A FURTHER CONTRIBUTION
TOWARDS THE
PATHOLOGY
OF THE
PERNICIOUS MALARIAL FEVERS OF
SIERRA LEONE
AND
OUR KNOWLEDGE OF THE PARASITE WITH WHICH
THEY ARE ASSOCIATED
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THERE is in the seventy-ninth volume of the 'Medico-Chirurgical Transactions' a note by myself on the appearances found in the tissues in a fatal case of pernicious malaria at Sierra Leone.

In this case the patient died comatose, and I found in the blood-vessels of the brain many parasites of malaria. Although a very few parasites could be found in the red blood-corpuscles in other organs, it was only in the brain that they were found in any number, and there they were

very numerous. Much pigment was found in the liver and spleen, and its disposition in these organs is described in the paper. The epithelium of the convoluted tubes of the kidneys was found much broken down. I pointed out that the appearances which I described coincided with those described by Bignami as being found in fatal cases of malignant malaria in the south of Italy. Since that paper was written I have examined in much detail tissues of four additional fatal cases which occurred at Sierra Leone,—three of them fatal from malaria, and one of them, in order to afford a basis of comparison, from a fatal case of pericarditis. For these tissues I have to thank Surgeon-Captain Duggan, who preserved and sent them to me from Sierra Leone, and both myself and (I may perhaps venture to say) the Society are much indebted to this gentleman for the interest and trouble he took in preparing and sending the specimens.

The subject is, I consider, sufficiently important to justify me in placing before the Society the details connected with a histological examination of the tissues in these additional cases.

In numbering the cases I take them in the order in which they were examined. The case previously described is taken as Case 1. The case of pericarditis, although not described in detail, is mentioned as Case 3.

CASE 2.—E. M— was admitted to hospital on the morning of the 1st of March, 1896, complaining of headache and pains all over the body. He had the appearance of a man who had been drinking heavily. His tongue was brown and dry and tremulous, and his hands were shaky. He denied that he had been drinking. His temperature was 103° , and his pulse good. Five grains of antifebrin, five grains of calomel, and twenty grains of quinine hydrochlorate were given. In the evening his temperature was 102° , and his pulse good. He had sweated freely, but his skin was again dry.

His bowels had been freely opened. The antifebrin was ordered to be repeated. During the night he was restless, and complained that he could not sleep. At 5 a.m. he got up and went to stool. At 6.30 a.m. he was comatose. Temp. 100°. On the arrival of Surgeon-Captain Thomson he had expired.

One of the orderlies saw this man drunk on the 29th of February.

Post-mortem (five hours after death).—The membranes of the brain were intensely congested. The lungs were congested. Heart: hypertrophy of the left ventricle. Liver congested. Kidneys normal.

Brain.—It was in the brain only that parasites were found in any number. In other parts of the body they were scarcely to be found at all. In the brain many of the capillaries of the grey substance were filled with corpuscles, and in many of those examined there was a parasite in every red corpuscle. Many parasites were also found in some of the veins of the smallest calibre. The parasites were found almost exclusively in one stage. The patient had therefore died very shortly after a fresh generation of parasites had been set free, and had attached themselves to the red corpuscles, as they were seen as minute round bodies in the red corpuscles, of which they only filled a very small part. Parasites in any other stage were extremely few. The blood-vessels in the pia mater contained many white corpuscles, and a considerable proportion of these contained pigment, which was the chief evidence of a previous generation having existed. Whilst in many of the blood-vessels the parasites were exclusively in the early stage, in some vessels a mixture was found of very early parasites, and some in the sporulating stage with central pigment, indicating that the stage of development of the latest generation of the parasites which existed when the patient died was not exactly the same in all the blood-vessels of the brain, although it was approximately so.

Spleen.—Pigment was found in large white corpuscles

scattered throughout the stroma, but compared with some of the cases it was not very abundant. There was a good deal of it in the small veins. In the lymphoid tissue of the spleen there was scarcely any pigment at all, and there was none in the Malpighian corpuscles. Only a very few small parasites were seen in the red corpuscles, and these were in the same stage as the most of those which were found in the capillaries of the brain. Their number was so small that whole fields of the microscope required to be searched before one was found, and they were apparently not so abundant as Surgeon-Captain Duggan's description would have led us to suppose would have been found from the blood in the finger in similar cases.

Liver.—The liver cells were for the most part apparently healthy, but in a few parts there was a zone of degenerated liver cells, indicated by vacuoles, and breaking down near the central vein of the lobules. These areas of degenerated liver cells were comparatively small, as compared with the apparently normal parts of the lobules. Although in certain parts no pigment was present, in other parts there was a moderate amount of pigment, the pigment being found in white corpuscles in the capillaries and in the endothelium of the capillary wall, and very sparsely in the liver cells themselves. Most of it was found in the endothelium of the capillaries. No parasites were observed in the red corpuscles in the liver.

CASE 3 was a fatal case of pericarditis, and the tissues were examined in order to ascertain the condition of the organs in fatal cases at Sierra Leone, in which malarial fever was not recognised as present. A careful examination of the brain, spleen, liver, and kidneys failed to show a single parasite or any pigment. The man had resided two years on the West Coast before he died.

CASE 4 was a case of fatal pernicious malaria which occurred in the military hospital. The tissues were sent

by Surgeon-Captain Duggan, who obtained them at the hospital when the post-mortem was made, but he has been unable to give me any detailed clinical account of the case. His recollection is that the symptoms did not differ essentially from those that characterised other fatal cases of fever at Sierra Leone.

Brain.—The number of parasites found in this case was not so great as in the other cases examined, but those observed were again all found in the brain. In the sections examined the large number of capillaries blocked with parasites found in the other cases were not observed, but still a certain number of capillaries of very small calibre were observed to contain red corpuscles infected by parasites in an early stage. Amongst the red corpuscles in the veins a very small percentage were observed to contain parasites well stained and distinct, and in size slightly exceeding that observed in the earliest stage of parasitic infection, but none of them had reached the size characteristic of the sporulating stage, and they contained no pigment. In the sections examined most of the capillaries contained very little blood.

Spleen.—There was pigment in the large white corpuscles in the pulp. The pigment in these corpuscles was observed in two forms. In some cases it was in the form of very fine needles; in others in rounded homogeneous spheres, and in some corpuscles there seemed a transition from the one form to the other. It would seem as if the needle-shaped pigment of the sporulating parasites is very soon collected into minute spheres when taken up by the white corpuscles. Most of the pigment was contained in the pulp. There was very little in the lymphoid tissue, but a good deal was accumulated around the Malpighian corpuscles, and streaks of rounded pigment were found in the walls of the vessels. In the spleen the pigment was observed to be accumulated in blocks in some parts, these blocks being found around the Malpighian bodies (none being found inside these structures), and a long streak of such blocks was found

on the border of a tract of fibrous tissue. Although I was not able to detect the walls of the lymphatic vessels, the position of the pigment and its arrangement suggested that, in this case, the pigment in the spleen was to some extent being taken up by the lymphatics after the manner described by Bignami. No parasites were found in the red blood-corpuscles, either in the splenic pulp or in the veins, so there must have been very few of them in the spleen.

Liver.—Parasites were not found in the red corpuscles in the sections examined. The liver cells were, on the whole, fairly normal. The endothelium of the walls of the capillary blood-vessels contained much pigment, the endothelial cells being frequently swollen and degenerated. The degenerated cells stained deeply in cochineal. The swollen capillaries contained also white corpuscles in which there were often deposited small spheres of pigment. Occasionally a shapeless block or mass of pigment is to be seen outside the capillary vessels. In some parts of the sections pigment was found in the liver cells, mostly in the form of small round spheres, but in many parts the liver cells were free from pigment. In the interlobular vascular tracts large shapeless blocks of pigment are to be found, mostly outside the sheaths of the blood-vessels, and therefore presumably in lymphatic vessels, although no such vessels could be distinctly made out. The pigment in the interlobular tracts is more pronounced than in the lobules, as it is no longer scattered in the cells, but accumulated in blocks.

CASE 5.—The tissues in this case were obtained from the patient whose case is described by Surgeon-Captain Duggan in a paper read before the Society last session. It is Case 7 of that paper.

Brain.—In this case the brain was found to contain many parasites, vessels being frequently filled with blood-corpuscles, every one of which was infected. Examples of several stages of development of the parasite

were found, but very frequently capillary vessels contained parasites in only one stage. For example, in many of the vessels the small round parasite with only one nucleolar element was found occupying a small part of the red corpuscle, whilst in other vessels parasites had for the most part reached the stage in which sporulation was beginning, and in others the central pigment with the occasional evidence of distinct spores showed that the sporulating stage had been reached. Specimens stained deeply in methylene blue showed the young form of the parasite as a minute spherical body with one deeply stained nucleolar point. The later stage showed, when the staining was sufficiently successful, three to four nucleolar bodies.

On account of imperfect preservation it was difficult to say what was the number of spores which might be considered characteristic. Three and four were usually observed. In one instance six spores were counted, and were very distinct, occupying more than two thirds of the sphere of the parasite. Supposing them to have remained in their place, and that the other spores had occupied the vacant place, and had been removed in the cutting of the section, that would imply that in this particular sporulating body there might have been eight or nine spores. Yet, making allowance for the possibilities of some of the spores having been cut off in preparing the sections, and for deficiencies in staining, the number of instances in which only three and four spores were observed was comparatively large enough to justify me in assuming that some at least of the parasites had not produced more than six to eight.

The brain was the seat of small hæmorrhages. The area of free red corpuscles lying in the brain substance was not always observed in connection with a blood-vessel, but this was probably due to an accident of the plane of section, because in most cases the blood-vessel from which the corpuscles had escaped was found in their midst, and in one or two cases I was able to detect the breach or

breaking down in the vascular wall through which the blood had escaped.

The young parasites observed in the blood-vessels of the brain in this case are similar to those described by Surgeon-Captain Duggan as having been observed in the blood from the finger taken before the patient died.

Spleen.—The spleen contained a considerable amount of pigment, which was observed in large white cells scattered through the pulp, the veins of which particularly contained many pigment-bearing white corpuscles. The lymphoid tissue contained only a few pigmented cells; none were observed in the Malpighian follicles. The pigment in the white cells in the spleen in this case is mostly needle-shaped, but has already begun to take the form of minute spheres. In some white corpuscles the part of the protoplasm immediately surrounding the nucleus was entirely free from pigment, whilst the peripheral part of the corpuscle was filled with needle-shaped pigment in crystalline form. Tracts of pigmented white cells were observed in the course of the veins external to the vascular wall,—probably, therefore, in lymphatic vessels, or in the perivascular spaces. A very few parasites in the early stage were observed in the red corpuscles in the spleen. These were so isolated and were so few in number that frequently a whole field of the microscope would be searched without finding one.

Liver.—The chief feature in sections of the liver was the great distension of all the capillary blood-vessels, which were filled with blood and enormously dilated. A very few liver cells were in a state of fatty degeneration, but the most of them appeared to be healthy. White corpuscles containing pigment were found in the blood-vessels. Many endothelial cells of the vessels contained pigment spheres, and were swollen and in various stages of degeneration, and differed from the uninfected endothelial cells by taking on deeply the cochineal stain. A few liver cells contained pigment, and those of them that contained pigment were in some cases slightly changed in

appearance, and seemed to be less sound than the other cells.

If we compare the description of the first case of this disease, which was published in the seventy-ninth volume of the 'Transactions,' and the three cases which I have now described, it is at once evident that we are dealing with the same parasite in each case, and that the changes which it causes in the tissues are uniform. In the case of pericarditis, without any history of malarial fever, which was carefully examined, in none of the organs was there found any parasite or pigment, or any change suggestive of parasitic infection. As the man had been resident at Sierra Leone for two years the result is so far interesting, as it shows that residence there does not necessarily imply infection by the parasite of malaria of that coast. Dealing, then, with the four cases which were fatal by malarial fever, we find the following facts regarding the parasite. The habitat of the parasite in these cases is the brain, whilst the circulating blood, as observed in the blood-vessels of the other organs, contains only an extremely small number of isolated parasites, not even so many as Surgeon-Captain Duggan found in blood taken from the finger. The capillaries in the brain were in three of the cases filled with red corpuscles in which sometimes every one, and frequently a great number contained parasites.

In the fourth case the capillary blood-vessels of the part of the brain which was examined were mostly empty, and it consequently was very difficult to find the parasites in them, but a certain number were found. In all the cases a small proportion of infected red corpuscles were found in the veins, but the number of infected corpuscles in the veins was comparatively few. In Case No. 4, in which fewer parasites were found in the capillaries, comparatively more were found in the veins. In all the cases white corpuscles containing pigment were found in the veins, and especially in the veins of the pia mater. Pigment in the endothelium of the brain capil-

laries was more or less prevalent, but in far less proportion than what was found in the capillaries of the spleen or liver. In two of the cases the brain was the subject of small hæmorrhages.

The parasite in the four cases presented the same appearance and size in its early stage, when it is seen as a small rounded or ovoid body, of which the diameter is not more than a fifth or fourth of that of the red corpuscles. In this early stage, when stained with hæmatoxylin, it is seen as a very minute circular body, and this stained body probably represents only the nucleolar element. When successfully stained by methylene blue it is seen to consist of a deeply stained nucleolar element, surrounded by a zone of more lightly stained protoplasm, the nucleolar element being often placed eccentrically.

In the next stage it has become larger, but still only occupying a small part of the red corpuscle, and shows an appearance of spores, which, in my preparations, were usually indistinct. In the third stage, in which there is central pigment with a spore formation surrounding it, the size of the parasite is still comparatively small, its diameter not exceeding a third or a half of that of a red corpuscle. It was only in one of the cases, Case 5, that the preservation of the tissues was sufficiently good to enable the spores to be seen. (It is well known that in order to get good preparations of the parasite of malaria the tissue must be fixed and hardened very shortly after death.) For the most part, even in this case, the spores were either not visible or were too indistinct to be counted, the part of the parasite surrounding the central pigment being seen as a narrow stained zone without distinct elements. But occasionally I obtained preparations in which spores were distinct.

I have already given my reasons for believing that in this case the number of spores varied from five and upwards, to as many as eight or nine. The amount of pigment formed by this minute parasite is comparatively large.

Usually one stage of the parasite prevails in one brain, and sometimes almost exclusively. In one case (Case 5) in which all the stages were observed, one stage prevailed over the others ; and when two stages were visible in the same case all the parasites in one blood-vessel were often of one stage exclusively, whilst those in another vessel were exclusively in a different stage. The stage which prevailed in all the four cases was the early stage with one nucleolar element, and it is interesting to note that the death of the patient must have coincided with the prevalence of the early form of the parasite.

We may infer also that in this form of malarial fever the tendency to periodicity is associated with a certain rhythm in the development of the parasite, a fact which is well ascertained for other forms of malarial fever associated with the varieties of the parasite of malaria.

It is noteworthy that not only were no forms of the crescent body found in the tissues in these four cases, but none of the rounded forms of parasite which the descriptions of authors and my own experience have shown me to be characteristic of crescent forms in the early stage were seen.

I will not go here into the differences that exist between this parasite and that which causes the tertian and quartan fevers. My description, and the drawings which accompany this paper, ought, I think, to satisfy on that point those who are familiar with these fevers, and those who are not have only to compare this parasite with the tertians and quartans described by Golgi and other Italian writers, or with the description given of them by Dr. Marshall and myself in the seventy-ninth volume of these 'Transactions.' If, more particularly, the drawings which accompany this paper be compared with the drawings of the quartan and tertian parasite, the difference is so distinct that it cannot be overlooked. In its morphology it so closely resembles the parasite of the summer-autumn fever of Marchiafava, and of the same or similar parasite which causes the more severe fevers in the south of

Spain, that I am unable to observe any essential difference.

We have seen that the veins in the brain, and especially in the pia mater, contain large numbers of white corpuscles laden with pigment, and presumably red corpuscles containing a parasite, swallowed as it were whole, of which I have figured one example.

One stage of development usually predominated in all the four cases—the early stage. When two or three stages were observed in the same case all the parasites in one vessel would be of one stage, and in another vessel all or nearly all in another stage, one capillary being filled with the young parasite, and another capillary containing many sporulating forms.

The walls of the blood-vessels that contain parasites sometimes break down, leading to capillary hæmorrhages.

We next find morbid appearances in the spleen. In the spleen, in all the four cases, much pigment was found, contained mostly in large white corpuscles. Very few parasites were found, so that in these cases it cannot be considered that the spleen is a habitat of the parasite, in this respect contrasting with what is known to be the case with many of the fevers that prevail in Southern Italy. Blood aspirated during life from the spleen in these four cases would not have contained the parasite in the various forms of development, such as has been described by the Italian investigators. That this negative result was not due to bad preservation of the tissue was evident from the fact that in the very few isolated infected red corpuscles that were found the parasite was sufficiently well preserved. The spleen in these cases becomes a storehouse, in which the pigment-bearing white corpuscles are collected, and these are collected almost entirely in the spleen pulp, as they are found scattered thickly through the pulp and also in the splenic veins and in the perivascular spaces.

From the spleen they find their way to the liver through the portal vein, and it was interesting to note in one

case, that while in many white corpuscles in the spleen the pigment was still in the needle form, after they had reached the branches of the portal vein the pigment had all assumed the form of small spheres.

The appearances to be described in the liver fall into two categories : first, the condition of the pigment in that organ ; and secondly, the changes observed in the tissues of the organ itself. White corpuscles containing pigment are observed in greater or less number in the capillaries according to the case, but in these cases the most of the pigment was contained in the endothelial cells of the vessels. From the endothelial cells of the capillaries some of it is seen to find its way into the perivascular spaces. When once outside the capillaries it has a tendency to accumulate in the form of blocks ; the largest of these blocks were seen (and some of them were of considerable size) in the perivascular tissue of the interlobular veins. (In connection with this description I refer to an epitome of Bignami's descriptions of the Italian fevers, which I gave in my paper of last year.) It will be seen that in all essential particulars the disposition of pigment in the spleen and liver described by Bignami holds good for these Sierra Leone cases, and the appearances were uniform in the four. It is clear, therefore, that they correspond to a general law, which may be briefly expressed by the statement that the pigment is collected in the spleen, carried to the liver, and there becomes eliminated or absorbed.

The appearances observed in the liver tissues show that this process is not carried out without a destructive effect on that organ. I pass over the small amount of fatty degeneration in the cells as not being greater than is often found in persons who have died of other diseases, but the capillary injection observed to some extent in all the cases, and to an enormous extent in Case 5, shows that the poisonous effete matters produced by the parasite have a highly irritating effect on the blood-vessels of the organ. This is made still more apparent when it is

observed that under the contact of the pigment the endothelial cells of the capillaries swell and degenerate, leading to injurious effects on the integrity of the vascular wall. The liver cells, which absorb a certain amount of the pigment, cannot fail to be injured by the contact with this foreign substance, although an apparent destruction of the cells was not observed to any great extent.

The appearances found in the liver explain the congestion and enlargement of that organ frequently found as a symptom and sequela of these fevers. It is a condition familiar to all physicians who have had much to do with the treatment of malaria. The congested and enlarged spleen, so frequent in these fevers, is readily explained in a similar way. It is impossible for an organ to be so full of foreign matters capable of exercising an injurious effect on the tissues without undergoing morbid change, but clinical observers have not hitherto associated the affection of the liver in malarial fever to the same extent with the disturbance caused by the destructive effect of pigment on the endothelium of the vessels. Surgeon-Captain Duggan informs me that the condition of the liver in the fevers of Sierra Leone is often a more important complication than that of the spleen. Whatever injurious effect is produced in the liver, as in other tissues of the body, by the poison set free by the parasite in its development, we must, in the light of the anatomical changes which I have described in these four cases, consider that a large share of the mischief is caused by the blood-vessels of that organ being charged and injured by the pigmentary refuse left by the sporulating body.

The changes in the kidney described by me in the first case were found repeated in a still more marked form in Case 2, and it is interesting to note that the destructive effects observed in the kidney epithelium were not found to be due to pigmentary accretion, or to any visible products of the parasite, and must therefore have been due to the effect produced during elimination of the intangible toxins which it generates.

It would be an interesting task to endeavour to detect the cause of the selection of the cerebral vessels by the parasite which produces these fevers, and it would not be difficult to advance various hypotheses to account for this selection ; but I do not think it is desirable to burden this paper, which is mainly a record of facts, with the exposition of speculative theories.

In this connection, however, naturally the first circumstance that occurs to our consideration is the fact of the small calibre of the cerebral capillaries. Bevan Lewis remarks that, taking the capillaries of all regions, excepting the enormous capillaries of marrow, the average dimensions are between 7μ and 10μ , that is, when full of blood. The capillaries of the cortex are very often not over 4μ in diameter ($\frac{1}{8250}$ of an inch), and they are of less calibre than the red blood-corpuscle. It follows from this fact that in the ordinary course of the circulation the blood-corpuscles must come into closer contact with the capillary wall of the cerebral vessels than in the larger capillaries of the other parts of the body, and with this close contact there is probably also associated a slow circulation.

Now we know that in these fevers in the small veins the infected red corpuscles are mostly found lying on the wall of the vessel, showing that, once they are infected, there is a tendency to their remaining adherent to the endothelium, instead of being carried on into the general circulation. The infected corpuscles can thus only be driven through the capillaries of the brain into the cerebral veins, when the *vis a tergo* is sufficient to overcome the tendency which they have to adhere to the endothelium. If this power is not sufficient, we have necessarily an arrest of the circulation of the infected corpuscles in the delicate capillaries.

Against this theory is to be placed the fact that, in tertian and quartan fevers, and in many of the cases of the fevers of the severe type associated with the parasite of the summer-autumn fevers, no such special selection of

the brain occurs. In these fevers the infected corpuscles must find their way through the cerebral capillaries without any special blocking of the calibre; and in this connection we must remember that the red corpuscle which harbours the tertian parasite becomes larger than the ordinary red corpuscle. Are we, then, to seek for the cause of the blocking of the small brain capillaries by the corpuscles infected with the parasite of these pernicious fevers, not only in the small calibre of the vessels, but in some increased toxic quality of the parasite itself, which so alters the physical properties of the red corpuscle that it adheres to the vascular wall instead of gliding on in the circulation, coupled with the fact of the short period required to produce its spores; the arrest of the circulation in the vessels and the rapidity of its reproduction leading to the capillary vessels becoming the habitat and breeding place of the parasite, comparatively few of the infected corpuscles ever passing from the brain into the veins of the general circulation? According to this theory the primary cause of the special selection of the brain is the small calibre of the cerebral capillaries in conjunction with the severe toxicity of the parasite as compared with the other forms of the parasite of malaria.

(For report of the discussion on this paper, see 'Proceedings of the Royal Medical and Chirurgical Society,' Third Series, vol. x, p. 6.)

DESCRIPTION OF PLATES I AND II

A Further Contribution towards the Pathology of the Pernicious Malarial Fevers of Sierra Leone, and our Knowledge of the Parasite with which they are Associated (GEORGE THIN).

N.B.—All the figures were drawn as seen by a magnifying power of about 500 diameters, except Figs. 4 and 5, which represent a magnifying power of about 1000 diameters, and Fig. 10 one of 580 diameters.

PLATE I

FIG. 1.—A capillary vessel in the brain from Case 2 in which all the red corpuscles are infected by the parasite. The parasite is in an early stage.

FIG. 2.—Transverse section of a vein of the brain in Case 4. Three corpuscles are seen to be infected by the parasite, which is in an intermediate stage of development. In two of the infected corpuscles the lighter staining shows that the corpuscle had already begun to lose its hæmoglobin.

FIG. 3.—A red corpuscle in a capillary infected by two parasites, the size of which shows that they had already begun to develop. From Case 4. (Compare with the size in Fig. 1.) Figs. 1, 2, and 3 are stained in hæmalum and cochineal.

FIG. 4.—A blood-vessel from the brain in Case 5. Under the borax methylene blue staining the protoplasm and nuclear element of the parasite are differentiated. The parasite is in an early stage, and a minute deeply stained nucleolar point is observed in each.

FIG. 5.—Part of a vessel from the brain in Case 5 showing the formation of spores. A parasite with five spores is seen on the lower part of the drawing.

FIG. 6.—From the same brain as Figs. 4 and 5. Parasites are shown with central pigment, in one of which, at the top of the drawing, two spores are visible. In the infected red corpuscle, at the bottom of the drawing, pigment is seen with three spores.

FIG. 7.—Part of a capillary from the brain in Case 5. At the lower end a red corpuscle is recognised by its outline. It contains a sporulating parasite, in which the pigment is seen on the left and four spores on the right. The lower two spores were partly joined as if in the act of division.

FIG. 8.—Also from the brain in Case 5. Sporulating forms with the central pigment are seen in the upper part of the drawing. At the lower part a group of six spores is observed occupying little more than a semi-circle. The pigment is observed in the upper part. It is impossible to say

whether some spores had disappeared, or been in another plane of section, or whether they had been displaced. The staining had almost entirely disappeared from the red corpuscles.

FIG. 9.—From Case 5. Showing a hæmorrhage in the brain. On the left in a transverse section of a small vein the remains of parasites with central pigment are seen. The vein is surrounded by red corpuscles which have escaped into the brain substance.

PLATE II

FIG. 10.—Part of a vein from the brain of Case 4. Two white corpuscles (*a* and *b*) are seen with pigment spheres. In *c* a white corpuscle is seen containing three spheres of pigment, and in its interior a red corpuscle, and inside the red corpuscle a parasite with a nucleolar element stained. The colourless sphere in the white corpuscle represents the red corpuscle.

FIG. 11.—From the liver in Case 4. A section of a capillary containing a white corpuscle with pigment spheres. On the left an endothelial cell is seen swollen and deeply stained.

FIG. 12.—Transverse section of a small blood-vessel in the liver in Case 4. A white corpuscle with two pigment spheres is seen inside the vessel, and two pigment spheres in the endothelium of the vascular wall.

FIG. 13.—Shows the distension of a small vessel in the liver with degenerating vascular endothelium. The endothelial cell contains two pigment spheres, and is swollen, and takes on deeply the red stain. From Case 5.

FIG. 14.—To illustrate further the degenerating endothelium in the distended capillary vessels of the liver. The endothelial cells, *a*, *b*, and *c*, are seen swollen and breaking up, taking on the red stain, and containing pigment spheres.

FIG. 15.—Shows a block of pigment which, under the microscope, could be seen to be outside the vascular wall.

FIG. 16.—A group of liver cells containing minute spheres of pigment. In the upper part of the drawing a larger block of pigment is seen lying on a liver cell between it and the degenerating wall of a capillary vessel.

FIG. 17.—Shows four liver cells to illustrate the various forms in which the pigment is observed in the cells of the liver.