spherical bodies of average size, but not many.

13th.—New attack of fever; at 1.30 p.m. 39·6° C.; at 6 p.m. 37·4° C. Sulphate of quinine was continued in doses of 0·80 grm.; afterwards 0·60 grm. till July 20th. No relapse. The patient went out on July 20th.

Obs. XI.—*Palustral fever, first attack; continued form of intermittent fever with subintrant attacks. Hæmatozoa of paludism; crescent-shaped bodies.*

N., soldier in the 3rd zouaves, aged 24, admitted to the hospital of Constantine July 24th, 1881.

N. has been three years in Algeria; says he is a patient for the first time. On July 20th he felt some headache, general malaise, a violent heat without shivering and without regular attacks. According to the patient, the fever has persisted with-

out notable remission till admission to the hospital. At the time when the illness took place the patient was drafted to Ain-el-Bey, *i. e.* in a notoriously unhealthy locality. Before entering the hospital N. took an ipecac. emetic; no sulphate of quinine. From July 23rd the patient has had several attacks of vomiting, and without having taken any vermicide has vomited long fragments of tænia.

24th.—Very intense fever; 40·6° C. in the morning, 40·4° C. in the evening. General malaise, great and intense headache, no stupor, intense thirst, anorexia, no diarrhœa; belly soft, without pain. The spleen has notably increased in size (diet lemonade).

25th.—Fever persists; 38·6° C. in the morning, 41·3° C. in the evening. Headache, anorexia, intense thirst (diet, lemonade). Sulphate of quinine 0·80 grm.

26th.—39·1° C. in the morning, 37·1° C. in the evening. Sulphate of quinine 0·80 grm. in the morning, 0·60 grm. in the evening.

27th.—37° C. in the morning. In the evening apyrexia persists. Half a dose of sulphate of quinine 0·60 grm.

28th.—Apyrexia in the morning. The patient takes 0·60 grm. sulphate of quinine. In spite of that he has an attack during the day at 4 p.m. Axillary temperature is 39·7° C. Sulphate of quinine 0·80 grm. in the evening.

29th.—Apyrexia persists; 37° C. in the morning. Examination of blood on July 29th. Crescent-shaped bodies; melaniferous leucocytes. Sulphate of quinine 0·80 grm. morning and evening.

30th.—Apyrexia persists. Appetite and strength come back. One dose; sulphate of quinine 0·60 grm., cinchona wine. The sulphate of quinine is continued in doses of 0·60 gr. until August 5th. Cinchona wine, coffee. During all the month of August the apyrexia persists. Anæmia disappears little by little. Examination of blood on August 31st. No more parasitic elements. Patient went out September 1st, 1881.

Obs. XII.—*Quotidian intermittent fever, first attack. Hæmatozoa of paludism; crescent-shaped bodies.*

P., aged 21, soldier in third zouaves, entered the Constantine Hospital July 25th, 1882. P. has been eight months in Algeria; says he is ill for the first time since he came. On July 22nd he was attacked about 6 a.m. with shivering, accompanied by general malaise, headaches, and bilious vomiting; heat after the shivers; great thirst; the fever persisted on July 23rd and 24th. The patient took on the 24th, at Ain-el-Bey, ten pills containing sulphate of quinine, and came to Constantine.

July 25th.—Attack of fever 38·4° C. at 9.30 a.m.; 39·8° C. at noon; 37·9° C. at 4 p.m. Very profound anæmia; general weakness. Sulphate of quinine 0·80 grm. in the evening.

26th.—A new onset of fever which began at 5 a.m.; at 6 a.m. 39·8° C.; at noon 40° C.; at 4 p.m. 38·4° C. Examination of blood at 8 a.m. on July 26th. Crescent-shaped bodies; numerous melaniferous leucocytes. Sulphate of quinine 1·60 grm. in two doses.

27th.—Apyrexia; general weakness very marked; the patient can only stand with difficulty. On the following days the apyrexia persisted; strength and appetite returned. Sulphate of quinine was continued till August 4th, 0·80 grm.; afterwards 0·60 grm. doses.

August 18th.—A slight attack. Sulphate of quinine was given again, and continued till August 27th. No fresh relapse. Patient leaves hospital on August 29th on sick leave.

Obs. XIII.—*Quotidian intermittent fever, first attack. Hæmatozoa of paludism; crescent-shaped bodies.*

Vand., aged 29, a soldier in the third African battalion, entered the Constantine Hospital on August 16th, 1882.

First attack of fever on August 11th; daily attacks from August 11th to 15th. The attacks were very characteristic; they were repeated every day at about 8 a.m. The patient took two doses of sulphate of quinine before entering the hospital.

August 16th.—Apyrexia; anæmia; general weakness; anorexia. The splenic dulness measures 11 cm. by 13 cm. I prescribed nothing but cinchona wine. Apyrexia persisted till August 20th.

20th.—Attack of fever; 39·3° C. at 8 a.m.; 41° C. at 11.30 a.m.; 40·8° C. at 4 p.m. Examination of blood at 8.30 a.m Crescent-shaped bodies. New examination of blood on the same day at 2 p.m. Crescent-shaped bodies; oval bodies derived from crescent-shaped bodies; melaniferous leucocytes. The sulphate of quinine was prescribed from the evening of August 20th until August 28th. On August 22nd the patient had another slight attack. The patient left the hospital on September 1st on sick leave.

Obs. XIV.—*Quotidian intermittent fever (relapse). Hæmatozoa of paludism; spherical bodies.*

Du., aged 22, soldier in second regiment of artillery, is admitted to the hospital of Constantine on May 20th, 1882.

Du. has been in Algeria from April 10th, 1881. First attack of fever at Bona on July, 1881, quotidian intermittent fever, very characteristic, which was treated by sulphate of quinine.

Relapse of fever on April 28th, 1882, quotidian intermittent fever. Sulphate of quinine. Fresh relapse on May 19th. Attacks on May 19th and 20th.

May 20th.—At 2 p.m. the axillary temperature is 40° C., at 4 p.m. 38·2° C. Examination of blood on May 20th at 2.30 p.m.; pretty numerous spherical bodies of average or small size, free or adherent to blood-corpuscles. Melaniferous leucocytes.

21st.—Fresh attack of fever; at 7 a.m. shivering, when the axillary temperature was 39·4° C., at 4 p.m. 38·8° C.; sweating. Examination of blood on May 21st at 8.30 a.m. gave the same results as the examination on May 20th. Sulphate of quinine 0·80 grm. on May 21st in the evening.

22nd.—Apyrexia; very marked anæmia, general weakness, anorexia. The area of splenic dulness is 14 cm. by 13 cm. Sulphate of quinine 0·80 grm. morning and evening.

On the following days the apyrexia persists; the quinine was prescribed in a dose of 0·60 grm. till May 26th. The examination of the blood made on June 2nd does not show the existence of any parasitic elements. Relapse of fever on June 9th; shivering at midday; at 1 p.m. the axillary temperature was 40·9° C.

Examination of blood made June 9th at 2 p.m.; spherical bodies of small or average size, free or adherent to red blood-corpuscles. As in the previous examination, no crescent-shaped bodies were found. On June 9th, at 5.30 p.m., the axillary temperature was 38·2° C.

June 10th.—37° C. in the morning; at midday new attack; at 1 p.m. 40·9 C.°; at 4 p.m. 38·2° C. Examination of blood at 2 p.m.; same results as in previous examination. Spherical bodies of small or average size, free or adherent to blood-corpuscles. Sulphate of quinine is prescribed from June 10th to June 19th, 0·80 grm. first, then 0·60 grm. No fresh attack of fever.

Obs. XV.—*Quotidian intermittent fever (relapse). Hæmatozoa of paludism; spherical bodies; segmented bodies.*

C., aged 32, soldier of the eighth squadron of artillery, admitted to Constantine Hospital on August 18th, 1881.

C. has been in Algeria from December 11th, 1880, located at Bardo. First onset of intermittent fever last July 20th. Quotidian intermittent fever from July 20th to 30th. The patient has been treated with sulphate of quinine. Relapse on August 15th; regular attacks on August 15th, 16th, and 17th at 10 a.m. Before coming to the hospital the patient has had several doses of sulphate of quinine.

18th.—High fever; 41° C. at midday; 40·4° C. at 4 p.m. Very

severe headache. The splenic dulness was 7 cm. by 12 cm. Examination of blood on August 18th, at 2 p.m. showed amœboid bodies containing frequently mobile pigmented granules. These spherical bodies of different sizes were free or adherent to blood-corpuscles; bodies of the size of a red blood-corpuscle showing in the centre a heaping up of pigment and all around round shining corpuscles (segmented bodies). Sulphate of quinine was prescribed from the evening of August 18th to 26th. No new attacks.

September 3rd.—Anæmia was still very marked. The examination of the blood on September 3rd did not reveal any more parasitic elements. The patient was discharged on September 10th, 1881.

Obs. XVI.—*Quotidian intermittent fever (relapse). Hæmatozoa of paludism; spherical bodies; segmented bodies.*

Rob., aged 24, soldier in the third squadron of artillery, was admitted to the Constantine Hospital November 15th, 1881.

Rob. has been two years in Algeria. First onset of fever in August, 1881; from that time the patient has had several relapses of fever, and took for each several doses of quinine. Since November 3rd regular quotidian attacks with initial rigors beginning towards 4 a.m. The patient took several doses of sulphate of quinine before entering the hospital.

15th.—Attack of fever at 4 p.m.; 39·7° C. Very marked anæmia; general weakness. The splenic dulness was 12 cm. by 14 cm.

16th.—37·9° C. in the morning. Examination of blood same day in the morning; spherical bodies in large numbers, free or adherent to blood-corpuscles; some were very small, non-pigmented, and gave to the blood-corpuscles to which they are adherent the appearance of fenestrated blood-corpuscles; the others of average size contain mobile pigmented granules; bodies segmented regularly, with a heap of pigment in centre; melaniferous leucocytes. Another examination of the blood made the same day—at 1.30 p.m., at the time when the attack of fever begins—gave the same results as the examination in the morning. On November 16th, at 3 p.m., rigors; at 4 p.m. axillary temperature 39·8° C.

17th.—37° C. in the morning; during the day the patient had another attack of fever; at 4 p.m. 39·3° C. Sulphate of quinine 0·80 grm. morning and evening.

On the following days the apyrexia continued. Sulphate of quinine was continued in doses of 0·80 grm., then of 0·60 grm. until November 27th. No relapse. The patient was discharged on December 8th, 1881.

Obs. XVII.—*Quotidian intermittent fever (relapse). Hæmatozoa of paludism; spherical bodies; flagella.*

Vien, aged 25, soldier in the eighth squadron of artillery, entered the Constantine Hospital on March 18th, 1881.

First attack of fever in August, 1879; relapse in August, 1880 (quotidian fever), and in February, 1881. On March 18th the patient entered the Constantine Hospital under different treatment from mine. He had several attacks, and took a few doses of quinine. On April 17th he was sent to me.

April 17th.—Apyrexia, very marked anæmia, earthy colour, pinched; general weakness; anorexia. The splenic dulness measured 11 cm. by 10 cm. Examination of blood on April 17th in the morning. Spherical bodies; flagella.

18th.—A regular attack of fever well marked, which was repeated on April 19th. Sulphate of quinine was prescribed for three days. The apyrexia persisted till April 23rd. Examination of the blood on April 22nd. Spherical bodies. On April 23rd, at 11 a.m., an attack of fever; at 3 p.m. 40·7° C.

25th.—A new attack during the day; at 3.30 p.m. the axillary temperature 39° C. Examination of blood on April 24th in the morning (before the onset of the attack of fever). Spherical bodies in rather large numbers, some showing mobile pigmented granules; others flagella; free flagella were also found. Sulphate of quinine 0·80 grm. The quinine is continued on the following days. The apyrexia persisted.

Obs. XVIII.—*Quotidian intermittent fever (relapse). Hæmatozoa of paludism; spherical bodies; flagella.*

Al., aged 25, sergeant in the third rifles, is admitted to the Constantine Hospital on May 28th, 1881.

Al. has been in Algeria from December 17th, 1887. He had intermittent fever for the first time in September, 1880, in the neighbourhood of Jemmapes, and was treated during three weeks at the hospital of Philippeville for quotidian intermittent fever. Since that time the patient had remained weak, anæmic, and was subject to palpitation of the heart.

On May 19th Al. felt headache; some general malaise; vague pains in limbs. Nevertheless he continued his duties. On May 24th the patient, who was at the butts, felt weaker than on the previous days, and had great difficulty in coming back to the barracks. On May 25th the general malaise and fever had for the most part disappeared, but on May 26th Al. had a very severe attack of fever, with initial rigors, during the night of May 27th to 28th; a new attack of very severe fever; he was

quite delirious. On the morning of May 27th the patient took 0·80 grm. sulphate of quinine.

28th.—Slight fever; 38·2° C. in the morning, 38·3° C. in the evening. The patient complains of very severe headache, prostration, general weakness, very marked anæmia. Tongue white and furry; belly soft, painless; no diarrhœa. The splenic dulness was 15 cm. by 14 cm. Examination of blood on May 28th in the morning. Spherical bodies containing pigmented granules, mobile or with flagella. (Broth, lemonade). Sulphate of quinine 1·20 grm.

29th, 36·6° C. in the morning; in the evening the apyrexia persists. The general state is more satisfactory (half a dose; sulphate of quinine 0·60 grm.).

30th.—The apyrexia persisted. Great anæmia; earthy appearance of the face; general weakness (one dose; sulphate of quinine 0·60 grm.; cinchona wine). Examination of blood made on May 30th. No more parasitic elements. The sulphate of quinine was continued till June 8th in doses of 0·60 grm. a day. No relapse. Cinchona wine; black coffee. From June 13th to 18th I still gave sulphate of quinine. No relapse. The patient, who obtained sick leave, was discharged June 18th.

Obs. XIX.—*Quotidian intermittent fever (relapse). Hæmatozoa of paludism; spherical bodies; flagella.*

Mach., aged 23, soldier in the twenty-first section of the workmen of administration, was admitted to the Constantine Hospital on July 3rd, 1881.

Mach. came to Algeria November 9th, 1879. Had intermittent fever for the first time in October, 1880, at Biskra. The patient has had several relapses of fever. Admitted twice into the hospital of Biskra. The fever returned a month ago at Biskra, with the quotidian type. Last of all, during the journey from Biskra to Constantine, there was another relapse. Last week quotidian attacks came on at 2 a.m. Last attack on July 3rd, when he came under my care. For a fortnight the patient has not had any relapse of fever.

July 3rd.—The attack ended at the time he entered the hospital. Very marked anæmia. The skin of the face had an earthy tint. The mucous membrane is colourless. General weakness. Pain in the region of the spleen. The splenic dulness was 8 cm. by 8 cm. Sulphate of quinine 0·80 grm. on the evening of July 3rd. Examination of blood on July 3rd at 4 p.m. (the attack being over). Spherical bodies in large numbers, motionless or with flagella (three flagella). Spherical bodies of small size.

4th.—Apyrexia. Sulphate of quinine 0·80 grm. administered.

5th.—The apyrexia persisted. Strength and appetite came back (one dose sulphate of quinine, 0·60 grm.; cinchona wine). The sulphate of quinine was continued in doses of 0·60 grm. till July 12th. No relapse of fever. Examination of blood on July 13th. No parasitic elements seen. The patient was sent home on sick leave.

Obs. xx.—*Quotidian intermittent fever (relapse). Hæmatozoa of paludism; spherical bodies; flagella.*

Gra., aged 23, soldier in third Algerian rifles, admitted to the Constantine Hospital November 1st, 1881.

Gra. had been in Algeria since November, 1879. During the summer of 1880 he had been admitted on two occasions to the hospital of Biskra for dysentery. Had not had fever till September 10th, 1881. The patient happened then to be in the bush. He was admitted into the hospital of Millah on September 17th for intermittent fever. He was discharged October 28th. On October 30th relapse of fever and dysentery.

November 1st.—Fever rather severe at the time of entering the hospital; 39·6 °C. at 4 p.m.

2nd.—Apyrexia in morning; towards 5 p.m. the patient had another attack of fever; at 6 p.m. the axillary temperature is about 39·9° C. Anæmia; general weakness; dysentery, very characteristic; small stools, frequent, mucous and bloody, accompanied with severe colic and tenesmus. The splenic dulness measured 8 cm. by 9 cm. Sulphate of quinine 1·60 grm.; Seidlitz water two glasses in the morning; calomel 1·50 grm. in the evening.

3rd.—38·6° C. in the morning, 37·3° C. in the evening. The colic was less severe. The stools were more abundant, but they still contained blood. Sulphate of quinine 0·80 grm.; Seidlitz water a glass in the morning; calomel 1 grm. in the evening.

4th.—Apyrexia. The stools were very loose; did not contain any more blood. The colic and tenesmus had disappeared (soups; sulphate of quinine 0·60 grm.; four pilules of Segond). The days following the patient's state continued to improve. The apyrexia persisted. The stools became normal. The sulphate of quinine was continued in doses of 0·60 grm. up to November 12th.

December 5th.—The state of the patient was very satisfactory. The dysentery had disappeared completely, when the fever reappeared. Attack on the 5th towards midday; at 1 p.m. 40·3° C. Examination of blood made on December 5th at 2.30 p.m., that is to say, during the attack; spherical bodies, free or adherent to the blood-corpuscles; spherical bodies of small size in great

numbers, free or adherent to the blood-corpuscles. On December 5th, at 4 p.m., temperature 38·8° C.

6th.—36·5° C. in the morning, 37° C. in the evening. Sulphate of quinine 0·80 grm. morning and evening. Examination of blood made December 6th at 8.30 p.m.; spherical bodies in great number; the greater part of these contained mobile pigmented granules, and were provided with flagella endowed with very active movements; melaniferous leucocytes (rare).

7th.—38·4° C. in the morning, apyrexia in the evening; there was another slight attack this morning (soups; sulphate of quinine 0·80 grm.).

8th.—Apyrexia morning and evening. Profound anæmia; general weakness. The splenic dulness measured 9 cm. by 12 cm. The dysentery did not reappear. A little appetite (one dose sulphate of quinine 0·60 grm.; cinchona wine, coffee). The sulphate of quinine was continued in doses of 0·60 grm. a day up to December 16th. No recurrence of fever. The patient went out on December 20th on sick leave.

Obs. XXI.—*Quotidian intermittent fever (relapse). Hæmatozoa of paludism; spherical bodies; flagella.*

Eng., aged 23, soldier in the 47th of the line, admitted to the Constantine Hospital January 9th, 1882.

Eng. landed at Bona in the month of July, 1881. He came by stages from Bona to Saint Charles, passing through very unhealthy localities. At the end of July Eng. experienced the first attack of fever (quotidian intermittent fever), very characteristic. Since that time incessant relapses. The patient had not remained more than a week without fever. He had been admitted successively to the ambulance of Akbou, then to the hospital at Bougie, latterly to the hospital at Ain-Beida. The last attack took place on January 9th in the morning; before being admitted to the hospital regular attack with initial rigors. The patient said he had not taken sulphate of quinine for about a fortnight.

January 10th.—Apyrexia morning and evening. Anæmia; general feebleness. The splenic dulness measured 11 cm. by 14 cm. Slight bronchitis.

11th.—The patient said he had an attack of fever in the evening which was not noticed.

12th.—Apyrexia (one dose cinchona wine). Examination of blood made on January 13th at 9 a.m.; spherical bodies, free or adherent to the blood-corpuscles; melaniferous leucocytes.

26th.—The only medicine the patient has taken was cinchona

wine; nevertheless there was no relapse of fever. Examination of blood made on January 26th; spherical bodies of average or small size, free or adherent to blood-corpuscles; spherical bodies provided with flagella. A relapse of fever seemed imminent.

28th.—The patient was seized with a rigor at midday; at 2 p.m. the thermometer registered 38·9° C. in the armpit. Examination of the blood made on January 28th during the attack; spherical bodies, containing pigmented granules, mobile or provided with flagella.

29th.—Apyrexia in morning. New attack of fever during the day; at 2 p.m. axillary temperature 39·6° C. Sulphate of quinine 0·80 grm. morning and evening.

30th.—Apyrexia morning and evening (one dose sulphate of quinine 0·80 grm. morning and evening).

31st.—Apyrexia persists (one dose sulphate of quinine 0·80 grm.; cinchona wine, coffee). The sulphate of quinine was continued in doses of 0·60 grm. until February 8th. No return of fever. Discharged February 18th.

Obs. XXII.—*Quotidian intermittent fever* (*relapse*). *Hæmatozoa of paludism; crescent-shaped bodies; spherical bodies; flagella* (Obs. 13 of my 'Traité des fièvres palustres;' it is in the blood of this patient that I noticed, for the first time, the presence of flagella).

D., aged 24, soldier in the eighth squadron of artillery, had been in Algeria since December 5th, 1879, and entered the Constantine Hospital November 4th, 1880.

The patient was at Bardo barracks, *i. e.* in a place notoriously unhealthy on the banks of the Rummel. On October 10th he had fever for the first time. He was admitted into the hospital of Constantine on October 12th. He took several doses of sulphate of quinine; the fever yielded readily, and the patient was discharged on October 24th. Relapse of fever on October 26th; quotidian attacks came on about 10 a.m.

On November 4th I noticed that the patient had grown thin; was markedly anæmic; the skin had the earthy tint characteristic of the cachexia of paludism. At 4 p.m. the axillary temperature was 39·5° C. Tongue white, moist; great thirst. The splenic dulness measured 12 cm. by 11 cm. Sulphate of quinine 0·80 grm.

5th.—Temperature is 38·5° C. in the morning, and 38·6° C. in the evening. Examination of blood made November 5th in the morning; numerous crescent-shaped bodies. I prescribed sulphate of quinine 0·60 grm.

6th.—Apyrexia. 36·8° C. in the morning, 37·2° C. in the evening. Examination of blood on November 6th; crescent-shaped bodies still numerous; spherical bodies provided with mobile flagella, whose existence I noticed for the first time. On November 6th the patient took again 0·60 grm. sulphate of quinine.

7th.—Apyrexia. Examination of blood; crescent-shaped bodies still numerous. I again noticed the existence of the spherical elements provided with flagella. The patient again took, on November 7th, morning and evening, 0·60 grm. sulphate of quinine; on the following days the quinine was omitted. The apyrexia persisted. Examination of blood on November 9th; numerous crescent-shaped bodies; spherical bodies with flagella. The principal doctor, Aron, and MM. Petit and Troussaint, army assistant surgeons, verified the existence of the flagella, which were endowed with very quick movements.

From November 10th to 25th the apyrexia persisted. The anæmia was still very pronounced. Examination of blood on November 17th; crescent-shaped bodies still numerous; spherical bodies also numerous; flagella. I noticed that the flagella end in a little knob at their free extremity. Examination of the blood on November 25th; crescent-shaped bodies; spherical bodies; these were not so numerous, but larger than in the previous examinations; the granules of pigment were endowed with very quick movements within some of these elements. For the first time I noticed that the flagella, at first adherent to the spherical elements, detach themselves after a variable time, and became free in the serum; the free flagella continued to move among the blood-corpuscles, to which they gave very free movements.

26th.—Attack of fever at 10.30 a.m. Sulphate of quinine 0·80 grm.

From the 27th to the 30th the patient takes every day 1·60 grm. of sulphate of quinine in two doses; and from December 1st to 8th 0·80 grm. quinine every day, or 12·80 grms. of quinine in twelve days. The fever did not reappear. Examination of blood on December 10th; no parasitic elements found.

December 12th.—The patient left the hospital on sick leave.

It is worthy of notice that in this case the flagella had resisted the sulphate of quinine several days, contrary to what generally happens, and very large doses of quinine were necessary to make them disappear. This was therefore a case exceptionally favourable for studying these bodies.

Obs. XXIII.—*Quotidian intermittent fever; acute palustral*

cachexia; hæmatozoa of paludism; spherical bodies; crescent-shaped bodies.

B., aged 25, a soldier in the third squadron of artillery, admitted to the Constantino Hospital August 22nd, 1881.

B. has been eighteen months in Algeria; he was recently employed at Ain-el-Bey. During the last five weeks general malaise; weakness; pains in the limbs; for the last fortnight œdema, first of the lower limbs, then of the face. The patient says he has not had any attack of fever, but on August 22nd, 23rd, and 24th I noticed every evening considerable fever of which the patient is not conscious (there is no shiver at the commencement of the attacks), and I am quite sure that this quotidian intermittent fever has been existing a long time. The patient has not taken any sulphate of quinine before entering the hospital.

August 22nd.—At 4 p.m. 39·8° C.

23rd.—37·8° C. in the morning; at 4 p.m. 40° C. Great anæmia; earthy tint of skin; the face is puffy; a little œdema of the lower limbs; no albumen in urine. The splenic dulness is 10 cm. by 12 cm. No diarrhœa. Slight laryngitis. Examination of blood on August 23rd at 9.30 a.m. Crescent-shaped bodies; small spherical non-pigmented bodies, or containing a few granules of pigment, adherent to red blood-corpuscles; melaniferous leucocytes. Examination of blood on August 23rd at 4 p.m. (during the attack). Same results as in the morning.

24th.—38·3° C. in the morning, 40·6° C. in the evening. Sulphate of quinine 0·80 grm. morning and evening.

25th.—Apyrexia, which persists on the following days. The sulphate of quinine is continued in doses of 0·80 grm., then 0·60 grm. till September 3rd. Strength and appetite return. The œdema of the face and lower limbs disappears. The examination of blood on September 11th no longer shows the existence of any parasitic elements. The patient leaves the hospital on September 18th on sick leave.

Obs. XXIV.—*Quotidian intermittent fever (relapse). Hæmatozoa of paludism; crescent-shaped bodies; spherical bodies; flagella.*

D., aged 24, soldier in first foreign regiment, enters the hospital at Val-de-Grâce on October 23rd, 1888.

No serious previous illness. D. entered military service in November, 1883; was seized with intermittent fever in Tonquin in April, 1887. On August 15th, 1888, he disembarked at Algiers, and was treated at the Dey Hospital till September 1st. He then returned to France on sick leave for two months. The intermittent fever reappeared soon after his return

to France. He had to enter the hospital at St. Martin, where his fever was arrested after several doses of sulphate of quinine. A new relapse of fever brought him to the Val-de-Grâce on October 23rd. Attacks of fever on October 23rd and 24th. The morning temperature of October 24th is 39·8° C. The pulse beats 100 per minute.

October 24th.—Apyrexia in the morning; the patient is very anæmic; the skin has the earthy tint of palustral cachexia; the mucous membrane is pale; the spleen is very much hypertrophied; the splenic dulness is 12 cm. by 14 cm. Examination of blood on the morning of 24th. Crescent-shaped bodies rather numerous; no amœboid bodies or flagella. On the evening of October 24th the patient has a little fever.

25th.—General malaise; fever this morning; pain at the occiput. Examination of blood on the morning of October 25th. Crescent-shaped bodies; pigmented spherical bodies, immobile or provided with flagella; free flagella. I inoculated with the blood of this patient some tubes containing cultivation broth and gelatine. The blood was taken with all the necessary precautions to avoid the introduction of foreign germs. The tubes are placed in the stove at 37° C. On the 25th during the day the patient took 0·60 grm. of hydrochlorate of quinine.

26th.—The patient has another slight attack during the day; 38° C. at 4 p.m. (hydrochlorate of quinine 60 centigrammes).

27th.—Apyrexia. I stop the hydrochlorate of quinine. Examination of blood on October 27th: crescent-shaped bodies; amœboid bodies with or without flagella. The broth inoculated with blood has remained limpid, and no growth had taken place in the gelatine. The examination of these media of cultivation was also negative on the following days. The attempts at cultivation on potato succeeded no better.

30th.—No new attack. Examination of blood; crescent-shaped bodies rather numerous; amœboid bodies with or without flagella. The latter are very rare.

November 2nd.—The patient shows great malaise and nausea, which makes one think that a relapse is imminent. Examination of blood on November 2nd in the morning, in the presence of Professor Bouchard: crescent-shaped bodies; amœboid bodies with or without flagella. The flagella are more numerous than at examination on October 30th.

3rd.—Relapse of fever; violent shivering at 2 p.m. At 3 p.m. the axillary temperature is 39·8° C.

4th.—Apyrexia. Examination of blood on the morning of

November 4th, before Professor Straus and Dr. Hanot; crescent-shaped bodies; amœboid bodies with or without flagella. MM. Straus and Hanot have no doubt as to the parasitic nature of these elements.

5th.—Vomiting; attack of fever. Hydrochlorate of quinine 0·60 grm.

6th.—Apyrexia. Examination of blood; crescent-shaped bodies; motionless spherical bodies. Only one of these elements presents flagella, whose movements stop very quickly. Hydrochlorate of quinine 0·60 grm.

9th.—No fresh attack. Examination of blood; crescent-shaped bodies rather numerous; a few amœboid bodies.

12th.—The patient had a slight attack during the night; general malaise; sweating. Temperature still a little above normal in the morning. Hydrochlorate of quinine 0·60 grm. Examination of blood; crescent-shaped bodies; amœboid bodies, motionless or provided with flagella.

13th.—Apyrexia. Hydrochlorate of quinine 0·60 grm.

21st.—Apyrexia persists. The blood only contains some crescent-shaped bodies very rare; in two preparations of blood examined with the greatest care I only found two of these elements, no amœboid bodies or flagella. I prescribed two more doses of hydrochlorate of quinine. The anæmia is much less than when the patient came in; his strength has partly returned; the spleen has remarkably diminished in size. The patient leaves the hospital November 24th.

Obs. XXV.—*Tertian intermittent fever (relapse). Hæmatozoa of paludism; spherical bodies; flagella.*

Car., aged 20, soldier in the 3rd zouaves, enters the Constantine Hospital on December 5th, 1882.

Car., who is serving voluntarily, is in the military service, and has been in Algeria one year. He says he had typhoid fever in his infancy; since then he has not had serious illness. He had intermittent fever for the first time in July, 1882, at Ain-el-Bey; he was readmitted at Constantine on July 29th; ill for four days.

Quotidian intermittent fever. Car has been treated at the infirmary twenty days. Relapse of fever early in September; a fortnight's treatment at the infirmary. New relapse at the beginning of November. Third admittance to the infirmary; twelve days' treatment. On November 19th the patient returned to service, and has continued till December 2nd. On December 2nd relapse of fever; attack about 5 a.m. with initial shivering. Fresh attack on December 4th at same hour.

December 5th.—Apyrexia; profound anæmia, emaciation, general feebleness, vertigo. The tongue is a little pale; anorexia; no diarrhœa. The splenic dulness measures 11 cm. by 12 cm. (half a dose; sulphate of quinine 1 grm. in the evening). Examination of blood made on December 5th, 8.30 a.m. Spherical bodies of small or medium size in quite a large number, free or adherent to the blood-corpuscles; spherical bodies containing mobile pigmented granules and provided with flagella, flagella free; melaniferous leucocytes.

6th.—The patient takes another 1 grm. sulphate of quinine at 6 a.m. In spite of that he has an attack of fever; at 7.30 a.m. the axillary temperature is about 40° C.; he has not had initial shivering; headache; much thirst; at 4 p.m. 37·3° C. Examination of blood made on December 6th in the morning, during the attack. Spherical bodies of medium or small size, free or adherent to the blood-corpuscles; spherical bodies containing mobile pigmented granules; melaniferous leucocytes.

7th.—37·3° C. in the morning; in the evening apyrexia persists (a half dose of sulphate of quinine 0·80 grm. morning and evening; cinchona wine). Examination of blood made on December 7th. Spherical bodies in very small numbers; melaniferous leucocytes.

8th.—Apyrexia persists (one dose; sulphate of quinine 0·80 grm.; cinchona wine, coffee). The sulphate of quinine is continued in doses of 0·60 grm. up to December 14th. No return of fever. The patient goes out on December 21st on sick leave.

Obs. XXVI.—*Tertian intermittent fever* (*relapse*). *Hæmatozoa of paludism; spherical bodies, flagella.*

Sim., aged 23, soldier in the second company of discipline, admitted to the military hospital, Constantine, on April 27th, 1881, after leaving the hospital of Soukharas.

Sim. had intermittent fever for the first time on July 20th, 1880. He was admitted to the hospital of Soukharas for tertian intermittent fever; he was afterwards sent on sick leave to France. The patient returned to Algeria on February 4th last, and on February 5th had a relapse of fever. The patient has taken several doses of quinine; the fever disappeared for a week, then gave place to new attacks. For a month the patient took only cinchona wine; for a week regular attacks, returning every two days towards 7 a.m.; last attack April 27th. The patient has had, moreover, for the last few days an area of splenitis, very painful; several blisters have been applied to the left hypochondrium.

April 28th.—Apyrexia; profound anæmia; the skin has an earthy tint, very marked on the face; mucous membrane pale; great feebleness, vertigo in the upright position, sharp pains at the side of the kidneys. The splenic dulness measures 10 cm. by 14 cm. Tongue clean; a little appetite; no diarrhœa (half a dose; cinchona wine). Examination of blood made on April 28th at 9 a.m.: spherical bodies containing mobile granules of pigment, or provided with flagella.

29th.—At 6 a.m. attack of fever; at 7 a.m. 39·7° C. (diet, lemonade; sulphate of quinine 0·60 grm. in the evening).

30th.—Apyrexia. Sulphate of quinine 0·60 grm.

May 1st and 2nd.—Apyrexia persists. The patient is better; a little appetite (one dose sulphate of quinine, 0·60 grm.; cinchona wine).

3rd to 8th.—Apyrexia persists. Strength returns. Examination of blood made on May 6th: nothing abnormal.

9th.—Relapse of fever; shivering at 1 p.m.; at 3 p.m. the axillary temperature is about 40·3° C.

10th.—Apyrexia. Examination of blood made May 10th in the morning: spherical bodies of average size provided with flagella; spherical bodies of small size. Sulphate of quinine 1·20 grm.

11th.—Attack of fever; at 7 a.m. shivering; at 8 a.m. 41·1° C.; at 3.30 p.m. the axillary temperature is still about 40° C. (sulphate of quinine 0·60 grm. in the evening).

12th.—36·5° C. in the morning. In the evening apyrexia persists (sulphate of quinine 1·20 grm.).

13th.—35·6° C. in the morning. The pulse is slower. Splenic area very tender. In the evening apyrexia persists (sulphate of quinine 0·60 grm.; blistering over the region of the spleen).

14th to 24th.—No relapse. Sulphate of quinine is continued in doses of 0·60 grm. a day (one dose; cinchona wine).

21st to 31st.—No return of fever. Strength returns. Examination of blood made May 31st; nothing abnormal.

Reckoning from June 1st, I gave sulphate of quinine up to June 6th (60 centigrammes a day) in order to prevent a relapse. On June 3rd the splenic dulness measures no more than 7 cm. by 8 cm. Patient went out June 11th, 1881.

Obs. XXVII.—*Tertian intermittent fever. Hæmatozoa of paludism; crescent-shaped bodies; spherical bodies of small size.*

Mont., aged 23, corporal in the 3rd zouaves, admitted to the Constantine Hospital October 11th, 1881.

Mont. has had fever for the first time September 4th. Regular

attack, quotidian at the beginning, since tertian type. Last attack October 9th; again on October 10th.

October 11th.—Attack of fever; 39·2° C. at 8 a.m.; 39·3° C. at 4 p.m. Anæmia very marked; earthy colour of the skin. The area of splenic dulness measures 9 cm. by 10 cm. Examination of blood made on October 11th at 8.30 a.m.: crescent-shaped bodies; small spherical bodies not pigmented, adherent to blood-corpuscles. Sulphate of quinine prescribed on leaving at 11 p.m. No new attack. Patient leaves the hospital on November 2nd on sick leave.

Obs. XXVIII.—*Intermittent fever tertian (relapse). Hæmatozoa of paludism; crescent-shaped bodies.*

Br., aged 22, overseer of military hospitals, admitted to the Constantine Hospital on February 24th, 1881.

Br. was attacked with fever for the first time in the middle of September, 1880, at Fort National. The fever took from the beginning the tertian type. It is the sixth time that the patient has been admitted to hospital for intermittent fever; the last relapse was February 23rd. The patient has not taken sulphate of quinine for some time.

February 24th.—Apyrexia; anæmia very marked, general weakness. The area of splenic dulness measures 11 cm. by 11 cm. Examination of blood on February 25th in the morning (before the attack): I demonstrated the existence of crescent-shaped bodies in large numbers without other parasitic elements.

25th.—The patient had attack of fever. Examination of blood on February 26th at 2 p.m.: crescent-shaped bodies. Sulphate of quinine 0·60 grm. from February 27th to March 4th. No new attacks. Examination of blood made on March 6th: very few crescent-shaped bodies. Examination of blood made on March 9th: crescent-shaped bodies in greater numbers than in preceding examination. In the night of March 10th the patient had an attack of fever. Examination of blood on March 11th: crescent-shaped bodies. Sulphate of quinine is prescribed for ten days; fever does not reappear. Examination of blood on April 3rd: I find still some crescent-shaped bodies. The patient goes out on April 4th.

Obs. XXIX.—*Tertian intermittent fever (relapse). Hæmatozoa of paludism; crescent-shaped bodies; spherical bodies; flagella.*

Gold., aged 26, soldier in the 4th hussars, admitted to the Constantine Hospital on December 19th, 1881.

Gold. arrived in Algeria in the month of November, 1880. In March, 1881, he entered the hospital of Setif for bronchitis; in

April entered same hospital for typhoid fever. During the expedition of Kroumyrie, Gold. was admitted to the hospital for dysentery. In October, during the march upon Kaïrouan, the patient had intermittent fever for the first time. Since then he has had several relapses, notably at Gafsa; at the same time there was dysentery. The patient was sent in succession to Tébessa, then to Constantine.

December 19th.—Apyrexia; profound anæmia, characteristic earthy tint; lips pale; emaciation, general feebleness very great; dysentery, the stools contain only blood; fatty stools, colic, tenesmus. I prescribed milk diet and several doses of seidlitz water; afterwards the pilules of Segond.

22nd.—The stools have become normal. The patient eat half a ration. No attack of fever since admission to the hospital.

January 11th, 1882.—Return of fever 39·5° C. at 3 p.m.

12th.—Apyrexia in the morning. In the evening the apyrexia maintained. The spleen percusses out beyond the lower ribs about two fingers' width. The splenic dulness measures 12 cm. by 12 cm. Examination of blood made on January 12th at 2 p.m.: crescent-shaped bodies in large numbers, motionless spherical bodies, or bodies provided with flagella, alive with very active movements; oval bodies.

13th.—Apyrexia in morning at 2 a.m., onset of fever at 10.30 a.m., the thermometer registers 39·6° C. Examination of blood made on January 13th at 2 p.m.: crescent-shaped bodies in great number, oval bodies, spherical bodies.

14th.—Apyrexia morning and evening. Anæmia, general feebleness, small appetite (half dose sulphate of quinine, 0·80 grm., morning and evening).

15th.—The apyrexia persists (a half dose sulphate of quinine, 0·80 grm., cinchona wine, coffee). The sulphate of quinine is continued up to January 18th. No return of fever. Strength returns quite easily. The patient goes out on January 18th on sick leave for three months.

Obs. xxx.—*Intermittent fever. Sixth relapse (tertian type), crescent-shaped bodies. Seventh relapse (tertian type), spherical bodies, flagella.*

God., aged 23, soldier in the third squadron of artillery, entered the Constantine Hospital January 25th, 1882.

God., who has been in Algeria for a year, had intermittent fever for the first time in September, 1881. Five admissions to hospital for intermittent fever. Last relapse was eight days ago; tertian

fever very characteristic; the patient has taken six doses of sulphate of quinine of 1 grm. each before entering the hospital.

January 26th.—Apyrexia. Anæmia very marked. General feebleness. The area of splenic dulness measures 14 cm. by 12 cm. Examination of the blood made January 26th: crescent-shaped bodies, oval bodies, melaniferous leucocytes. No new attacks. I prescribe only cinchona wine. The patient goes out of the hospital on February 8th. The fever reappears on February 8th, always with the tertian type, and the patient re-enters the hospital on March 24th. Last attack on March 22nd and 24th. Examination of blood made on March 24th, at end of attack: spherical bodies of small and medium size, free or adherent to the blood-corpuscles; melaniferous leucocytes.

March 25th.—Apyrexia. Anæmia very marked; earthy colour of the skin; intellectual indifference very marked. The splenic dulness measures 12½ cm. by 16 cm. Examination of blood made March 25th: spherical bodies rare; melaniferous leucocytes. The patient has taken several doses of sulphate of quinine before entering the hospital; I prescribed only cinchona wine.

29th.—Attack of fever; at 6 a.m. shivering; at 7 a.m. 39·8° C.; at 3 p.m. the apyrexia is complete. Examination of blood made at 9 a.m., at the end of the attack: spherical bodies of mean size, free or adherent to blood-corpuscles; some contain granules of pigment in motion.

30th and 31st.—Apyrexia persists. Examination of blood made March 31st at 9 a.m.: spherical bodies free or adherent to red blood-corpuscles; flagella.

The apyrexia continues the following days, though the patient only takes cinchona wine. Examination of blood made April 4th: I still find some spherical bodies. The patient leaves the hospital on April 10th, 1882.

Obs. XXXI.—*Tertian intermittent fever contracted in Algeria. Relapse after return to France; tertian type. Hæmatozoa of paludism; crescent-shaped bodies; spherical bodies; flagella.*

Bel., aged 22, admitted to hospital of Val-de-Grâce on October 15th, 1887, under Dr. Vaillard.

Patient contracted palustral fever in August last in Algeria; the fever had from the beginning the tertian type. On several occasions the patient took quinine, but the fever reappeared notwithstanding.

On admission to Val-de-Grâce profound anæmia; the skin and mucous membranes pale; œdema of the lower limbs; the pulse beats only 44 a minute. The spleen is markedly hypertrophied;

the splenic dulness measures 16 cm. in height. Apyrexia remains up to November 9th. Examination of blood made on November 8th: crescent-shaped bodies in rather large numbers, two or three are often in the field of the microscope.

November 9th.—Attack of fever very characteristic, with the three stages of cold, heat, and sweating.

12th.—The attack of fever is not repeated. Examination of blood: crescent-shaped bodies; spherical bodies; flagella. I showed these objects to M. Vaillard.

12th and 13th.—The patient took 0·80 grm. sulphate of quinine.

14th.—No fresh attack. Examination of blood: crescent-shaped bodies as numerous as before.

19th.—No fresh attack. Examination of blood: crescent-shaped bodies still as numerous as before. I showed them to Professor Straus.

December 5th.—Attack of fever very characteristic.

6th.—Apyrexia.

7th.—Fresh attack of fever. These two attacks of December 5th and 7th leave no doubt about the type of fever. At the end of these attacks the patient takes several doses of quinine, and leaves the hospital on December 20th, 1887, in a satisfactory state. The anæmia is very much less marked than on entering the hospital. The œdema of the lower limbs has disappeared, and the spleen has diminished in size.

Obs. XXXII.—*Tertian intermittent fever contracted at Tonkin (relapse). Hæmatozoa of paludism; crescent-shaped bodies; spherical bodies; flagella.*

G., aged 22, soldier in second regiment of infantry of marines, entered the hospital of Val-de-Grâce on May 6th, 1887.

G. spent eleven months in Tonkin from June, 1885, to May, 1886. He was attacked with intermittent fever for the first time at the end of September, 1885, at Haiphong. The fever showed from the beginning the tertian type. Several relapses during his sojourn in Tonkin. At each relapse patient took several doses of quinine.

In May, 1886, G. embarked for Madagascar, and remained there till the end of February, 1887. Several relapses of fever during his sojourn in Madagascar, and on several occasions the fever was complicated with pernicious symptoms. G. left Madagascar at the end of February, and having a furlough of three months he arrived in Paris on March 11th, 1887. From then to May 6th, the day of entering the hospital, the patient had several relapses of fever, which were treated with sulphate of quinine.

6th.—Anæmia very marked, no fever. The spleen is double its size; nervous complications; loss of memory; hesitancy of speech. At the end of an attack of fever in Madagascar the patient had aphasia for four hours. Slight nystagmus. The apyrexia persists up to May 20th.

20th.—Attack of fever during the day. At 3 p.m. the axillary temperature 39° C. Examination of blood made May 20th during the attack: crescent-shaped bodies; free spherical bodies.

21st.—Apyrexia morning and evening. The patient has not taken quinine. Examination of blood made May 21st: crescent-shaped bodies (rare); free spherical bodies, some show flagella. I showed these specimens to Dr. Maurel.

22nd.—Attack of fever, 39° C. at 4 p.m.

23rd.—36·2° C. in the morning. Examination of blood: free pigmented spherical bodies, some flagella: crescent-shaped bodies. I showed Dr. Roux a spherical body with a flagellum.

24th.—Attack of fever 39·2° C. in the morning (tertian fever anticipated).

28th.—The apyrexia continues. Examination of blood: pigmented spherical bodies rare.

June 1st.—There have been no new attacks. Examination of the blood gives no new results. The patient has only taken cinchona wine. The patient left the hospital.

Obs. XXXIII.—*Intermittent quartan fever. Hæmatozoa of paludism; spherical bodies.*

Ben., aged 24, soldier in the fourth zouaves, admitted to Constantine Hospital December 23rd, 1881.

Ben. had intermittent fever first at Aumale on August 10th, 1881. He was for a month under treatment at the hospital of Aumale for tertian intermittent fever. Relapses in September, November, and December.

December 23rd.—Apyrexia; anæmia very marked. The zone of splenic dulness measures 9 cm. by 11 cm.

30th.—Attack of fever at 4 p.m. The axillary temperature 40·2° C.

31st.—Apyrexia. Examination of blood made on December 31st at 2.30 p.m.: spherical bodies of small or average size, free or adherent to blood-corpuscles; melaniferous leucocytes.

January 1st, 1882.—Apyrexia continues.

2nd.—Attack of fever at 3 p.m.; at 3.30 the axillary temperature is about 39·6° C. Examination of blood made January 2nd at 4 p.m.: spherical bodies of average size, free or adherent to blood-corpuscles.

From January 3rd the patient took sulphato of quinine; nevertheless on the 5th in the ovening he had a slight attack. The sulphate of quinine is continued till January 11th. No relapse of fever. The patient left the hospital on January 18th on sick leave.

Obs. XXXIV.—*Quartan fever (relapse). Hæmatozoa of paludism; spherical bodies; segmented bodies.*

Dan., aged 25, soldier in the eighth company of mounted troops, admitted to the Constantine Hospital on September 11th, 1880.

Dan. had intermittent fever for the first timo in September, 1880. Since March, 1881, several relapses of tertian or quartan type. The patient took on several occasions sulphate of quinine.

September 15th.—Apyrexia; anæmia very marked, earthy tint of the face; general feebleness, apathetic, very great indifference. The zone of splenic dulness measures 9 cm. by 10 cm.

17th.—Attack of fever; at midday 40° C.; at 4 p.m. 41·3° C. Examination of blood made September 17th at 2 p.m. (during the attack): segmented bodies, or rose-shaped bodies, in rather large numbers; melaniferous leucocytes.

18th.—Apyrexia. Examination of blood made September 18th: spherical bodies of small or average size; segmented bodies are rarer than on September 17th.

19th.—Apyrexia continues.

20th.—Attack of fever, 40·6° C., at 7.30 p.m.

21st.—Apyrexia, which continues during September 22nd.

23rd.—Fresh attack; 39·6° C. in the morning, 40·9° C. at 6 p.m. Examination of blood made September 23rd at 8.30 a.m.: spherical bodies in rather large number; segmented bodies rare. From September 23rd sulphate of quinine is prescribed in doses of 0·80 grm., then of 0·60 grm. till October 3rd. No return of fever. Examination of blood made on October 2nd shows nothing abnormal. The patient leaves the hospital on October 3rd on sick leave.

Obs. XXXV.—*Quartan fever contracted in Tonkin (relapse). Hæmatozoa of paludism; spherical bodies; segmented bodies.*

Pois., aged 24, soldier in the marine artillory, entered the hospital of Val-de-Grâce on March 15th, 1890. Patient has had intormittent fever in Tonkin in September, 1888; relapse in August, 1889. Pois. landed at Toulon on February 6th, and obtained sick leave. New attack of fever since his arrival in Paris; last attack March 13th. On admission the patient was anæmic, but still fairly robust; apyrexia March 15th. The spleen is increased in size; the splenic dulness measures 8 cm. by 12 cm. The patient has not taken sulphate of quinine since he was in

Paris. Examination of blood made on March 15th: some spherical bodies, quite large, adherent to blood-corpuscles.

March 16th.—Attack of fever, which came on at 4 p.m. with shivering; at 6 p.m. the temperature was 40·8° C.; at 10 p.m. it was still 39° C. (sweating).

17th.—Apyrexia. Spherical bodies, free or adherent to blood-corpuscles; segmented bodies. No quinine.

18th.—Apyrexia. Examination of blood made on March 18th at 3 p.m.: spherical bodies of medium or small size, free or adherent to blood-corpuscles. No quinine.

19th.—Apyrexia in the morning. Examination of blood made at 2 p.m.: spherical bodies of small or medium size; segmented bodies. On March 19th at 4 p.m. shivering. Temperature rose after this time, and at 8 p.m. is 40·4° C.; at 10 p.m. it is not more than 38° C. (sweating).

20th.—Apyrexia. Hydrochlorate of quinine 0·60 grm. morning and evening. Examination of blood made on evening of March 20th: I find no more parasitic elements.

On the 21st and 22nd the patient again took 0·60 grm. hydrochlorate of quinine.

Obs. XXXVI.—*Quartan intermittent fever (relapse). Hæmatozoa of paludism; crescent-shaped bodies; spherical bodies; flagella.*

Fet., aged 24, soldier in the fourth squadron of artillery, admitted to Constantine Hospital February 24th, 1881.

Fet. had intermittent fever first at Mondovi in August, 1880. Several relapses during September, October, and November. The fever reappeared in January, 1881, and remains in the quartan type. Last attack on February 23rd.

February 24th.—Apyrexia. The patient is much weakened; anæmia, the skin has the characteristic tint. The area of splenic dulness measures 10 cm. by 12 cm. Examination of the blood made on February 24th in the evening: crescent-shaped bodies; spherical bodies.

26th.—Attack of fever during the day; the quartan type is then very characteristic. The patient has not taken quinine since admission to the hospital. Examination of blood February 26th in the morning, some hours before the attack: spherical bodies in rather large number; flagella.

From February 27th I prescribed sulphate of quinine, which is continued till March 5th.

March 10th.—No new attacks of fever. Examination of blood does not show any parasitic elements. The patient leaves the hospital without having any relapse.

Obs. XXXVII.—*Quartan fever. Hæmatozoa of paludism; crescent-shaped bodies.*

Bon., aged 20, soldier in the 16th regiment of artillery, admitted to Constantine Hospital November 19th, 1882.

Bon. has been in Algeria for seven months. He first had fever on October 8th, and has been treated at the hospital of Philippeville for continued fever with typhoid state.

November 19th.—Profound anæmia, general weakness; vertigo; emaciation; the zone of splenic dulness measures 13 cm. by 15 cm. Attack of fever, 38° C. at noon, 38·8° C. at 4 p.m.

20th and 21st.—Complete apyrexia.

22nd.—Attack of fever; 38·8° C. in the morning, 36° C. in the evening. Examination of blood made on November 23rd: crescent-shaped bodies; melaniferous leucocytes. Sulphate of quinine is prescribed from November 23rd to 30th, and from December 3rd to 7th. The fever does not reappear, and the state of the patient improves rapidly; he leaves the hospital on December 9th.

Obs. XXXVIII.—*Tertian intermittent fever (relapse). Hæmatozoa of paludism; crescent-shaped bodies; spherical bodies; flagella. Relapses with the quotidian, then with the tertian type; crescent-shaped bodies; spherical bodies; flagella.*

Patient enters the Constantine Hospital for a relapse of intermittent fever on November 12th, 1881. The fever shows the tertian type. Examination of blood, made some hours before the attack, shows crescent-shaped bodies, spherical bodies, and flagella.

The fever disappeared under the influence of quinine. Relapse on November 29th, with some quotidian attacks; new relapses on December 21st and 27th, with attacks of tertian type. I discovered again in the blood crescent-shaped bodies in rather large number, spherical bodies, and flagella (for details see Obs. 27 in my 'Traité des fièvres palustres,' p. 259).

Obs. XXXIX.—*Quotidian intermittent fever. Hæmatozoa of paludism; crescent-shaped bodies; spherical bodies; flagella (relapse); pernicious complications; spherical bodies.*

Patient admitted to Constantine Hospital November 7th, 1882, for quotidian intermittent fever. Examination of blood made on November 19th, 1882, during an attack: crescent-shaped bodies in great number; spherical bodies, flagella. Relapse of fever on 15th, 1883. Patient readmitted to Constantine Hospital on March 20th, 1883, for palustral cachexia, with severe symptoms. Examination of blood shows some spherical bodies of small or

medium size, free or adherent to blood-corpuscles. I do not find more crescent-shaped bodies (for details see Obs. XLVIII of my 'Traité des fièvres palustres,' p. 334).

Obs. XL.—*Tertian intermittent fever. Hæmatozoa of paludism; spherical bodies; flagella (relapse); quotidian attacks; crescent-shaped bodies.*

Patient admitted to the Constantino Hospital on December 16th, 1882, for intermittent fever (relapse), with tertian type. Examination of blood made in the interval of the two attacks. Spherical bodies of medium or small size. Examination of blood made during an attack. Spherical bodies of medium or small size, free or adherent to blood-corpuscles; flagella. Fever ceases after sulphate of quinine. Return of fever on January 19th, 1883; attack on the 19th and 20th (quotidian type). On examination of blood I find only some crescent-shaped bodies (for more details see Obs. XLIX of my 'Traité fièvres palustres,' p. 338).

Obs. XLI.—*Tertian intermittent fever, afterwards quotidian (relapse). Hæmatozoa of paludism; crescent-shaped bodies; spherical bodies.*

Th., aged 23, soldier in the third squadron of artillery, entered Constantine Hospital September 25th, 1881.

Th. has been in Algeria twenty-two months. He is said to have had the fever first at Collo; it lasted a fortnight. The attack returned every two days. Patient has taken several doses of sulphate of quinine. Last attack of fever on September 21st.

September 26th.—Apyrexia; profound anæmia; general weakness; indifference very marked; anorexia. The splenic dulness measures 14 cm. by 15 cm. Examination of blood made September 26th at 2 p.m.: crescent-shaped bodies; amœboid bodies, containing granules of pigment endowed with rapid movement.

27th.—Apyrexia in the morning. Examination of blood made on September 27th in the morning: crescent-shaped bodies. In the afternoon attack of fever without initial shivering; at 4 p.m. the axillary temperature is 39·1° C.

28th.—37·5° C. in the morning. Examination of blood made at 2.30 p.m.: crescent-shaped bodies; spherical bodies of small size; slight attack during the day; at 4 p.m. 38·5° C.; headache. Sulphate of quinine 0·80 grm. in the evening. On the following days apyrexia. Sulphate of quinine is continued till October 7th, 0·80 grm. first, then 0·60 grm. The patient went out on October 17th.

Obs. XLII.—*Quotidian intermittent fever. Hæmatozoa of palu-*

dism ; crescent-shaped bodies ; spherical bodies. Return of fever, tertian type ; new examination of the blood ; spherical bodies.

Du., aged 30, gendarme, admitted to the hospital of Constantine the 5th of August, 1882. He has been attacked with intermittent fever for the first time ; he was twelve days at Oued-Zenati. Quotidian fever attacks 3rd, 4th, 5th, 6th August.

August 6th.—39·2° C. in the morning, 39·7° C. in the evening. Anæmia very marked ; the zone of splenic dulness measures 11½ cm. by 13½ cm. Examination of blood made on 6th August in the morning : crescent-shaped bodies in great numbers ; oval bodies ; spherical bodies very rare ; melaniferous leucocytes. The fever yielded readily to sulphate of quinine ; the patient went out 22nd August.

Du. had a return of fever in the month of October, 1882, and a second relapse in the month of April, 1883, for which he re-entered the hospital 25th April. The fever reappeared 16th April ; slight attack at first, afterwards more and more severe, returning every two days ; regular attacks with initial shivering. From the 16th to the 24th there has been four attacks ; the patient has taken 2 grms. sulphate of quinine before entering the hospital.

April 25th.—Apyrexia ; anæmia very marked ; earthy tint of the face ; general feebleness ; want of appetite. The splenic dulness is 8 cm. in height by 10 cm. in breadth. Examination of the blood made 25th April : spherical bodies, free or adherent to the blood-corpuscles, in small numbers ; melaniferous leucocytes. I do not find any crescent-shaped bodies. No relapse. Examination of the blood made 4th May does not reveal any parasitical elements. I prescribed in the meantime some doses of sulphate of quinine. The patient leaves the hospital the 10th May.

Obs. XLIII.—*Continued palustral fever, first attack. Hæmatozoa of paludism ; spherical bodies of small size ; relapse of fever. Attack of tertian type, afterwards quotidian ; spherical bodies.*

Mar., aged 23, soldier in 3rd zouaves, admitted to the hospital at Constantine the 20th July, 1882.

The patient has taken fever for the first time 15th July at Ain-el-Bey ; continued fever, which remains up to the time of admission to the hospital. The 20th July at 4 p.m. the axillary temperature is 39° C. General malaise ; headache, very acute thirst, tongue dry and red at the point. The zone of splenic dulness measures 9½ cm. in height by 10½ in breadth. The patient has not taken quinine before admission to the hospital. Examination of the blood made 20th July at 4.30 p.m. : spherical bodies of small size, free or adherent to some blood-corpuscles.

21st July fever remains 40·4° C. in the morning, 41·4° C. in the evening. Typhoid state without abdominal symptoms. Examination of blood made 21st July at 2 p.m.: spherical bodies of small or medium size, free or adherent to red blood-corpuscles. Some of these bodies contain granules of pigment, endowed with very quick movement. Sulphate of quinine 1·60 grms. on the 21st. On the 22nd July 37·5° in the morning. General feebleness, apathy, indifference, want of appetite. Sulphate of quinine 0·80 grm. morning and evening. The sulphate of quinine is continued in doses of 0·80 grm., afterwards 0·60 grm. until the 30th July. No return of fever. The patient goes out the 16th August, 1882. The 11th March, 1883, relapse of fever of the tertian type. 29th March new relapse. The patient re-enters the hospital of Constantine the 3rd April, 1883. 3rd April, attack of fever; 40·2° C. at midday; 38·1° C. at 4 p.m. Examination of blood made 3rd April at 2 p.m.: spherical bodies of small and of medium size, free or adherent to the red blood-corpuscles; spherical bodies containing granules of moveable pigment; melaniferous leucocytes. Sulphate of quinine 1 grm. in the evening. 4th April, 38·3° C. in the morning, 38·4° C. in the evening. Anæmia very marked, earthy tint of the face, vertigo. The area of splenic dulness measures 12 cm. in height, 13 cm. in breadth. Examination of blood made 4th April: the same result as 3rd April. Sulphate of quinine 1·80 grm.

April 5th.—Apyrexia, which is continued on the following days. Sulphate of quinine is continued in doses of 0·80 grm., then 0·60 grm. till April 12th, and again from April 15th to 19th. Examination of blood made on April 18th does not show existence of any parasitic body. The patient leaves the hospital on April 20th on sick leave.

Obs. XLIV.—*Quotidian intermittent fever. Hæmatozoa of paludism; spherical bodies. Relapse of fever; spherical bodies; flagella.*

En., aged 22, soldier in the third zouaves, admitted to Constantine Hospital August 21st, 1882. First attack of fever August 15th at Ain-el-Bey, quotidian intermittent fever.

August 21st.—Apyrexia; anæmia; general weakness. The zone of splenic dulness measures 11 cm. by 13 cm. Patient took a dose of sulphate of quinine before entering the hospital.

29th.—Attack of fever at 11 a.m.; at noon 41° C.; at 4 p.m. 38·7° C. Examination of blood made August 29th at 2 p.m: spherical bodies free or adherent to blood-corpuscles. Sulphate of quinine 1 grm. on 29th in the evening; 1·60 grms. on August

30th; 0·80 grm. on August 31st; 0·60 grm. from September 1st to 7th. The fever did not reappear. Patient left the hospital on September 16th on sick leave for two months. No relapse during the furlough, which the patient spent in France. Eu. returned to Algeria on November 21st, 1882. A slight relapse of fever took place in December. On March 24th the fever reappeared with the tertian type.

April 16th.—Another relapse with quotidian type obtained from April 16th to 19th. The patient re-entered the Constantine Hospital on April 19th.

19th.—Attack of fever; at 10 a.m. 41° C.; at 4 p.m. 38·5° C. Examination of blood made on April 19th at 2 p.m.: spherical bodies, free or adherent to some blood-corpuscles, in great numbers; spherical bodies of small size; flagella. Sulphate of quinine 1 grm.

20th.—Apyrexia; anæmia very marked; earthy tint of the face; vertigo; painful spot over the spleen. The zone of splenic dulness measures 8 cm. by 10 cm. Sulphate of quinine 1·80 grms. Examination of blood made on April 20th at 2 p.m.: spherical bodies very rare; melaniferous leucocytes. Sulphate of quinine was continued in doses of 0·80 grm. or 0·60 grm. till April 27th. No relapse of fever. The patient left the hospital on May 4th on furlough.

Obs. XLV.—*Quotidian intermittent fever (relapse). Hæmatozoa of paludism; crescent-shaped bodies; spherical bodies. Relapse of fever, tertian type; spherical bodies of small or average size. Fresh relapse, quotidian type; spherical bodies of small or average size.*

Cl., aged 22, adjutant in the 3rd regiment of Algerian riflemen, admitted to Constantine Hospital on October 27th, 1882. First attack of fever September 3rd, 1881; quotidian intermittent fever, which was stopped by several doses of sulphate of quinine, but reappeared quickly. Last attack was on October 24th and 25th.

October 27th.—Apyrexia; anæmia very marked; general weakness; vertigo; breathlessness; palpitation of the heart on the least effort; slight trembling of the hands; the splenic dulness measured 13 cm. by 17 cm. Examination of blood made on October 27th: crescent-shaped bodies; spherical bodies.

From October 27th to 30th the apyrexia continued. I only prescribed cinchona wine.

30th.—Slight attack; headache; at 3 p.m. temp. 38·4° C. Examination of blood made on October 30th at 3 p.m.: crescent-shaped bodies more numerous than on October 27th; melaniferous leucocytes. I prescribed sulphate of quinine from October 30th

to November 5th; the fever did not reappear. The patient went out November 9th on furlough. Cl. passed his furlough in France. The fever reappeared at several intervals during the furlough. He returned to Algeria on February 17th, 1883. Relapse of fever on March 10th; renewed attacks on March 12th and 14th. The fever then took the tertian type.

Cl. readmitted to Constantine Hospital on March 13th, 1883. Apyrexia; anæmia very marked; general feebleness; vertigo; anorexia. The area of splenic dulness measures 8 cm. by 9 cm. Examination of blood made March 13th, in the morning: spherical bodies small or of medium size, free or adherent to blood-corpuscles; melaniferous leucocytes; no crescent-shaped bodies.

March 14th.—Attack of fever at 4 a.m.; at 6 a.m. axillary temp. 40·4° C., at 4 p.m. 38·6° C. Examination of blood made March 14th, at 8.30 a.m.: spherical bodies of small or medium size, the latter in great number; melaniferous leucocytes. Sulphate of quinine is prescribed from March 14th to 23rd, and April 5th to 9th. No relapse. The patient went out on April 12th, 1883.

After leaving the hospital the fever reappeared on several occasions; the last relapse June 12th; attacks on June 12th, 13th, 14th, and 15th, coming on in the morning. On June 15th the patient re-entered the Constantine Hospital. Attack at 7.30 a.m.; at midday temp. was 40·6° C.; at 4 p.m. it is only 37·8° C. The area of splenic dulness measures 15 cm. by 17 cm. Examination of blood made on June 25th at 2 p.m. (at the end of the attack): spherical bodies of medium or small size; melaniferous leucocytes. Sulphate of quinine was prescribed from June 15th to 23rd, 0·80 grm. and 0·60 grm. per day; and from June 28th to July 3rd there was no relapse. Examination of blood made June 17th: I did not find any parasitic elements. The patient leaves the hospital on July 4th, 1883, on a furlough of three months.

Obs. XLVI.—*Intermittent fever. Several relapses, of which one was of the tertian type. Hæmatozoa of paludism; spherical bodies; crescent-shaped bodies; segmented bodies.*

G., aged 23, soldier in first foreign regiment, admitted to Val de Grâce January 4th, 1888.

G. had fever for the first time on August 18th, 1887, in the province of Oran. Quotidian attacks; the patient remained in hospital fifty days; he was sent afterwards on a furlough to the island St. Marguerite, where the fever reappeared several times.

G. arrived in Paris on December 20th, 1887; the fever reappeared on December 25th, and from then to January 4th (day of admission to the hospital) G. has had several attacks of fever.

January 3rd.—An attack of fever at 10 a.m.

4th.—Very well marked attack at hospital; shivering at 11 a.m.; at 1.30 the axillary temperature is 41° C.; the return to normal was only complete at 7 p.m. Examination of blood made on January 4th at 11 a.m., at the height of the attack: spherical bodies in rather large number, pigmented, free or adherent to blood-corpuscles; some segmented bodies (rose-shaped elements); some melaniferous leucocytes.

5th.—37° C. in the morning; patient was very anæmic; the skin was earthy; the splenic dulness measured 16 cm. by 16 cm.; the liver is not perceptibly increased in size. Examination of blood made on January 5th in the morning, at beginning of attack: spherical bodies in large number, pigmented, free or adherent to blood-corpuscles; segmented bodies; several of these show a complete segmentation, and the rounded corpuscles arising from this segmentation were in part scattered. On January 5th at 9 a.m. severe shivering; at 10 a.m. the axillary temperature was 41° C. The attack ceased at 2 p.m. Hydrochlorate of quinine, 0·60 grm., on January 5th, 6th, 7th. The apyrexia continued till January 20th. Examination of blood made on January 8th: not one single parasitic body found. Examination of blood made on January 13th: some crescent-shaped bodies seen.

On the 20th and 22nd fresh attacks of fever. Complete apyrexia on January 21st; the quotidian fever was now changed into tertian. I prescribed three doses of hydrochlorate of quinine 0·60 grm. on January 22nd, 23rd, and 24th.

February 5th.—Slight attack of fever.

13th.—Relapse. Attack on February 13th, 14th, 15th. The fever had now taken the quotidian type. Four doses of hydrochlorate of quinine 0·60 grm. from February 14th. Examination of blood made February 16th: crescent-shaped bodies found.

From the 25th to 27th three doses of hydrochlorate of quinine were given. No relapse of fever.

From March 8th to 10th I again prescribed quinine. The general state was improved. The splenic dulness measured only 10 cm. by 10 cm. Patient left the hospital on March 18th. Relapse of fever in April. G. readmitted to Val de Grâce on April 17th. He had that day an attack of fever. Examination of blood made April 17th. Spherical bodies of small or medium size, free or adherent to blood-corpuscles; some of tho spherical bodies con-

tain granules of pigment alive with very active movement. I did not observe flagella or crescent-shaped or segmented bodies.

April 18th.—Apyrexia. Examination of fresh blood: pigmented spherical bodies, free or adherent to blood-corpuscles. Examination of the blood in suspended drop. On April 17th I easily distinguished round the edge of the drop of blood spherical bodies in the midst of blood-corpuscles. On April 20th the blood-corpuscles were a little distorted (the preparation made on April 17th had been kept at the ordinary temperature of the laboratory); the spherical bodies were more or less distorted, motionless. On April 25th, eight days after the blood had been taken, the spherical bodies could still be recognised in the midst of blood-corpuscles. The patient took from April 18th several doses of hydrochlorate of quinine, and left the hospital without another attack. Examination of the blood made April 30th was negative.

Obs. XLVII.—*Irregular intermittent fever contracted in Tonkin (several relapses). Hæmatozoa of paludism; spherical bodies; segmented bodies.*

Sp., aged 25, soldier in the first regiment of marines, admitted to hospital of Val de Grâce February 12th, 1890.

Sp. had spent two years in Tonkin, and has had several attacks of intermittent fever. He had been admitted three times into hospital for this cause, and sailed for France in August, 1889. Since his return to France he has had sick leave. Several relapses of fever since September, treated each time with sulphate of quinine.

February 13th.—Apyrexia; anæmia very pronounced. The splenic dulness measured 8 cm. by 8 cm. Appetite good.

17th.—Slight attack of fever; temperature rose to 39° C.; following days malaise; headache; temperature rose a little in the evening, on February 23rd 38·5° C.

24th.—37·5° C. in the morning. The patient complains of headache and sleeplessness. Examination of blood on February 24th in the morning: pigmented spherical bodies, rather large, free or adherent to red blood-corpuscles; segmented bodies. Attack of fever, which began a little before the blood had been collected. At 1 p.m. the temperature was 39·6° C. Examination of blood made on February 24th at 2 p.m during the attack. Pigmented spherical bodies (rare); melaniferous leucocytes; no more segmented bodies. I prescribed three doses of hydrochlorate of quinine of 1·60 grms. each. The fever reappeared on several occasions without regular type.

ADDENDUM.

This work was already out of the press when I received Vandyke Carter's treatise of which mention is made on page 42. I am happy to be able to give a *résumé* of this very interesting work, 'Note on some Aspects and Relations of the Blood Organisms in Agues by Vandyke Carter: Scientific Memoirs by Medical Officers of the Army in India,' part 3, Calcutta, 1888) from a translation, for which I am indebted to Dr. Anderson. One will see by this *résumé* that the researches of Vandyke Carter are absolutely confirmatory of mine

Carter has examined the blood, 1st, in those subjects attacked with different forms of paludism; 2nd, in those subjects attacked with other ailments. The hæmatozoa have never been met with in the second category of patients.

The author gives his observations on seven patients attacked with paludism, in the blood of whom the presence of hæmatozoa was demonstrated as follows:

1st. Small spherical bodies, hyaline, adherent to blood-corpuscles, which represented the initial form of these parasites. Carter says that the illusions by which the blood-corpuscles so altered may be confounded with blood-corpuscles presenting simply clear spaces, an appearance which is particularly frequent when one examines blood in the tropics must be had regard to.

2nd. Pigmented spherical bodies, free or adherent to blood-corpuscles. These elements in the fresh state present amœboid movements. The pigmented granules included in the spherical bodies are often alive with an intermittent movement more or less rapid.

3rd. Spherical bodies with some flagella.

4th. Crescent-shaped bodies.

It follows from the descriptions of Carter, as from the plate which accompanies his work, that the parasitic elements observed by him are identical with those which I have described.

The spherical bodies are those which have been met with most frequently.

Carter has ascertained that the flagella, after being detached

from the spherical bodies, are in motion from ten to thirty minutes; they afterwards disappear, and the spherical body from which they emanated remains motionless.

"It was with the greatest difficulty," says Carter, "that I succeeded in preserving two or three of these flagella in preparations of dried blood."

The crescent-shaped bodies remain often during several weeks, even in patients under treatment with quinine.

It is very probable that the different parasitic forms indicated above belong to one single species. These forms appeared under the same conditions, and the order in which they follow one another is in general the same.

The infection might be produced by means of drinking-water.

The spherical bodies and the flagella are destroyed by the phagocytes, which do not attack the crescent-shaped bodies, hence the persistence of these last elements; the absorption of the spherical bodies by the leucocytes is easy to prove.

The parasite of paludism ought to be ranked among the hæmatozoa; they approach, on the one hand, the Trichomonades, *Trichomonas sanguinis* (horses and rats), and on the other the Sporozoa (crescent-shaped bodies).

There is not any constant relation between the nature of the parasitic elements and the clinical form which the paludism assumes.

The presence of parasitic elements in the blood of a patient gives certainty to the diagnosis of paludism.

Quinine acts by increasing the activity of the phagocytes, and not directly upon the hæmatozoa.

LITERATURE.

My intention is not to give the whole literature of paludism. I propose merely to give a list, first, of the works which have appeared in recent years relating to paludism; secondly, to furnish a bibliography of the works relating to sporozoa in general, and in particular to the hæmatozoa of animals which resemble those of paludism. The study of these last parasites has become inseparable from that of the hæmatozoa of paludism.

A. *Hæmatozoa of Paludism.*

1880.

A. Laveran.—Note sur un nouveau parasite trouvé dans le sang de plusieurs malades atteints de fièvre palustre. Note communiquée à l'Académie de Médecine, séance du 23 Nov.

— "Deuxième note relative à un nouveau parasite trouvé dans le sang des malades atteints de fièvre palustre: origine parasitaire des accidents de l'impaludisme. Note communiquée à l'Académie de Médecine, séance du 28 Déc.

— Sur un nouveau parasite trouvé dans le sang des malades atteints de fièvre palustre: origine parasitaire des accidents de l'impaludisme. Société médicale des Hôpitaux, séance du 24 Déc. *Bulletins et mémoires de la Société médicale des Hôpitaux, Mémoires,'* p. 158.

1881.

A. Laveran.—Nature parasitaire des accidents de l'impaludisme: description d'un nouveau parasite trouvé dans le sang des malades atteints de fièvre palustre. Paris (chez Baillière), in-8vo, 104 pages, avec 2 planches.

— Troisième note relative à la nature parasitaire des accidents de l'impaludisme. Note communiquée à l'Académie de Médecine dans la séance du 25 Oct.

— Communication à l'Académie des Sciences sur la nature parasitaire des accidents de l'impaludisme, séance du 24 Oct.

1882.

E. Richard.—Communication à l'Académie des Sciences sur les parasites de l'impaludisme, séance du 20 Fév.

A. Laveran.—De la nature parasitaire de l'impaludisme. Société médicale des Hôpitaux, séance du 28 Avril, et *Revue scientifique* du 29 Avril.

— Deuxième communication à l'Académie des Sciences sur les parasites du sang dans l'impaludisme, séance du 23 Oct.

1883.

A. Laveran.—Article *Fièvres palustres* in 2me édition des *Nouveaux Éléments de pathologie et de clinique médicales* de Laveran et Teissier. Paris.

E. Richards.—Le parasite de l'impaludisme. *Revue scientifique*, p. 113.

1884.

A. Laveran.—Traité des fièvres palustres. Paris, in-8vo (chez O. Doin).

E. Marchiafava et A. Celli.—Sulle alterazioni dei globuli rossi nella infezione da malaria e sulla genesi della melanemia. Reale Accademia dei Lincei. Roma.

Tommasi Crudeli.—Les Altérations des globules rouges du sang dans l'infection malarique. Congrès de Copenhague.

1885.

A. Laveran.—Du paludisme et de ses microbes. Société médicale des Hôpitaux, séance du 24 Juillet.

E. Marchiafava et A. Celli.—Nouve Ricerche sulla infezione malarica. *Annali di Agricoltura*, Roma, et *Fortschritte der Medicin*.

Councilmann et Abbot.—A Contribution to the Pathology of Malarial Fever, in *American Journ. of Med. Sciences*, April.

Chassin.—Sur l'inoculation de la fièvre intermittente. Thèse de Paris.

1886.

E. Marchiafava et A. Celli.—Studi ulteriori sulla infezione malarica. *Annali di Agricoltura*.

Sehlen.—Ueber die Aetiologie der Malaria. *Arch. de Virchow*, No. de Mai, p. 319.

G. Sternberg.—The Malarial Germ of Laveran. *The Medical Record*, New York, Nos. du 1 et du 8 Mai.

Golgi.—Sull' infezione malarica. *Archivio per le scienze mediche*, t. x, No. 4.

Councilmann.—Sur certains éléments trouvés dans le sang des

sujets atteints de fièvre intermittente, in *Assoc. of American Physic*, 18 Juin, et *Maryland Med. Journ.*, Oct.

METSCHNIKOFF.—*Centralblatt f. Bacter.*, No. 21.

1887.

E. MARCHIAFAVA and A. CELLI.—Sulla infezione malarica. *Atti della R. Accad. med. di Roma.* Travail reproduit en français dans les *Archives italiennes de biologie*, 1888, t. ix, fasc. 3.

U. ARCANGELI.—Le Ricerche moderne intorno l'agente dell' infezione malarica. *Rivista clinica*, No. 1.

E. MARCHIAFAVA and A. CELLI.—Hémoplasmodie malarique. Association médicale italienne, session de Pavie.

METSCHNIKOFF.—Étude sur les affections malariennes. *Russkaïa med.*, No. 12.

E. MAUREL.—Communication au Congrès de l'Association médicale pour l'avancement des sciences. Toulouse.

— Recherches microscopiques sur l'étiologie du paludisme in-8vo de 210 pages (chez O. Doin).

COUNCILMANN.—Nouvelles observations sur l'état du sang dans les fièvres malariales. *Med. News.*

MOSSO.—*Arch. de Virchow*, p. 205, et *Rend. della R. Accad. dei Lincei*, vol. iii, fasc. 7, 8.

KLEBS.—Die allgemeine Pathologie, 1re partie (Étiologie).

COUNCILMANN.—Recherches complémentaires sur le germe de la malaria de Laveran. Communication à la réunion ann. de la Société pathologique de Philadelphie.

LAVERAN.—Les hématozoaires du paludisme. *Annales de l'Inst. Pasteur*, 25 Juin.

HALLOPEAU.—Traité élémentaire de pathologie générale, 2me édit., p. 253.

W. OSLER.—Communication à la Soc. pathol. de Philadelphie. *The Brit. Med. Journ.*, p. 556. Analyse in *Semaine médicale*, 1887, p. 27.

E. MARAGLIANO.—Sur la résistance des globules rouges du sang. *R. Accad. med. di Genova*, et *Berliner klin. Wochenschr.*, No. 43.

E. MARCHIAFAVA and CELLI.—Sui rapporti fra le alterazioni del Sangue di cane introdotto nel cavo peritoneale degli uccelli e quelle del sangue dell' uomo nella infezione malarica. *Bollett. della R. Accad. Med. di Roma*, fasc. 7.

PFEIFFER.—*Centralblatt f. Bacter.*

COHN.—*Même recueil*, No. 12.

TOMMASI CRUDELI.—*Deutsche med. Wochensch.*, Nov.

1888.

B. JAMES.—The Micro-organisms of Malaria. Communic. à la Société pathol. de New York, 25 Jan. *The Medic. Record*, p. 269.

A. LAVERAN.—Des hématozoaires du paludisme. Revue critique. *Annales de l'Institut Pasteur.*

SCHIAVUZZI.—Untersuchungen ueber die malaria in Polen. *München med. Woch.*, No. 24; et *Beiträge zur Biologie der Pflanzen Journ. de F. Cohn.* Breslau.

PAMPOUKIS.—Étude clinique et bactériologique sur les fièvres palustres de la Grèce.

E. MARCHIAFAVA and CELLI.—Notes sur les études modernes de l'étiologie de la fièvre malarienne. *Archivio per le scienze mediche*, t. xi; et *Archives italiennes de Biologie.*

COUNCILMANN.—Neuere Untersuchungen ueber Laveran's Organismus der Malaria. *Fortschritte der Medicin*, Nos. 12 and 13.

VANDYKE CARTER.—Note on some Aspects and Relations of the Blood Organisms in Ague. *Scien. mem. by Med. Offic. of the Army of India*, Part III. Anal. in the *Lancet*, 16th June, p. 1201.

GOLGI.—Il fagocitismo nell' infezione malarica. Communic. à la Soc. méd.-chirurg. de Pavie, 19 Mai. *Journ. la Riforma medica*, Mai.

JEUNHOMME.—L'Étiologie de la malaria d'après les observations anciennes et modernes. *Arch. de Méd. militaire*, t. xii, pp. 57 et 145.

EVANS.—État du sang dans les fièvres intermittentes. Soc. clinique de Londres. Analyse in *Bulletin méd.*, p. 608.

A. CATTANEO et A. MONTI.—Les parasites du paludisme et les altérations dégénératives des globules rouges. Communic. au douzième Congrès méd. de Pavie, et *Arch. per le scienze med.*, t. xii.

CELLI et GUARNIERI.—Sur la structure intime du plasmodium malariæ. *Riforma med.*, 7 Septembre et 12 Octobre.

N. A. SACHAROFF.—Recherches sur le parasite de la fièvre palustre. *C. r. des séances de la Soc. méd. de Tiflis; Centralbl. f. Bacteriol.*, 1889, p. 452; et *Arch. de méd. expérim.*, 1 May, 1889.

— Sur l'analogie du parasite de la fièvre intermittente avec celui

de la fièvre récurrente. *C. r. des seances de la Soc. de méd. de Tiflis,* No. xi; *Centralbl. f. Bacteriol.,* 1889; et *Arch. de méd. expér.,* May, 1889, p. 482.

CHENZINSKY (Odessa).—Zur lehre ueber den Mikro-organismus der Malaria-fiebers. *Centralblatt f. Bacteriol.,* Bd. iii.

SOULIÉ.—Étiologie du paludisme. Communic. à la Soc. de Biol. *C. r. de la Soc. Biologie,* p. 766.

GIARD.—Note sur l'infection paludéenne, Société de Biologie, séance du 24 Novembre.

1889.

NEPVEU.—Étude sur le sang des paludiques. Ass. française pour l'Avancement des Sciences, Paris, 14 Août, 1889.

GOLGI.—Intorno al preteso bacillus malariæ di Klebs, Tommasi Crudeli e Schiavuzzi. Torino.

— Sur le développement des parasites du paludisme dans la fièvre tierce. *Fortschr. der Med.,* iii, et *Arch. per le scienze med.,* t. xiii, p. 173.

A. CELLI and G. GUARNIERI.—Sull' etiologia dell' infezione malarica. *Ann. di Agricoltura.*

P. CANALIS.—Sopra il ciclo evolutivo delle forme semilunari di Laveran et sulle febbri malariche irregolari e perniciose che da esse dipendono. Roma.

CHENZINSKY.—Contribution à l'étude des micro-organismes du paludisme. Thèse de doctorat, Odessa.

T. GUALDI et E. ANTOLISEI.—Due casi di febbre malarica sperimentale. *Accad. med. di Roma,* Anno xv (1888–9), fasc. 6.

T. CORONADO CUERPOS DE LAVERAN.—Microbios del Paludismo. *Cronica medico-quirurgica de la Habana,* No. x.

GOLGI.—Communication sur les fièvres intermittentes à long intervalle. Soc. médico-chirurgic. de Pavie, 6 Avril.

— Sur l'étiologie du paludisme. Ass. méd. italiennes Congrès de Padoue.

P. CANALIS.—Studi sulla infezione malarica. Sulla varieta parassitaria delle forme semilunari di Laveran. Sulle febbri mal. che da esse dipendono, Torino, 1889, et *Giornale medico del esercito et della marina,* December.

CELLI.—Dei protisti citofagi. *Riforma medica,* May.

MARCHIAFAVA and CELLI.—Sulle febbri mal. predominante nell' estate e nell' autunno in Roma. *Riforma medica,* 13 September, 1889, et *Atti della R. Accad. med. di Roma,* Anno xvi, vol. v, serie 2.

R. Feletti et B. Grassi.—Sui parassiti della malaria (Nota preliminare). Catania, 22 Déc.

E. Antolisei and A. Angelini.—Due altre casi di febbre malarica sperimentale. *Riforma medica,* September.

T. Gualdi et E. Antolisei.—Una quartana sperimentale. *Riforma medica,* November.

— Inoculazione delle forme semilunar di Laveran. *Riforma medica,* November.

Paltauf et Kahler.—Communic. à la Soc. império-royale des Médecins de Vienne, 20 Décembre, 1889. *Semaine médicale,* 1890, p. 8.

Hayem.—Du sang et de ses altérations anatomiques, Paris, 1889, p. 347.

N. A. Sacharoff.—*Le Paludisme sur le chemin de fer de Trans-Caucasie.* Observations microscopiques, Tiflis, 1889.

Klein.—Examen des éléments figurés du sang au point de vue clinique. Collège des docteurs de Vienne, December, 1889. *Bull. méd.,* 1890, p. 40.

W. Osler.—Valeur de l'organisme de Laveran dans le diagnostic de la malaria. *Johns Hopkins Hosp. Bull.,* No. 1, 1889–90.

1890.

Jaccoud.—De la fièvre intermittente, son traitement, sa nature. *Semaine médicale,* p. 25.

Vallin.—Les hématozoaires du paludisme. *Revue d'hygiène,* p. 97.

A. Celli et E. Marchiafava.—Intorno a recenti lavori sulla natura della causa della malaria. *Bullettino della R. Accad. med. di Roma,* 1889–90, Anno xv, fasc. 2.

F. Plehn.—Beitrag zur Lehre der Malaria-infection. *Zeitsch. für Hygiene,* p. 78.

— Communic. à la Soc. de Méd. de Berlin, 5 Mars, et *Berlin klin. Wochensch.,* 31 Mars.

Hallopeau.—Traité élémentaire de pathologie générale, 3me édit., 1re partie.

R. v. Jaksch.—Ueber Malariaplasmodien. *Prager med. Wochensch.,* 4.

P. Canalis.—Contributo alla storia degli studi moderni sulla infezione malarica. *Spallanzani.*

— Intorno a recenti lavori sui parassiti della malaria. Lettera al Presidente della R. Accad. med. di Roma.

— Étude sur l'infection palustre. *Fortschr. der Med.,* Nos. 8 et 9, pp. 285, 325.

R. Feletti and B. Grassi.—Sui parassiti della malaria. *Riforma medica,* Mars.

Soulié.—Sur l'hématozoaire du paludisme. *Bull. méd. de l'Algérie,* p. 228.

E. Antolisei.—L'Ematozoa della quartana. *Riforma medica,* January.

E. Antolisei et A. Angelini.—Osservazioni sopra alcuni casi d' infezione malarica con forme semilunari. *Arch. italiano di clinica medica.*

E. Antolisei.—Sull' ematozoo della terzana. *Riforma medica,* Janvier.

E. Antolisei et A. Angelini.—Nota sul ciclo biologico dell' ematozoo falciforme. *Riforma medica,* Mars.

Cornil et Babès.—Les Bactéries, 3me édit., t. ii, p. 163.

H. de Brun.—Les Causes individuelles ou somatiques de l'impaludisme. *La Méd. moderne,* 8 May.

Bamberger.—De la plasmodie de la malaria. Soc. império-royale des Médecins de Vienne, 2 May.

A. Celli et Marchiafava.—Sulle febbri predominanti nell' estat e nell' autunno in Roma. *Arch. per le Scienze med. di Bizzozero,* t. xiv, p. 117 (avec une planche).

E. Antolisei.—Considerazioni intorno alla classificazione dei parassiti della malaria. *Riforma medica,* Avril.

A. Valenti.—Etiologia e patogenesi della melanemia e della infezione malarica. *Gaz. med. di Roma.*

A. Laveran.—Au sujet de l'hématozoaire du paludisme et de son évolution. Soc. de Biologie, séance du 21 Juin. *Comptes rendus,* p. 374.

Luzet.—Des agents infectieux du paludisme. *Arch. gén. de Méd.,* t. ii, p. 61.

C. Terni et G. Giardina.—Sulle febbri irregolari da malaria. *Rivista d' igiene e sanita pubblica,* 16 Mai.

— Même travail avec analyse des observations. Publication de la direction de la santé publique, Rome.

Paltauf.—Étiologie de la fièvre intermittente. *Wiener med. Wochensch.*

Dock.—Étude sur l'étiologie de l'infection malarienne et des hématozoaires de Laveran. *Med. News,* 19 Juillet.

A. Laveran.—Des hématozoaires voisins de ceux du paludisme observés chez les oiseaux. Communication à la Soc. de Biologie, séance du 5 Juillet. *Bull.,* p. 422.

T. V. Coronado.—El microbio de la malaria. *Cronica medico-quirurgica de la Habana,* No. vi, p. 287.

QUINCKE.—Ueber Blutuntersuchungen bei Malaria-kranken (sur l'examen du sang dans le paludisme). Kiel et *Mitth. d. Verein. Schleswig Holst. Aerzte,* No. 4.

ROSENBACH.—*Deutsch. med. Wochensch.,* No. 16.

L. PFEIFFER.—*Corresp. Bl. d. allg. arztl. Vereins v. Thuringen,* 145.

— Les Protozoaires pathogènes. Iéna.

KOLLMANN.—Les Pseudo-microbes du sang humain normal. Congrès de Berlin (Section de médecine interne).

T. GUALDI, BOZZOLO.—Discussion de la communication précédente. Congrès de Berlin.

GOLGI.—Représentation photographique du développement des parasites de l'infection paludéenne. Congrès de Berlin.

A. BIGNAMI.—Recherches sur l'anatomie pathologique des fièvres pernicieuses. *Atti della R. Accad. med. di Roma,* Anno xvi, t. v.

A. CELLI and MARCHIAFAVA.—Il reperto del sangue nelle febbri malariche invernali. *R. Accad. med. di Roma,* Anno xvi (1889–90), fasc. 6.

VERONESI.—Valeur clinique de l'examen du sang dans l'infection paludéenne. *Atti d. Accad. med. Perugia,* ii, No. 1.

DOLEGA.—Étiologie de la malaria, 9e Congrès de médecine interne de Vienne, 18 Avril.

— Blutbefunde dei Malaria (État du sang dans la malaria). *Fortsch. der Med.,* October 15.

ANDERSON.—The Malarial Fever in Mauritius. *The Lancet,* p. 391.

GOLGI.—Sur le cycle évolutif des parasites malariques dans la fièvre tierce. Diagnose differentielle entre les parasites endoglobulaires malariques de la fièvre tierce et ceux de la fièvre quarte. *Arch. ital. de biologie,* t. xiv, fasc. 1, 2.

D. RESHELILO.—Étiologie de la malaria, St. Pétersbourg.

G. TITOV.—Importance diagnostique des protozoaires de la fièvre paludéenne, St. Pétersbourg.

GRASSI et FELETTI.—Di un' ameba che si trova in vita libera e che potrebbe rapportarsi ai parassiti malarici (note préliminaire), Juin.

MARAGLIANO.—De la pathologie du sang. Congrès de la Soc. ital. de Méd. interne, Rome, Oct.

— Sur les fièvres intermittentes malariques à longs intervalles. Fondements de la classification des fièvres malariques. *Arch. ital. de biologie,* t. xiv, fasc. 1, 2.

J. M. ATKINSON.—*Annual Report on the Medical Department for the year* 1889, Hongkong, 1890. Appendix D.

A. LAVERAN.—De l'examen du sang au point de vue de la recherche

de l'hématozoaire du paludisme. Soc. méd. des Hôpitaux, séance du 28 Nov.

A. LAVERAN.—Au sujet des altérations des globules rouges du sang qui peuvent être confondues avec les hématozoaires du paludisme. Soc. de Biologie, 27 Dec.

DANILEWSKY.—Sur les microbes de l'infection malarique aiguë et chronique chez les oiseaux et chez l'homme. *Annales de l'Instit. Pasteur,* Dec.

ROMANOWSKY.—Sur la structure des parasites du paludisme. *Wratsch.,* No. 52, p. 1171.

L. PFEIFFER.—Vergleichende Untersuchungen ueber Schwarmsporen und Dauersporen bei den Coccidieninfectionen und bei intermittens. *Fortsch. der Medicin,* 15 Dec., 1890.

B. *Sporozoaires en général—Hématozoaires des animaux.*

G. VALENTIN.—Ueber ein Entozoon im Blute von *Salmo fario. Müller's Archiv,* 1841, p. 435.

G. GLUGE.—Ueber ein eigenthümliches Entozoon im Blute des Frosches. *Müller's Archiv,* 1842, p. 148.

GRUBY.—Sur une nouvelle espèce d'hématozoaires, *Trypanosoma sanguinis.* Acad. des Sciences, 1843. *Comptes rendus,* xvii, p. 1134.

GROS.—Observ. et inductions microscopiques sur quelques parasites. *Bull. de la Soc. imp. des Naturalistes de Moscou,* 1845.

C. WEDL.—Beiträge zur Lehre von den Hematozoen. *Denkschr. der Wiener Akad. der Wissen.,* 1850.

E. RAY LANKESTER.—On Undulina. *Quarterly Journal of Microsc. Science,* 1871.

A. SCHNEIDER.—*Arch. de zoologie expér.,* t. x, 1878.

T. R. LEWIS.—Flagellated Organisms in the Blood of Healthy Rats. *Quarterly Journal of Microsc. Science,* 1879, p. 109.

J. GAULE.—Ueber Wurmchen welche aus den Frosch-blutkorperschen auswandern. *Arch. für Physiologie,* 1880–81.

WALLERSTEIN.—Ueber *Drepanidium ranarum. Inaug. Diss.,* Bonn, 1880.

W. FLEMMING.—Die Cytozoen. *Biolog. Centralblatt,* 1881.

RAY LANKESTER.—On *Drepanidium ranarum. Quarterly Journal of Microsc. Science,* 1882.

KUNSTLER.—Recherches sur les infusoires parasites. *Comptes rendus de l'Acad. des Sc.,* 1883, p. 755.

GRASSI.—Sur quelques protistes endoparasites appartenant aux classes des Flagellata, Lobosa, Sporozoa, et Ciliata. *Arch. ital. de biologie,* 1882–3.

MITROPHANOW.—Beiträge zur Kenntniss der hematozoen. *Biol. Centralblatt,* 1883.

BALBIANI.—Leçons sur les sporozoaires, Paris, 1884.

E. M. CROOKSHANK.—Flagellated Protozoa in the Blood of Diseased and apparently Healthy Animals. *Journ. of the R. Microsc. Soc.,* p. 913, 1886.

DANILEWSKY.—Materiaux pour servir à la parasitologie du sang. *Arch. slaves de biologie,* 1886–7.

— Contribution à la question de l'identité des parasites pathogènes du sang chez l'homme avec les hématozoaires chez les animaux sains. *Centralbl. f. med. Wiss.,* 1886–7.

— Recherches sur la parasitologie comparée du sang: Zooparasites du sang des oiseaux. Kharkov, 1888 (Ouvrage publié en langue russe).

R. BLANCHARD.—Art. "Hématozoaires" in *Dictionn. encyclop. des Sc. méd.*

— Bibliographie des hématozoaires, *Bull. de la Soc. zoologique de France,* t. xii, 1887.

VANDYKE CARTER.—Sur la maladie infectieuse du rat et du cheval dans l'Inde. Extrait des *Mémoires scient. des médecins militaires de l'armée des Indes.* Calcutta, 1888.

CHALACHNIKOV. Recherches sur les parasites du sang chez les animaux à sang froid et à sang chaud (en langue russe). Kharkov, 1888.

DANILEWSKY. Nouvelles recherches sur les parasites du sang des oiseaux. Kharkov, 1889.

— Recherches sur les hématozoaires des tortues. Kharkov, 1889.

J. STEINHAUS.—Karyophagus salamandræ. *Arch. de Virchow,* 1889, t. cxv.

T. SMITH.—Sur la fièvre du Texas du bœuf. *The Medical Record,* Dec., 1889.

GRASSI and FELETTI.—Les parasites du paludisme chez les oiseaux. *Bull. mensuel de l'Acad. des Sc. naturelles de Catane,* 23 Mars, 1890.

W. KRUSE.—Ueber Blutparasiten. *Arch. de Virchow,* 1890, t. cxx, p. 541.

— Ueber Blutparasiten. *Arch. de Virchow,* 1890, t. cxxi, p. 359.

DANILEWSKY.—Développement des parasites malariques dans les leucocytes des oiseaux (leucocytozoaires). *Annales de l'Institut Pasteur*, 1890, p. 427.

GABRITCHEWSKY.—Contribution à l'étude de la parasitologie du sang. *Annales de l'Institut Pasteur*, 1890, p. 440.

GRASSI et FELETTI.—Ancora sui parassiti degli uccelli. *Bull. de l'Acad. des Sc. nat. de Catane*, Juin, 1890.

PFEIFFER.—Les protozoaires pathogènes. Iéna, 1890.

INDEX.

PRINTED BY ADLARD AND SON,
BARTHOLOMEW CLOSE, LONDON, E.C., AND 20, HANOVER SQUARE, W.

PLATE I.

1. Normal red blood-corpuscle.

2—6. Blood-corpuscles, to which are attached small spherical bodies without pigment, numbering from 1 to 4.

7—13. Blood-corpuscles, to which are attached some pigmented spherical bodies, numbering from 1 to 4.

14—18. Blood-corpuscles, to which are attached pigmented spherical bodies which have almost completely destroyed the blood-corpuscles.

19, 20. Free spherical bodies at their full development.

21. Small free pigmented spherical bodies.

22. Spherical bodies massed together.

23—28. Different phases of development of segmented bodies.

29—31. Spherical bodies with flagella, numbering from 1, 3, or 4; the flagellum of body 31 shows, towards its middle, a slight swelling.

32. A flagellum detached.

33—36. Crescent-shaped bodies; one of the bodies (34) is adherent to a blood-corpuscle, another (36) shows a double outline.

37, 38. Oval bodies derived from crescent-shaped bodies.

39—41. Melaniferous leucocytes.

42—44. Pigmented hyaline bodies representing dead forms of the hæmatozoon of paludism.

All these bodies have been drawn under a power of about 1000 diameters.

Plate I.

Laveran del

Nicolet lith

Imp Lemercier & Cie Paris

PLATE II.

Figure A.

Hæmatozoa of paludism in fresh blood. In the midst of normal red blood-corpuscles are seen the following bodies:

a. Group of three blood-corpuscles, to which are attached small spherical bodies.
b. Small free spherical bodies.
c. Spherical body of medium size, adherent to a red blood-corpuscle.
d. Spherical body come to its full development, free.
e. Spherical body with two flagella.
f. Detached flagellum.
g, *g*. Crescent-shaped bodies.
h. Melaniferous leucocytes.
i. Normal leucocyte.

(× 500 diameters.)

Figure B.

Hæmatozoa of paludism in the blood, dried and stained with methyl blue. In the midst of normal blood-corpuscles the following bodies are seen:

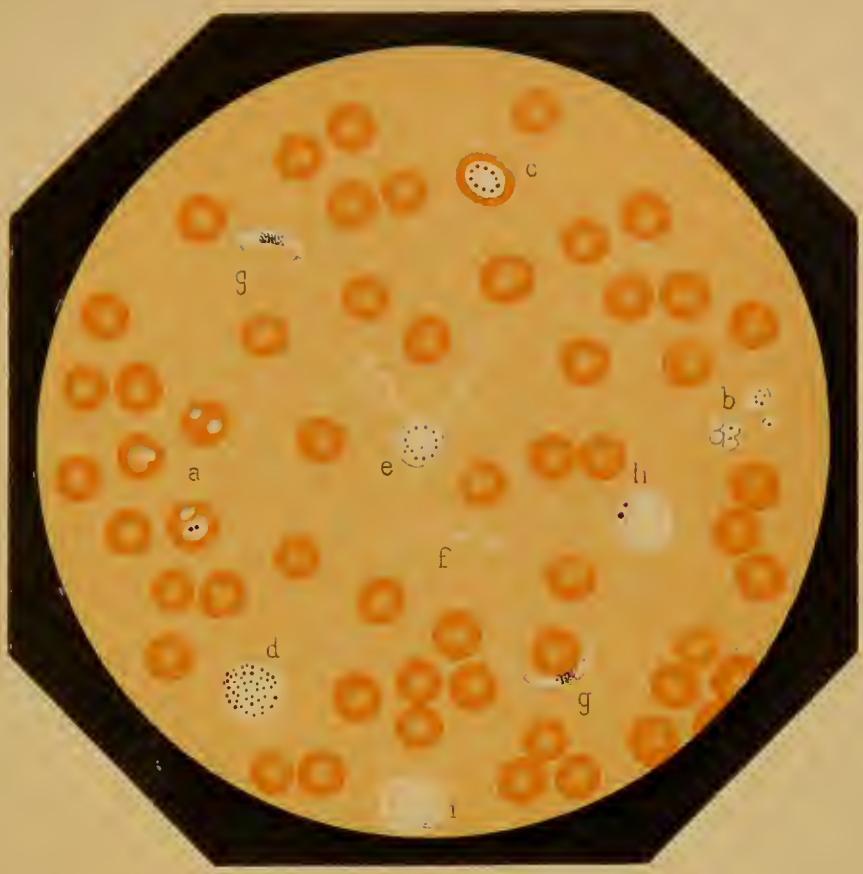
a, *a*, *a*. Blood-corpuscles, to which are attached spherical bodies in different stages of their development.
b, *b*, *b*. Detached spherical bodies.
c, *c*, *c*. Crescent-shaped bodies.
d, *d*. Leucocytes.

(× 500 diameters.)

All the parasitic bodies in Figures A and B of this plate have been drawn from nature; they have been grouped into the same field of the microscope in order not to multiply the figures. The same applies to Figures A and B of Plate III.

Plate II.

A



B

Laveran del

Nicolet lith

Imp. Lemercier & Cie, Paris

PLATE III.

Figure A.

Hæmatozoa of paludism in the blood, dried and submitted to the double stain of eosin and methyl blue. In the midst of normal red blood-corpuscles, stained rose colour by eosin, the following bodies are seen:

a, a, a, a. Spherical bodies adherent to red blood-corpuscles.
b. Two free spherical bodies come to their full development.
c. Two crescent-shaped bodies.
d. Segmented bodies.
e, e. Leucocytes.

(× 500 diameters.)

Figure B.

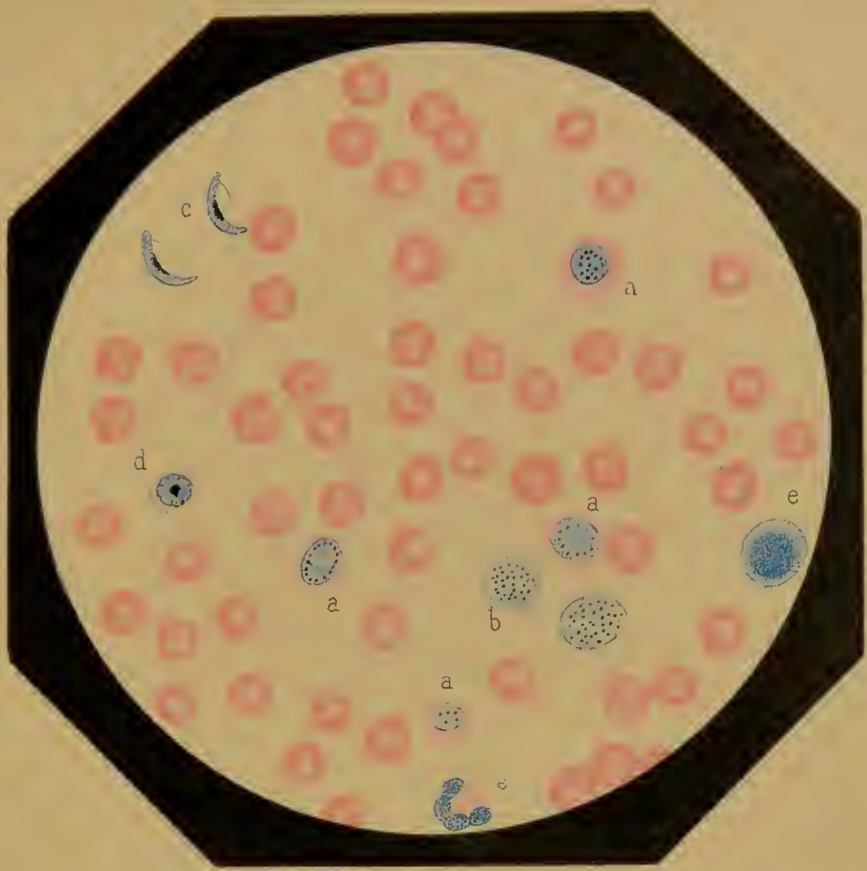
Hæmatozoa in the blood of birds, dried and double stained with eosin and methyl blue. Among the normal red blood-corpuscles the following bodies are seen:

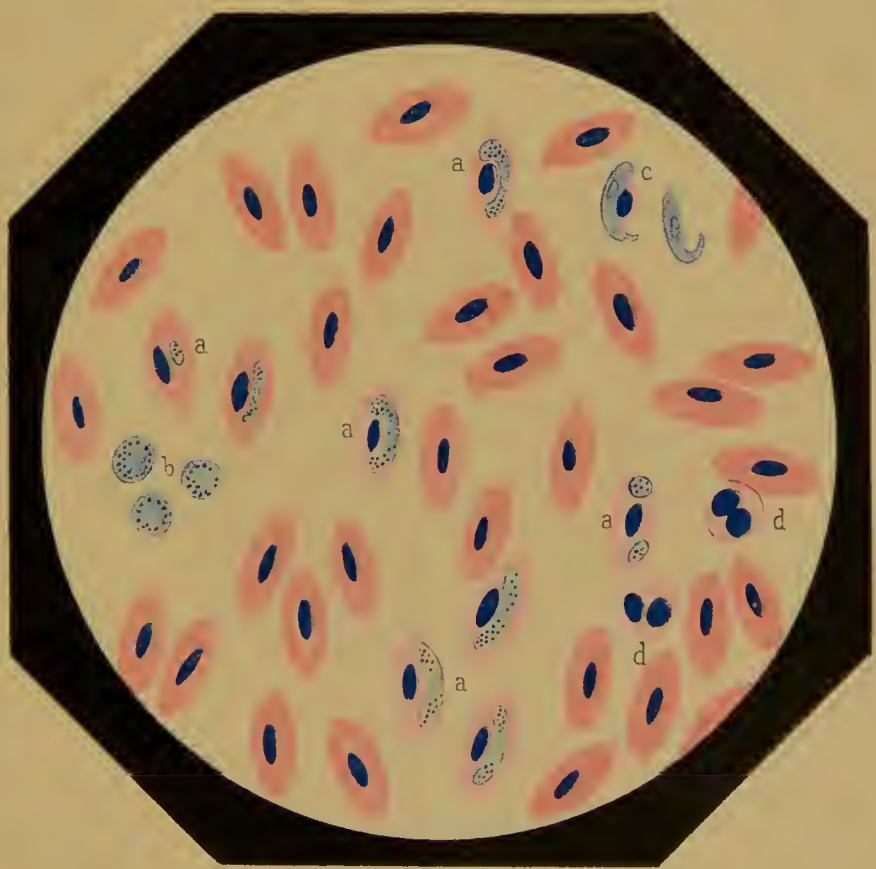
a, a, a. Red blood-corpuscles containing cytozoa more or less developed.
b. Three free cytozoa.
c. Free vermicules; to one of them the remains of a blood-corpuscle is still attached.
d, d. Leucocytes.

(× 500 diameters.)

Plate III

A





B

Laveran del

Nicolet lit.

imp. Lemercier & Cie, Paris

PLATE IV.

Figure A.

Different appearances of the hæmatozoa of the tortoise (after Danilewsky).

1, 2, 3, 4. Red blood-corpuscles containing one or two hæmocytozoa of small size; by the side of the cytozoa, which form clear spots, the nuclei of the blood-corpuscles can be recognised.

5, 6. The hæmocytozoa take an elongated form in the interior of the blood-corpuscles; a nucleus in each vermicule is seen.

7, 8. Vermicules become enlarged; they are folded on themselves.

9, 10, 11, 12. Vermicules with the remains of red blood-corpuscles.

13. Free vermicule.

14. Free vermicule, with the constrictions which they form when in motion.

15. Commencement of segmentation; the parasitic mass has the appearance of a raspberry.

16. Cytocyst, with its parasitic embryo.

17. Crushed cytocyst.

18. Mobile falciform embryo, with transverse constriction.

Figure B.

Some appearances of the hæmatozoa of birds (after Danilewsky).

1, 2, 3, 4. Different forms of pseudo-vacuoles—that is to say, hæmocytozoa at different phases of their incomplete development; the red blood-corpuscles are more or less distorted, some of them containing several hæmocytozoa. By the side of the hæmocytozoa, which form clear spots, are seeu the nuclei of the blood-corpuscles.

5. Mobile pseudo-vermicules, containing each a nucleus; oue of these pseudo-vermicules shows a constriction produced during movement.

6. Red blood-corpuscle with cytozoon, from which are escaping spirilliform bodies.

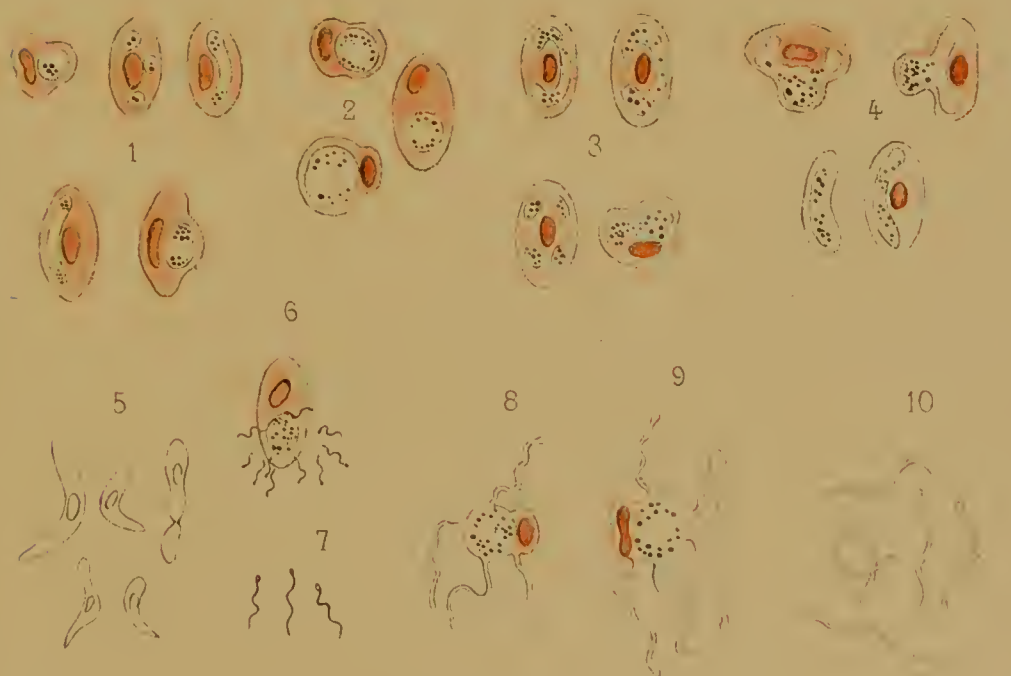
7. Spirilliform bodies under a high power.

8, 9. Polimitus of the blood of birds, with flagella. By the side of the polimitus body the nuclei of the blood-corpuscles are still seen.

10. Pseudo-spirilla, or otherwise called flagella, detached.

Plate IV.

Fig. A. — Hœmatozoa of tortoises



Laveran del. Nicole, lith.

Fig. B. — Hœmatozoa of birds

Imp. Lemercier et Cie Paris

PLATE V.

(The photographs reproduced in this plate and in the following one have been taken by Monsieur Yvon from my preparations.)

Figure 1.

Hæmatozoa of paludism. Dried blood. In the midst of normal blood-corpuscles two bodies becoming pigmented may be distinguished towards the centre.

(Magnified 700 diameters.)

Figure 2.

Hæmatozoa of paludism. Dried blood doubly stained with eosin and methylene blue. In the midst of normal blood-corpuscles a pigmented spherical body may be distinguished.

(Magnified 500 diameters.)

Figure 3.

Section of the brain of a subject who died from an attack of pernicious coma. The section made after hardening in the usual way has been stained with carmine and mounted in Canada balsam. The capillary vessel found in the section shows a very characteristic black piqueté formed by the agglomeration of pigmented parasitic elements (melanæmia).

(Magnified about 100 diameters.)

Figure 4.

Histological section of the liver of a subject who died from an attack of pernicious coma. Section made after hardening, stained with picro-carmine and mounted in Canada balsam. The capillary network contains numerous pigmented elements. The pigment forms black spots of variable size and shape (melanæmia).

(Magnified about 100 diameters.

Fig. 1

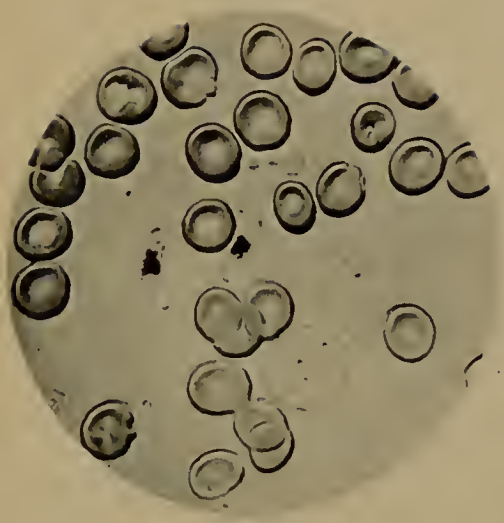


Fig. 2

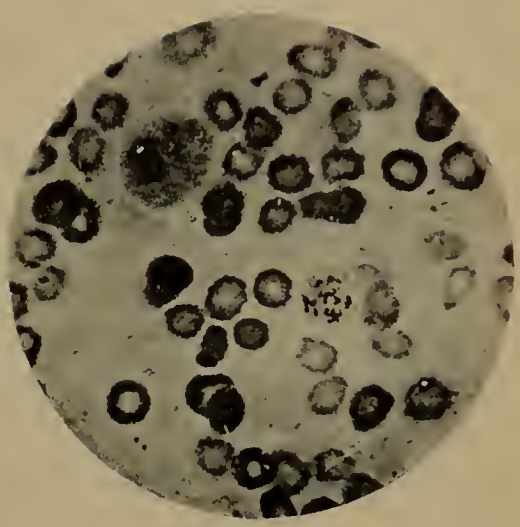


Fig. 3

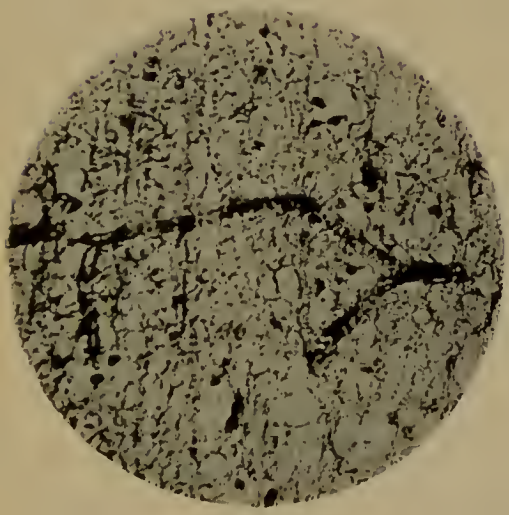
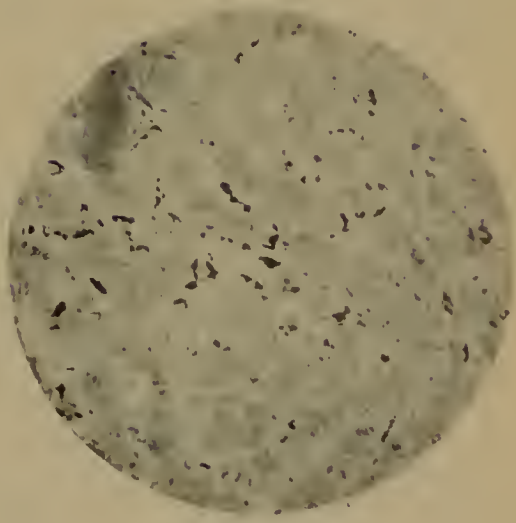


Fig. 4



Masson, Editeur

Héliotypie H. Rack Paris

PLATE VI.

Figure 1.

Hæmatozoa of birds. Dried jay's blood. In the midst of normal blood-corpuscles there may be distinguished three corpuscles with pigmented rounded parasites. The corpuscle which is in the centre of the preparation is deformed, the parasite occupying its greater part, and pushing the nucleus aside. The two other corpuscles invaded by the parasites are less deformed, the parasites twisting round the nucleus.

(Magnified 500 diameters.)

Figure 2.

Dried pigeon's blood. In the midst of normal blood-corpuscles five corpuscles may be distinguished containing rounded hæmatozoa.

Figure 3.

Dried jay's blood. By the side of normal blood-corpuscles there is seen a corpuscle with a pigmented rounded parasite, which is beginning by its extremities to alter the shape of the nucleus. The part of the corpuscle which is not altered is plainly distinguished from the part invaded by the parasite, the latter being paler.

(Magnified 1200 diameters.)

Figure 4.

Blood of the chaffinch. In the midst of normal blood-corpuscles there is a pigmented spherical body furnished with a flagellum (the preparation has been stained with gentian violet).

Fig 1.

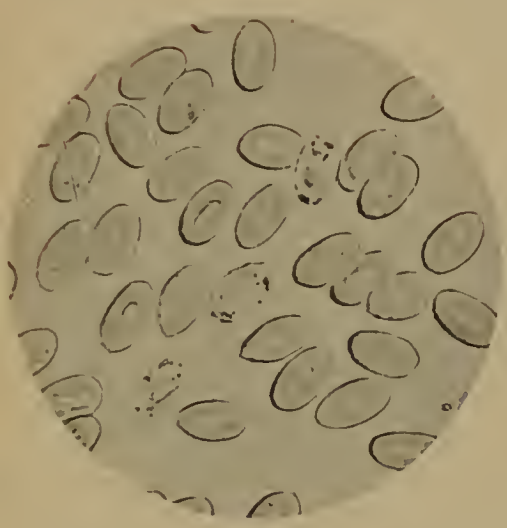


Fig 2

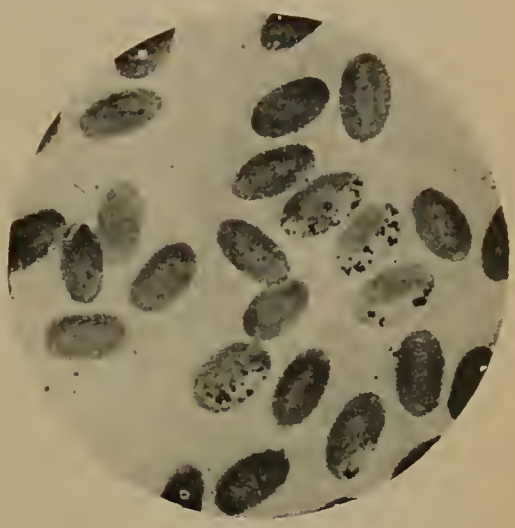


Fig 3

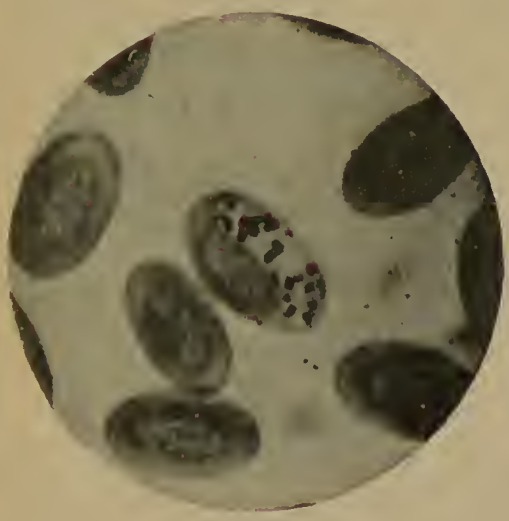
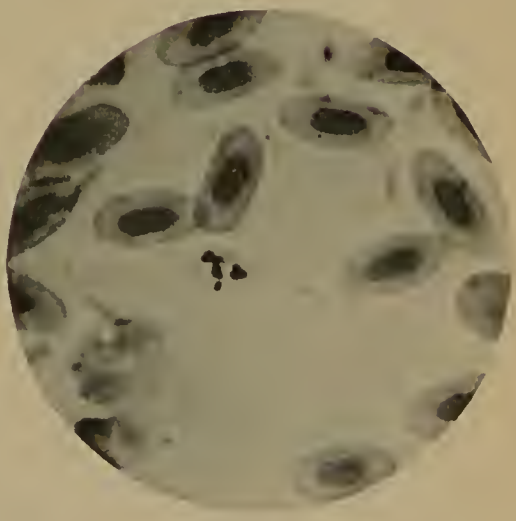


Fig 4



Masson, Editeur

Héliotypie H Racle, Paris

41