

## SOME OBSERVATIONS ON THE PATHOLOGY OF RELAPSING FEVER.

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Relapsing fever is endemic in Mesopotamia, and was the cause of a considerable amount of sickness in the Mesopotamian Expeditionary Force, particularly amongst Indian troops and followers.

The seasonal incidence was very marked, as more than half of the total cases for the year occurred in the first quarter (1918-19), and this, of course, is accounted for by the influence of the very cold winter on the personal habits of the population. The month of the greatest incidence is March, and the lowest, October.

The disease was undoubtedly the louse-borne variety, but I am unable to say whether the causal organism should be classified as *Sp. obermeyer*i or *Sp. carter*i; indeed, if such differentiation can be made, it would appear to be unnecessary for the purpose of this paper.

In this connection it must not be forgotten that a variety of the disease closely resembling African tick fever, and probably conveyed by a tick, is prevalent in Persia<sup>(1)(2)</sup>; but though it is possible that some of the cases on the Persian lines of communication may have been of this variety, there is no evidence of its occurrence in Mesopotamia.

In the beginning of 1919 a number of cases occurred in and about Bagdad, with a considerable mortality. During the period 6th October, 1918, to 26th June, 1919, the case mortality was 3·63 per cent (British, 6·49 per cent., Indian, 4·51 per cent, local, 2·53 per cent.). The predominant clinical feature of these cases was very marked cerebral symptoms (delirium, coma).

That there is a type in which cerebral symptoms predominate is not a new observation, though brought to notice by several writers<sup>(3)(4)(5)(6)</sup> recently, as it is mentioned in VANDYKE CARTER'S monograph.<sup>(7)</sup>

The brain of one of these cases was sent to me for examination, and interested me so much that I eagerly sought the chance of obtaining more post-mortem material.

I may mention that the chief point of interest to me lay in the variety of inclusions to be found in the endothelial cells.

Shortly after, by the courtesy of the O.C. Isolation Hospital, I was able to be present at the post-mortem of one case, but unfortunately, from my point of view, it was the last fatal case that was obtainable.

Before describing the results of the examination of this post-mortem material, let me briefly consider what is the present state of the morbid anatomy and pathology of the louse-borne relapsing fever. Text-book descriptions are meagre, and the literature on the subject is not very enlightening, while some of the best work was carried out some time ago, when histological methods were crude compared with the present day. But no doubt it is the scarcity of suitable material that has handicapped research in this line.

In a very comprehensive review of the literature on spirillar fevers up to 1908, MACKIE<sup>(8)</sup> says, with reference to the European variety:—

“There are no characteristic changes in the organs of persons who have died of

relapsing fever; such morbid appearances as are met with are those generally associated with severe septicæmia. Thus, there is marked fatty degeneration of the heart muscle, whilst the spleen and liver are enlarged and show necrotic patches, which are due either to infarction or to local concentration of spirillar toxins. Hæmorrhages are not infrequent, especially in the kidneys.

"Some degree of bronchitis is constant. The bone marrow shows necrotic patches, which are apparently due to infarction."

Again, referring to Asian relapsing fever, he says:

"The very careful description of post-mortem examinations in VANDYKE CARTER'S monograph serves only to leave the impression that there are no lesions characteristic of the disease. If the tissues are stained by those methods usually chosen for revealing bacteria or protozoa, the spirilla are demonstrated with difficulty. They are seen to occupy the blood vessels and the tissues in the neighbourhood of hæmorrhages. From this I believed that the spirillum was a true blood parasite and lived only in the circulating blood. More recently, by using Levaditi's silver impregnation method, this view has been modified. The spirilla were seen to be scattered throughout the liver, and not confined to the blood-vessels, though it is true no special relation to the tissue cells could be demonstrated."

Since 1908 the more important observations have been made in relation to fatal cases of the meningeal type (*e.g.*, BABES), but I have not come across any very detailed account of the histology, though BABES notes atrophic cirrhosis of the liver.

The case which provided the material for this paper was that of an Arab cooly who died in the Isolation Hospital, Bagdad, on the 15th May, 1919, and the following are the clinical notes extracted from the hospital register.

Admitted 15th May, 1919, from I.G.H., with a note of illness lasting four days, enlarged spleen and spirilla in blood. Aged, poorly nourished, debilitated, expression dull and lethargic. Semi-conscious, drooping of eyelids, marked jaundice. Sub-conjunctival hæmorrhage in right eye and injection of left. Tongue coated white and dry. Rash petechial, purple character on abdomen, chest, arms and thighs. No abdominal distension. Abdominal reflex present. Marked retraction of abdomen. Knee jerks absent. Heart beats soft, distant but regular. Pulse good volume, strong and regular. Lungs, left base dull, moist crepitations, V.F. and V.R. increased. At 9.30 p.m. patient collapsed suddenly after vomiting up some milk. The heart did not respond to treatment and he died at 10.20 p.m. on the day of his admission.

In view of the subsequent findings, it is rather important to ascertain the duration of the illness, but this is not possible. It can be stated, however, that death occurred after at least five days' illness.

The autopsy was performed next morning, twelve hours after death, and the following brief notes were made at the time:—

On removing the skull cap the meningeal vessels were found to be engorged with blood, and the pacchionian bodies were more prominent and more adherent than normal. The surface of the brain was very congested, and the subarachnoid spaces in the sulci were filled with extravasated blood. This was most marked on the vertex, on the occipital lobe and on the mesial aspect of the hemispheres. The ventricles contained blood-stained fluid, and the choroid plexus was congested. The vessels of the internal capsule were engorged. The spleen was very large and dark in colour, but not particularly friable. The liver was very large and fatty in appearance. The kidneys were enlarged.

The following specimens were removed for detailed examination, heart's blood and portions of brain, spleen, liver, kidney and bone marrow.

#### EXAMINATION FOR SPIROCHÆTES.

No spirochætes could be found in the heart's blood though they were reported present in the blood on the morning of death. Indeed, microscopic examination of smears and sections failed to reveal them, except in the case of the brain, when they were found in

smears of the surface of the brain and in sections lying in the superficial layer of the cortex.

#### EXAMINATION OF THE BRAIN.

The appearances may be summarised thus :—

1. Great engorgement of the meningeal vessels, and, to a less extent, of the vessels passing into the cortex.
2. Extravasation of red cells into the perivascular spaces of the pia-arachnoid with a few round cells and polynuclears.
3. Hæmorrhages on the surface of the cortex immediately under the pia mater.
4. Small areas of round cell infiltration in the same situation as in 3.
5. Proliferation of large mononuclear (endothelial) cells, particularly in the perivascular spaces round the meningeal vessels.
6. A great deal of pigment.
7. A few spirochætes, as detailed above.

The pigment was of two kinds, (a) a golden brown pigment in needles or rhomboids, and (b) an amorphous brown pigment. Both kinds were found lying free or phagocytised by large endothelial cells. A large amount of the crystalline form was lying free in the vessels or attached to the endothelium, and in spaces containing extravasated blood. The amorphous form was for the most part inside large endothelial cells, or collected in large black masses in the perivascular connective tissue.

The extraordinary proliferation of the endothelial cells was the most striking histological feature. This was particularly marked in sections of the cerebellum, and in smears from the surface of the brain these cells showed up in large numbers. They were actively phagocytic, containing pigment, red cells and even polynuclears; some were absolutely gorged with red cells. Some were full of vacuoles, and the protoplasm stained irregularly an olive or greenish-blue tint with Romanowsky. A considerable number contained spirochætes.

As mentioned above, spirochætes were found only in the brain. In sections stained by Levaditi's methods, it was only in the superficial layer of the cortex that they could be found, and then in very scanty numbers. In smears from the surface of the brain a few were lying free, but more often were inside endothelial cells. Most of them stained faintly and irregularly (*cf.* stage of disease). An occasional one presented an appearance suggesting Leishman's "buds," but a large number, and those chiefly intracellular, had a granule or small spore-like body attached, which was usually terminal.

Polynuclear leucocytes attracted attention, for the reason that many of them contained small round or oval bodies, of very uniform size, which could not be stained by any of the methods employed—Romanowsky, Heidenhain or silver methods. They were probably digestive vacuoles, but they gave one a different impression, and the appearance of a cell containing a number of these uniformly sized bodies (or vacuoles) was unusual.

#### EXAMINATION OF THE LIVER.

The histological changes in the liver were striking, and may be enumerated as follows :—

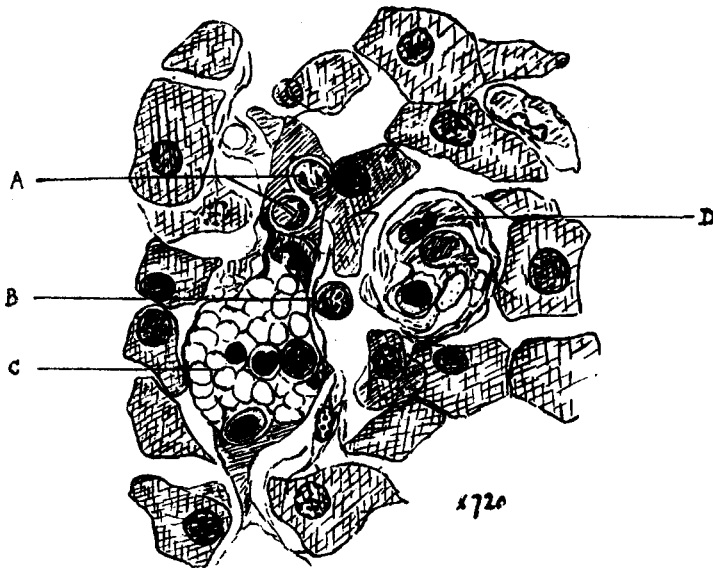
1. Great destruction of the liver cells, the periphery of the lobule being the least affected.
2. Infiltration of round cells into Glisson's capsule.
3. Engorgement of the intralobular capillaries.
4. Proliferation of large endothelial cells.
5. Deposition of a considerable amount of pigment.
6. The presence of numerous round or oval bodies, the nature of which I am unable to determine.

The destruction of liver cells is the most marked feature, and is most evident in the

centre of the lobule, the columns of liver cells being replaced or displaced by distended capillaries or blood spaces, in which large endothelial cells or Kupffer cells are prominent. This presumably is the condition noted by earlier workers (CARTER in India and PONFICK<sup>(9)</sup> in Europe), and described as a necrosis due to infarction or to the action of toxins.

The vacuolated appearance of the degenerating cells suggests fatty degeneration but I was unable to demonstrate it with osmic acid. On close examination one was led to wonder how much of the degeneration was primary and how much secondary to an endothelial proliferative reaction as the result of which the columns of liver cells are invaded and broken up. At the same time the gland cells show vacuolations, pigment inclusions, inclusions of other bodies of undetermined nature, fragmentation and nuclear degeneration.

The next thing that strikes one is the capillary engorgement and the prominence of large endothelial cells of Kupffer type. Under the low power, cross-sections of these dilated capillaries containing Kupffer cells are prominent, and remind one of "cell nests." With suitable staining the Kupffer cells are seen to contain a variety of inclusions, pigment, leucocytes, red blood cells and inclusions of undetermined nature.



CAMERA LUCIDA DRAWING OF A SECTION OF THE LIVER FROM A CASE OF RELAPSING FEVER, DEMONSTRATING—

- A—Cell inclusions of undetermined nature (?altered leucocytes in Kupffer's cell).
- B—Free "body" of undetermined nature.
- C—Distended capillary blood-vessel.
- D—Proliferation of endothelium—Kupffer's cell with inclusions.

The pigmentary deposit in the liver is considerable; it is dark brown to black, and arranged in granule clumps, or in circles or spheres with a clear centre, giving a "signet ring" appearance. It is found in the liver cells but for the most part lying free in spaces amongst cellular debris or phagocytied by endothelial cells.

The epithelium of the bile ducts was unaffected, though there was some round celled infiltration in the capsule.

Being of the opinion that the relapses of spirillar fever can best be explained by a cycle of development, and that the clue to this cycle is probably the granule, I studied this liver condition carefully, endeavouring to find some indication of a granule phase.

This idea occupied my mind to such an extent, that it was some time before I realised that certain bodies which I had passed over as altered leucocytes were in fact something quite distinctive, and unlike anything of a histological nature that I was acquainted with. A further examination revealed the fact that these bodies could be found inside the liver cells, chiefly towards the outer parts of the lobule where the liver cells had not undergone such extensive degeneration. In the more degenerated portions at the centre of the lobules these bodies were quite numerous. They are generally to be found lying free, or apparently so, in relation to degenerating gland cells, or in capillaries or inside Kupffer's cells. Their reaction to ordinary stains is feeble, but their structure can be fairly well picked out by Heidenhain's or Weigert's iron hæmatoxylin, or deep staining with Leishman's stain.

I was unable to determine the nature of these bodies and came to the conclusion that they could not be leucocytes or degenerating nuclei, and thereupon, perhaps somewhat hastily, sent a note to the *R.A.M.C. Journal*<sup>(10)</sup>, suggesting that they were protozoal bodies, possibly having some relation to the spirochæte, and waited expectantly for more post-mortem material.

However, I have not been able up to the present to extend this research, and recently returned to a careful reconsideration of the original material, with the result that my faith in the accuracy of my former deduction has been shaken. In this state of mind I showed specimens to Dr. WENYON and Dr. STEVENSON, whose criticisms, though kindly, did not help to dispel my doubts.

If these bodies are not of a specific nature, then they are probably a phase of degeneration of polynuclears, but there is to me something unique in the characters of the nuclei when well stained that I find difficult to attribute to degeneration.

It is obvious, therefore, that no useful purpose will be served by doing more at present than note the presence of these bodies, and I content myself with showing the specimens under the microscopes in the hope of obtaining further enlightenment from the members.

With regard to the spleen, the kidney and the bone marrow, I have nothing further to add to what is already known and described.

In the spleen the amount of pigment deposited is very great, the "signet ring" form being prominent; the presence of necrotic areas and of large phagocytic endothelial cells is noted.

I am afraid that these observations are not of a startling character, but they are perhaps sufficiently interesting as indicating two points in the pathology of relapsing fever which will repay further study, viz. :—

1. The reaction of the endothelial cells.
2. The histological changes in the liver.

The endothelial reaction is a feature of some protozoal infections—notably leishmaniasis—and we are tempted to cite it as a point in favour of the protozoal nature of spirochætes.

The changes in the liver may be simply the result of toxic action combined with a reaction of the endothelial elements, but in the presence of such marked histological changes one is led to hope for the key to the life history of the parasite.

Keeping this point in view, and in conclusion, let me quote VANDYKE CARTER'S summary of his observations on the condition of the liver in 74 post-mortems :—

"The minute structural changes which I have seen consist chiefly of cloudy swelling and pigmentary or fatty transformation of the gland cells. The extremely localised degeneration sometimes evident may be peculiar to this infection, and it would indicate stasis of circulation in the finer branches of the portal vein.

"As to the cause of morbid alterations, there is, earliest, enlargement of the liver with uniform or disseminated pallor, and friable consistence, all of which quickly supervene on the pyrexia, and are most pronounced in the first attack. At this time there is a general turgescence of the gland cells, probably general, and the interlobular connective tissue is only seldom implicated; fatty transformation of the cell substance is yet scarce.

"With cessation of pyrexia the turgid condition subsides, or it passes into a condition of fatty metamorphosis, which I have found to be commonly present in casualties at post-invasion periods, whether or not accompanied by cloudy swelling of the cells.

"Recurrence of pyrexia entails repetition of enlargement (though to less amount) and gland cell alterations. Finally, the organ tends to resume its normal dimensions, but traces of cell lesion may long persist."

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#### DISCUSSION.

The PRESIDENT: Colonel KENNEDY is to be congratulated on the very careful and complete record he has made of the pathological changes found in this one post-mortem examination, and I hope he will have opportunities of pursuing his investigations further, after the Fellows of this Society have had the opportunity of commenting on his work.

Dr. C. M. WENYON: As Colonel KENNEDY was kind enough to show me his preparations the other day—which I examined in consultation with Dr. STEVENSON—perhaps I may say a word about the bodies he had been directing attention to. Apparently the case of relapsing fever he has been talking about was a very severe one, so that the changes must not be regarded as the ordinary ones which occur in the disease.

With regard to the particular bodies which have been found in the endothelial cells, I cannot give a suggestion as to their nature. In the endothelial cells there occur polynuclear leucocytes, red-blood corpuscles and other things. We do not always recognise the extraordinary phagocytic power of the large endothelial cells in some acute infections. They are not limited to the blood-vessels. They break loose from the walls of the vessels and migrate through them, and wander about the extra-vascular tissues. They seem to be ravenous cells, ingesting anything which comes their way, whether polynuclear leucocytes, red-blood corpuscles, or bacteria. They have powerful digestive properties, and digest these cells. Some years ago I injected a mouse intraperitoneally with material containing leishmania, and the mouse developed an enormous peritoneal exudate. I withdrew some of the fluid from its abdominal cavity, and found a large number of these large endothelial cells, and they contained an extraordinary assemblage of structures in their cytoplasm. Some were lymphocytes, others were polynuclear cells, others were red cells, and some were structures of unexplained origin. Every kind of digestive process seemed to be going on in the vacuoles. So it is not strange we should come across bodies the nature of which we cannot explain.

What I think may give rise to structures like these within the cells is this: A large endothelial cell is a very large structure; it may be twenty microns in length and fifteen microns in thickness. In sectioning tissue, one may get slices of these big cells and of the bodies which are in them. Perhaps a polynuclear cell in the endothelial cell has the top of it cut off; its nucleus may or may not be included, or only a part of it. It would be