

the remaining cervical glands cannot be stated otherwise than in general terms. These glands also have many intercommunicating channels. From this it follows that one or more glands may be infected from a common source of infection, and no deductions can be drawn with certainty as to the sequence. Fortunately, it is practically never necessary for a meat inspector to make such a fine distinction. Similarly in the case of the lumbar glands: these receive lymph from practically all the glands which drain the abdominal cavity and the muscular and bony structures of the abdominal walls and of the hind extremities, so that infection of them would, if considered alone, be unproductive of suggestion as to the original seat of infection.

On the other hand, there are glands respecting which a fairly positive statement may be made that lymph entering them has been received from a well-defined area, and if such a gland shows a tuberculous lesion that the infection was derived from the area drained. Such glands are those connected with certain organs, particularly the portal gland, the renal gland, and the internal inguinal or supra-mammary gland, according to sex. There are others which receive lymph only from the muscles, bones, and joints of the extremities—e.g., the prescapular, the precural, and the popliteal—and infection of these has a similar definite significance.

Obstruction to the flow in a system with marked anastomotic features will therefore, on occasions, show almost unexpected variations to improve any impaired efficiency. For example, the lymph of the pleural region normally reaches the main lymph channel either direct or through the prepectoral glands, but, as pointed out by Buckley and Castor,<sup>6</sup> in case of obstruction the lymph-vessels may become fused with deep-lying lymph-vessels on the pectoral wall, and these in turn pass over the shoulder to the prescapular glands. This is a roundabout course, and probably rarely, if ever, happens, but it serves to illustrate the point that surprising variations in flow may be noticed and infection be transferred to unexpected situations. Another example, but as a normal condition, is found in the case of the pig, in which animal (and perhaps also in cattle), a small part of the fundus of the stomach drains into the splenic gland, from which it will be gathered that tuberculosis of the spleen may cause lesions in one or more of the multiple gastric glands without the stomach being the seat of origin.

The venous blood stream receives infection from infected lymph which enters by way of the thoracic duct or right lymphatic channel, or by the infection gaining direct entrance through the erosion of a vein which has become implicated in a tuberculous process, either within a gland or otherwise.

Having reached the blood stream, the bacilli are conveyed to the lungs (except in the case of the portal system to be mentioned later), and from thence may pass into the arterial blood stream to reach other organs. The organs apparently do not show uniformity in results. The lungs are most generally affected, as would be expected, and the next most frequently the liver. The spleen<sup>7</sup> and kidneys may be affected, but the latter more frequently. Muscular tissue rarely shows lesions, whilst bony structures are much more frequently affected in pigs than in cattle. The brain and spinal cord are infected from the blood stream. The reasons for the differences in glandular structures may be found in the varying amount of blood transmitted to them, differences in the speed of flow, and perhaps the action of the gland contents on the organism.

The blood itself seems able to get rid of organisms or to destroy their pathogenicity in a few days, as has been shown by McFadyean and others, and in this the filtering action of the various glands assists, but there is also a direct lethal effect, and probably excretion is not a negligible factor.

<sup>6</sup> Buckley and Castor: Lymph Glands of Food-Producing Animals. Twenty-seventh Report of Bureau of Animal Industry.

<sup>7</sup> The substance of the spleen rarely, if ever, develops lesions in cattle infected after the calf age.

**LECTURES FOR WOUNDED SOLDIERS.**—The Victoria League has done good service in organising lectures to soldiers in hospitals, and an appeal is being made for £500 in order that the scheme may be considerably extended. The work is supplementary to that undertaken by the Y.M.C.A. and the Workers' Educational Association. Contributions should be sent to the honorary treasurer, 2, Millbank House, Westminster, marked "Hospital Lectures Fund."

## A CONTRIBUTION TO THE MICROSCOPICAL HISTOLOGY OF MALARIA,

AS OCCURRING IN THE SALONIKA FORCE IN 1916, AND  
A COMPARISON OF THESE FINDINGS WITH  
CERTAIN CLINICAL PHENOMENA.<sup>1</sup>

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### *Scope of Investigations.*

THESE investigations were undertaken for the purpose of ascertaining the cause of death in some of the rapidly fatal cases of malaria. Also whether the lesions produced were more severe than those already recorded in the history of this disease, and more especially, if any facts could be obtained to explain the sudden death which has occurred, and the observed frequency of cardio-vascular phenomena. The cardio-vascular symptoms have been carefully studied by our French colleagues among the troops of the Levant Army, so that it may be taken as an accepted fact that these cardio-vascular phenomena have been of frequent occurrence among the troops of the Allied Armies.

These observations include the investigations of the cerebrum, cerebellum, medulla, heart muscle, adrenal glands, liver, spleen, kidneys, and intestinal tract from cases which died in coma, those who died quite suddenly, and those who died with general malarial toxæmia. A case of malaria which succumbed to blackwater fever is included as the examination of the tissues in this case serves as a valuable contrast with the other cases of malaria.

A special investigation of the adrenal glands has been made from some cases of malaria which died in one of the General Hospitals.<sup>2</sup>

The tissues were fixed in 10 per cent. formaldehyde in normal saline (in a few cases 50 per cent. spirit was employed) and also potassium bichromate. The tissues were stained for fat with Scharlach R., and as a general stain hæmatoxylin was employed and also iron hæmatoxylin, while for certain features which were specially required to be developed the staining with hæmatoxylin was modified in certain details. Staining for Nissl granules, Van Gieson's stain, Giemsa's stain, and Leishman's stain and staining of the tissues for free iron were employed. Strengths of hydrochloric acid varying from 2 per cent. to 25 per cent. acting at 37° C. were used for testing for the presence of free iron.

It has been noticed during this epidemic of malaria in the Salonika Army that sudden death was not uncommon, and the committee<sup>3</sup> which was appointed to inquire into and report on the fatal cases of malaria which occurred in the Salonika Army noted that a large proportion of the cases died within 24 hours and no less than 57 per cent. died within the first two days of admission to hospital. Further, collapse and even sudden death occurred as an initial phenomenon of the disease in this epidemic.

Now before the microscopical findings are referred to, attention must be drawn to another factor which has been considered in relation to the death-rate—viz., the high temperature this summer. As far as these results are concerned, every fatal case which has been investigated died after August 8th, while the intense heat was previous to this date. This point is only mentioned because of the importance which some have attached to the temperature experienced by the troops this summer.<sup>4</sup>

### *Heart Muscle.*

It is now definitely known that the most important cause of death in acute diphtheria is fatty degeneration of the heart muscle and, to some extent, of the diaphragm. At the

<sup>1</sup> A paper read before the Salonika Medical Society.

<sup>2</sup> We are specially indebted to Captain Richards, officer in command of the laboratory of this hospital, for his assistance with the examination of the adrenals.

<sup>3</sup> The committee consisted of Colonel Stewart, C.B., Lieutenant-Colonel Aldridge, C.S.I., C.M.G., Lieutenant-Colonel Lionel Smith, and Lieutenant-Colonel L. S. Dudgeon.

<sup>4</sup> Manson and certain other writers consider that "heat-stroke" simply means "syncope," caused by heat alone or a combination of heat and lowered bodily resistance.

suggestion of Dr. Foord Caiger, one of the most distinguished authorities on specific fevers, examination of the heart muscle from fatal cases of diphtheria in the acute stages of the disease was undertaken by me.<sup>5</sup> It was shown that the heart muscle, and often the diaphragm, undergoes fatty degeneration which is the cause of sudden death in the early stages of this disease. Experimentally fatty changes in the heart muscle and diaphragm of rabbits and guinea-pigs poisoned with diphtheritic toxin were induced within a few hours.

It is recognised that absolute rest is a cardinal rule in acute diphtheria because of these changes which the heart muscle undergoes.

Examination of the heart muscle in six cases of malaria showed fatty degeneration in each instance, and in five out of the six cases diffuse fatty change similar in all respects to that which is found in acute diphtheritic toxæmia occurred. In the one exceptional case referred to this degeneration was irregular in its distribution, but the heart muscle was obtained from a case of sudden death. In the muscle cells the fat is present chiefly as fine droplets, but medium-size and large droplets are seen which again simulates the fatty change in acute diphtheritic toxæmia. This fatty degeneration of the heart muscle, using the term in the sense which modern teaching directs, is of the utmost importance in the therapy of malaria.

In addition to the fatty degeneration, blocking of the capillaries with infected red cells is present in most instances. This appearance of the heart muscle, which, apart from affording such a striking feature to the microscopical specimens, no doubt plays a rôle in the etiology of fatty degeneration of the muscle wall.

These results afford a satisfactory explanation for the sudden collapse and death which, as already stated, has occurred during this epidemic. As in diphtheria, so in the treatment of severe malaria every effort should be made to protect the heart from undue exertion as far as this is possible under the prevailing circumstances.

#### Adrenals.

The microscopical changes in these glands are very numerous, and in some respects the appearances are similar in all the glands examined. The most constant alteration from the normal histology is the diminution in the lipid substances which give such a characteristic appearance to the normal gland. The loss of lipoids occurs in all layers of the cortex, although this effect is much more obvious in some areas than others. In every gland examined lipid substances can be demonstrated, but by comparison with the normal adrenal the loss is often considerable, and in 11 specimens out of 12 which have been examined there are large areas of cortical tissue in which the lipid content is reduced to a minimum.

The chromaffin substance in the medulla is also greatly reduced in amount as far as can be demonstrated by microscopical methods, so that in some of the adrenals the chromaffin, although deficient, can be recognised in the cells of the medulla; in other glands it is a matter of considerable difficulty to find this pigment.

Elliott,<sup>6</sup> in his monograph on the adrenal glands, states that he regards the chromaffin reaction as unreliable in adults, so that it is quite fallacious to estimate residual adrenalin with the depth of staining of the tissues. For accurate work he considers that the adrenalin must be extracted from the gland and its amount determined by quantitative methods. Among his conclusions, Elliott makes this statement: "The adrenalin is lessened in many infective diseases, but probably not to such a degree as to endanger the circulation."

In many of the adrenals the deep cortical pigment is found to be abundant.

Malarial pigment is present in each specimen which has been examined, and can be easily recognised, as is the case with this pigment in other organs. It is found free, lying in the adrenal cells, in spider cells from the connective-tissue framework which bounds the glandular tissue, and in large mononuclear cells in the sinuses. Vacuolation of the cortical tissue is apparent in many of the specimens and also areas of necrosis, but these changes vary in the specimens examined.

Necrosis of the cortical and medullary tissue is especially well marked in those cases in which there is thrombosis of blood-vessels. Congestion of blood-vessels is present in every case, although, as one would expect, it is much more marked in some of the glands than in others, and, further, this congestion of blood-supply is apparent throughout the cortex and medulla, and also in the capsule. In three cases the congested vessels contain numerous small ring parasites and spores in the red cells, so that this appearance gives a

characteristic feature to the sections. In one case which has frequently been referred to in this report all the blood-vessels of the adrenals are congested, but many of the capillaries and arterioles are thrombosed. The thrombi contain agglutinated red cells, which are in various stages of hæmolysis, and also yellow pigment granules, free, and taken up by large mononuclear cells within the blood-vessels.

Small parasites and spores are found in most of the glands, but they are far more numerous in some cases than in others; while in one instance crescents are present, although few in number.

The free iron reaction was only demonstrated in two of the cases, and even in these the reaction was very feeble.

Hæmorrhages are present in those adrenals which show marked congestion of the blood-supply, and also phagocytosis of the red blood cells.

Paisseau and Lemaire<sup>7</sup> have examined the adrenal glands from cases of malaria occurring among the French troops in the Orient. The glands from three cases were submitted to careful microscopical examination, and it was found that profound changes had occurred, the most important of which were arterial thrombosis, hæmorrhages, and foci of degeneration. The cortical cells in some areas were almost completely necrosed. These observers consider that the asthenic condition met with in malaria may be accounted for by the profound changes which can be demonstrated microscopically in the adrenals, and even recommend the employment of adrenalin for such cases.

Further, Monier-Vinard has also drawn attention to the low blood pressure noted from daily observations in numerous cases of malaria occurring among the French troops.<sup>8</sup> Not only are the cardio-vascular lesions sufficiently serious, but the widespread changes found in the internal organs afford abundant evidence of a severe general toxæmia.

#### Brain.

The cerebrum, medulla, pons, and cerebellum have been examined from three cases,<sup>9</sup> and in all three the lesions are both severe and widespread. In each case the patients died in coma. It was noted at the time of the examination of the brain that thrombosis was present, and that it was more especially marked in the white matter. It was a matter of considerable difficulty to disengage the clots from the vessel walls, and while in one case no parasites could be found in the red cells from the clot, yet in the other specimens parasites were abundant.

The microscopical appearances will be described separately, as in one case parasites could not be detected in any of the specimens, while in the other two cases they were present. The first case occurred in a sapper who had been energetically treated with quinine by intravenous and intramuscular injections, but died in coma as already stated. Portions of the brain tissue from various areas were examined microscopically and were found to show identical changes, so that it is sufficient to describe one area of brain tissue in detail. The capillaries are engorged with blood, as also the arterioles, while many of the blood-vessels are thrombosed and the thrombi are composed of agglutinated red cells, partially hæmolysed red cells, and blood pigment. This pigment is taken up by the endothelial cells which are found lying free in the lumina of the vessels.

It also appears that the vessel walls are themselves more prominent than from the cases to be described, although there is no evidence of inflammatory reaction. Smear preparations of blood clot made soon after the autopsy failed to show any parasites, while careful examination of numerous sections of the brain have led to a similar result.

The cerebral tissue itself shows the effect of these changes, as the nerve cells have undergone all forms of cell degeneration in the specimens which were prepared for that purpose. Some of the cells are nuclear-free; in others the nuclei are eccentric. The cell granules are either absent or present in very deficient numbers, and while some of the cells are swollen much above the original size, others are shrunk.

In the other two cases the microscopical changes are very similar, whether the portions of tissue examined have been taken from the medulla, cerebellum, or cerebrum, and thrombosis was very readily recognised at the autopsy. The vessels are engorged with blood and a large proportion of the red cells in the capillaries and arterioles contain engulfed parasites which are present in the form of rings or dots. Some of the capillaries show as many as 100 per cent. infected red cells, while it is uncommon to find less than

<sup>7</sup> G. Paisseau and H. Lemaire: *Accès Pernicieux Palustres*. Sur-rénales Aigues, Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris. (Séance du 20 Octobre, 1916.)

<sup>8</sup> Quoted by MM. P. Armand-Delille, G. Paisseau, and H. Lemaire: *Le Paludisme de Première Invasion observé en Macédoine pendant l'été 1916*. Extrait des Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris. (Séance du 13 Octobre, 1916.)

<sup>9</sup> From material recently obtained from a fatal case of malaria, the retinal and choroidal vessels, and the blood-vessels in the optic nerve contain numerous infected red cells, while some of the vessels in front of the eye are blocked with infected red cells.

<sup>5</sup> Leonard S. Dudgeon: *The Pathology of Acute Diphtheria Toxæmia*, Brain, 1906.

<sup>6</sup> T. R. Elliott: *Pathological Changes in the Adrenal Glands*, Quarterly Journal of Medicine, October, 1914.

70 per cent. of the red cells in a vessel containing parasites. The black pigment of malaria is present and not the brownish-yellow pigment resulting from the action of hæmolytic; in fact, pigment other than the true malarial pigment can be disregarded in the specimens from these two cases, with the exception of the yellow pigment present in the nerve cells in this and many other conditions. Vascular thrombosis is present in both the white and grey matter, but more marked in the white matter. There is complete absence of perivascular inflammation throughout the brain tissue. The nerve cells show all stages of degeneration, from the cell merely represented by "wall outline" to the apparently healthy cell.

By comparison it can be readily appreciated that the changes in these two classes of cases, which may have been to some extent similar on clinical evidence and which died in coma, yet differ widely in their microscopical characteristics. In both varieties thrombosis of blood-vessels has occurred, engorgement of vessels and nerve-cell degeneration, but while in the two cases the vascular phenomena are those which have been widely described in fatal cerebral malaria, yet in this one case the vascular changes which are present do not suggest that the malarial parasite was the etiological factor in the fatal issue. There is evidence of a toxin (apart from the plasmodium) acting on the red cells and tissues throughout the body. In the splenic films of this case parasites were not found, although during life one ring form was seen. A general vascular thrombosis has occurred with destruction of blood in the vessels. That this condition may have been induced by too active treatment with quinine seems to us extremely probable, although absolute proof-positive evidence cannot be established. In the two typical malaria cases vascular thrombosis is present as a widespread lesion, but due to the blocking of the vessels with infected red cells.

While referring to the microscopical changes in the brains in our cases of coma, it is of importance to consider the work which has been recently recorded by workers in the laboratories of the Levant Army under Dr. Armand Delille. The cerebro-spinal fluid was examined from 33 cases of malaria, both with and without symptoms suggesting a lesion of the central nervous system, by Monier-Vinard, Paiseau, and Lemaire. In 10 cases the fluid was found to be normal, but in 23 cases, of which a certain number were suffering from violent headache, delirium, convulsions, and coma, the cerebro-spinal fluid was shown to contain a marked increase in the number of lymphocytes and an increase in the protein content.<sup>10</sup>

#### *Spleen.*

The changes found on microscopical examination of the splenic tissue are very numerous and most interesting.

There is congestion in all cases, free hæmorrhages are present in some, while in several instances necrosis of the splenic pulp has occurred. This necrosis affects chiefly the pulp, but there is some necrosis of the Malpighian corpuscles in a few instances, while in the case of blackwater fever<sup>11</sup> the necrosis of the Malpighian corpuscles is the most striking feature. These necrosed corpuscles showed considerable enlargement on naked-eye examination, and it therefore appeared probable that the enlargement was due to activity in these centres. In this case, however, the enlarged corpuscles consisted of necrosed endothelial cells, while the lymphoid cells, which give the appearance to the healthy corpuscles, are few in number.

In all the malarial spleens examined the areas of necrosis contain black pigment. In one case infarction of a large area of splenic tissue had occurred, which had all the appearances of a typical infarct. Microscopical examination of the spleen in this case showed congestion of the splenic tissue adjacent to the infarct, and here red cells containing either rings or dots are very abundant and also free and engulfed malarial pigment, while in the necrotic tissue parasites are very scanty, even in the few red cells which have escaped autolysis. Pigment in the infarcted area is also very scanty.

Thrombosis of the capillaries and arterioles in many of these cases is a striking feature. This thrombosis is similar to that which is figured in some of the cerebral specimens, and the red cells which are present in the thrombi are heavily infected with parasites. It is in those specimens in which thrombosis of vessels is present that foci of necrosis predominate. Pigment is present in abundance in most cases, but, like the pigment which is found in other tissues, it has little tendency to give a free iron reaction. This pigment (fine, medium, and coarse) is found free, in the mononuclear cells and small giant cells in the sinuses. Phagocytosis of red cells is present in all the specimens in excess of that which occurs in the spleen in non-infective

conditions; in some cases the red cell phagocytosis is very marked. Crescent parasites were only found in three cases, while other forms of parasites were found without difficulty in all cases but one. The splenic sinuses may be very much distended, although the walls can be readily recognised, while in other areas in the same specimen the congestion of the sinuses is such as to render the outline indistinct.

Evidence of amyloid degeneration, either in the central bodies or in the splenic pulp, is wanting in every case.

#### *Liver.*

The hepatic changes are numerous, but the deposit of pigment, which has long been regarded as one of the most constant characteristics of the malarial liver, is present in every case. This black pigment is found lying free in the sinuses and also in cells in the blood spaces. It is engulfed by large mononuclear cells from the sinus walls, in spider cells, and cells which closely simulate detached liver cells. Free iron is present, but the reaction without exception is very feeble, while some liver cells contain yellow pigment in fine dots.

Fatty change is present, but it is only in a few cases that the fat droplets are abundant. In the one case of blackwater fever the fatty change is very marked, but it is limited to the central zones, which consequently are beautifully mapped out by this degeneration. Necrosis of liver tissue in isolated areas is of common occurrence, and the focal necrosis is similar to that which occurs in many infections. In the case of blackwater fever the necrosis is well mapped out in the central zones of liver tissue in which the fatty "degeneration" occurs, while free nuclei are found here together with polynuclear leucocytic invasion of the necrotic tissue. In the other cases of malaria this central necrosis of liver tissue has occurred, but to a less extent. Parasites are found in the red cells in the sinuses and in the blood-vessels, while the vessels in a section of the liver which shows thrombosis contain numerous infected red cells in the thrombi, and also a few crescents. It can be taken from these observations, however, that the invasion of the liver with infected red cells is not such a striking feature as is seen in the spleen, brain, and heart muscle. There is no evidence of amyloid disease in any case.

It is important to note that the bile was examined from some of the fatal cases of malaria by Captain Clarke and found to be sterile, and Captain Clarke and I examined 35 cases of malaria, at a mobile laboratory, and in every instance the blood was found to be sterile. Captain Elworthy, officer i/c of one of the laboratories in Salonika, made blood cultures in 13 cases of proved malarial fever, with negative results in each instance, while samples of bile from eight cases of fatal malaria and cultures of the spleen from six cases were found to be sterile.

These bacteriological results are important, as it might be suggested that some of these pathological findings were induced by bacilli of the enterica group acting on the liver tissue. Bacillary dysentery is the only other probable bacterial infection which might account for some of these changes, but no dysenteric symptoms are recorded and ulceration of the bowel was not found in any of these cases in which the liver was examined microscopically. It is necessary, however, in the Balkans, as it was on Gallipoli, fully to realise the possibility of double infections.

#### *Kidney.*

The microscopical examination of the renal tissue has shown that certain changes in the kidney are similar to those already referred to in the account of the other viscera. Fatty degeneration of the renal epithelium has occurred in several specimens, especially in that of the convoluted tubules, while in some cases the vessels are thrombosed in various areas, and here foci of necrosis occur. In two cases the kidney changes are widespread. Diffuse nephritis is present on microscopical examination of one of these cases, and during life the man had suffered from subtertian malaria, finally succumbing to the effects of acute nephritis. The renal changes are extreme and the lesions are widespread. The tubules show the most marked changes, which include fatty and other degeneration of the tubular epithelium and obstruction of the lumina of the tubules by blood casts and epithelial products, while in addition there is exudation into the glomerular tufts.

In the other case the patient died of blackwater fever. There is extreme degeneration of the whole renal tissue, but fatty change is more marked in the products of degeneration in the tubules than in the degenerated epithelial cells lining the walls. The lumina of the tubules are blocked by (1) clots chiefly consisting of red cells and red-cell debris, (2) coagula of blood serum, (3) thick granular deposits. The epithelial cells of the tubules which themselves show all possible degenerative changes have been widely shed into the lumina of the tubules. Some of the blood-vessels are filled with blood serum, while the capillaries of the glomeruli are engorged with red cells and red-cell debris. Some vessels contain definite thrombi of agglutinated red cells. There is

<sup>10</sup> MM. Monier-Vinard, Paiseau, and Lemaire: *Extrait des Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris*, Séance du 20 Octobre, 1916.

<sup>11</sup> The microscopical changes are those of a severe toxic action on the various tissues of the body, and not dependent on the mere hæmolytic of red cells.

no inflammation of any portion of the renal tissue. The free iron reaction is very slight.

#### Intestines.

There is the only case, apart from those cases of proved bacillary dysentery associated with malaria, in which the intestines were examined microscopically. Considerable congestion of the vessels in the mucous and submucous layers of the gut is manifest, and numerous parasitic red cells are found in the vessels. Necrosis of the mucosa has occurred at various points, but there is no inflammation of the bowel wall to suggest a reaction from a bacillary infection. There are large areas of degeneration present with replacement of the muscular coat by mucoid tissue. This patient had not suffered from diarrhoea, and there was no history that he had passed blood or mucus; ulceration of the bowel wall, although present microscopically, was not observed at the autopsy, but the intestine from this area was deeply stained with bile. Whether this case is an example of necrosis of the bowel wall due to malaria, or an undiagnosed bacillary dysentery, is open to question, but against the latter view is the absence of evidence of inflammatory changes in the intestinal wall.

#### Causation of the Drastic Changes in the Tissues.

There is no question that the effects produced on the tissues in these cases of malaria which we have examined are widespread. Further, no other disease with which we are acquainted could have produced more drastic changes in the tissues. The rapid progress of the infection in so many cases on the one hand, and the cardio-vascular phenomena on the other, have led "some" to believe that this outbreak of malaria is different from all others.<sup>12</sup> It has been suggested, as one would expect, that this difference depends on the virgin soil which has been placed at the disposal of the parasites, or on the parasites, or on the quinine.

Special differences as regards the parasites must be left to the decision of those who have advanced this view. We cannot do better, however, than quote the remarks made by Sir Ronald Ross on this question. He says:—

Some authors consider that there are two, if not three, varieties (or ? species) of malignant parasites. I am inclined to agree with them, but have not yet satisfied myself on the point sufficiently to admit it in my classification.<sup>13</sup>

When we come to the question of quinine it is necessary to remember that the treatment of malaria depends on so many factors besides the mere administration of the drug that each of these should be considered on its own merits, more especially in relation to the fact that we are dealing with an army exposed to exceptional conditions of active service. As regards the toxic effect of quinine on the cardio-vascular system it is stated by Manson that it may produce depression, gastric disturbances, and even death from syncope. Professor A. R. Cushny, in a letter to me on this subject, states that he cannot supply any data to support the view that quinine is a cardio-vascular poison, but, on the other hand, he emphasises that as the drug has been used so extensively and under such special circumstances our views may have to be modified. These remarks by Professor Cushny, together with the views of those who have had wide experience of the successful treatment of malaria with quinine, seem to us to afford no evidence that quinine correctly administered is able to provoke such widespread toxic action on the tissues of the body.<sup>14</sup> It has to be remembered that our French colleagues consider that the cause of these various effects on the tissues is due to the action of the malarial parasites; a view which has abundant evidence to support it.

#### Blocking of Blood-vessels in Malaria.

Complete or partial occlusion of blood-vessels with red cells heavily infected with parasites has long been known to occur in malaria. Bass and Johns offer an explanation for this phenomenon, which is as follows:—

The substance of malarial plasmodia is very different in consistency from that of red blood cells, and therefore they cannot pass through the smallest capillaries like the more yielding fluid-like red cell. That the consistency of the

protoplasm of the parasite is less yielding than that of the red blood cell is shown by the fact that when a small quantity of a culture containing large parasites is spread over a slide with the end of another slide, the parasites are dragged to the end of the spread, though the red blood cells are left behind.

This observation, however, refers to the smallest capillaries which are obstructed, while as a matter of fact it is not only the smallest but the large capillaries and arterioles which are plugged, and this vascular obstruction would seem to be most marked in the brain, spleen, and heart muscle. Heavy infection of the red cells with parasites will assist in obstructing the blood-supply by mechanical means quite apart from the general toxic action on the tissues and endothelium of blood-vessels; fatty degeneration of the heart muscle must lead to diminished blood pressure; while the changes in the adrenals are also of importance in this direction. It would appear probable, however, that blocking of blood-vessels with heavily infected red cells may be a temporary condition apart from the serious pathological lesions, thrombosis and embolism, while there is little doubt that obstruction of the blood-supply to the tissues in malarial fever is dependent upon many factors.

## TREATMENT OF TUBERCULOUS EYES BY LOCAL APPLICATION OF TUBERCULIN.

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DURING the investigations into the cutaneous reactions of tuberculin, recorded in the article "Diagnosis of Tuberculosis by Tuberculin," published in *THE LANCET* (Oct. 7th, 1916), and certain other investigations into tuberculin reactions on lupus, not yet published, there arose a strong conviction that some form of local application of tuberculin would be the right way of treating the tuberculous conditions affecting the superficial tissues of the eye.

Up to the present the treatment of tuberculous eye conditions has been rather unsatisfactory, not only because of duration of the disease, but also on account of its great tendency to relapse. There has also been considerable difficulty in recognising which conditions were due to tuberculous infection and which were not.

#### Extent of Cases of Tuberculous Origin.

These tuberculous conditions seem especially prevalent in children, interfering not only with their welfare, but also with their education.

The early recognition of tuberculosis in many of the cases herein recorded was rendered possible by the systematic application of the multi-papillary-cutaneous method of diagnosis, which amply demonstrated that chronic eye affections in children were generally much more due to a tuberculous condition than would have been anticipated. In the cases observed every superficial part of the eye and appendages has been found to be tuberculously infected. The cases so far recorded have been blepharitis, phlyctenular conjunctivitis, and keratitis.

It is now routine practice to test every superficial recurrent inflammatory condition of the eyes and lids, generally with positive results, and the conclusion is being arrived at that nearly all superficial nebulae and maculae are of tuberculous origin. Of course, this generalisation does not include effects of superficial injuries, acute conjunctivitis, or the congestive conditions due to errors of refraction, but it is astonishing how often in the latter condition the congestion produced by these errors is complicated by tuberculosis; the error of refraction lighting up the tuberculous condition, and *vice versa*. It must be remembered that syphilitic and tuberculous eye affections may exist simultaneously. In fact, one case sent for diagnosis was undoubtedly syphilitic, but as a tuberculous reaction also occurred, the tuberculous element was treated for a short time, to the great improvement of

<sup>12</sup> It would be as well for all who believe this to be the case to study the work of Sir Ronald Ross on "The Prevention of Malaria" and the article on Malaria by Major Christophers, "Flies and Disease," by Edward Hindle. Cambridge, 1914.

<sup>13</sup> Ross: *The Prevention of Malaria*, p. 89.

<sup>14</sup> Baermann reported in 1909 a death due to two doses of 0.5 gm. quinine hydrochloride—collapse, blood in dejecta, extravasation in organs. Quoted from "Prevention of Malaria," p. 136, by Sir Ronald Ross.