NOTES ON THE HISTO-PATHOLOGY OF TYPHUS FEVER.*

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(PLATES XII.-XIV.)

THANKS to the kindness of Captain F. E. Reynolds, R.A.M.C., now Professor of Pathology at the Kasr-el-Aini School of Medicine, Cairo, but formerly for a time o/c 28th Mobile Bacteriological Laboratory at Baku, we have had the opportunity of studying the tissues from five fatal cases of typhus fever occurring in the Caucasus. Of these, four were British soldiers and one an Indian soldier. Three of the former and the Indian case were diagnosed as uncomplicated. The complication in the remaining British case was stated to be hæmorrhagic pneumonia, but it is possible that this was directly due to the typhus infection.

Captain Reynolds kindly furnished full details of the gross pathology of the cases as determined by post-mortem examinations, which were performed from three to fifteen hours after death. We do not think that, for our purpose, it is necessary to reproduce his very careful and complete notes, and would content ourselves with saying that the microscopic appearances coincide closely with the naked-eye findings, save possibly as regards the extent of fatty change in some of the organs, which appeared less marked when studied under the microscope.

The tissues handed to us had been embedded in paraffin after fixation in Pick's fluid, *i.e.*, sod. salicylat., 10 grms.; sod. bicarb., 4 grms.; sod. chlorid., 2 grms.; formalin, 50 c.c.; water, 1000 c.c. Our object in undertaking their examination was to compare the histo-pathological changes with those which have already been described by numerous authors, mostly Continental and American, and to see if appearances resembling what have been regarded as Rickettsia bodies could be demonstrated.

It seems advisable in the first instance to give a brief and general résumé of the more important recent work which has already been accomplished on these subjects.

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HISTORICAL.

Recent research may, as indicated, be divided into (a) that dealing with histological changes, and (b) observations directed towards the occurrence of Rickettsia or similar bodies in the tissues.

(A) As regards (a) it should be noted that, prior to the War, Fraenkel's examination of the rash in typhus (1914⁷) had led to the discovery of the so-called "typhus nodule" affecting the endothelium and elastic layers of the walls of the skin capillaries. Further investigation by Fraenkel (1915⁸) himself and by many others has led them to believe that there is a localised necrosis of the walls of these small vessels, together with the formation of discrete nodules composed of cells of the adventitia, lymphocytes, and plasma cells.

It is now recognised that typhus is really a systemic disease of the smaller arteries and capillaries, and that the vessel changes are not limited to the skin. They occur in all the viscera, as has been demonstrated by such workers as Aschoff (1915²), Jaffé (1918¹¹), Jarisch (1918¹²), Bauer (1916³), Herzog (1918¹⁰), Ccelen (1916⁴), Kuczynski (1918-20¹³), Otto and Dietrich (1917²¹), Nicol (1919¹⁵), Doerr and Kirschner (1919⁵), Grzywo-Dabrowski (1918⁹), Wolbach and Todd (1920²⁷), and others. It would seem that the vessels of the brain and upper part of the spinal cord are specially liable to be affected.

This arteriolitis, with resulting irritation, stenosis and thrombosis, explains in large measure the symptoms of the disease and throws light on the nature of the rash, the frequent occurrence of gangrene of the legs, and the nervous phenomena which are characteristic of typhus.

There are perivascular as well as vascular changes, and the former, like the latter, are localised and associated with an infiltration of leucocytes. The view that this nodule formation is constantly accompanied by necrosis of endothelial cells is not acknowledged by all observers.

Parodi (1919²²), for example, holds a somewhat different opinion and his conclusions are thus summarised in *Medical Science* for March, 1920 :—

(1) He does not think that the vascular changes observed in the brain are due to a primary lesion of the intima, and in particular to a primary circumscribed necrosis. He does not deny that the virus of typhus may cause changes of a necrobiotic type in the small vessels, but in his opinion they are not constant, and the perivascular changes appear to develop independently of necrobiotic lesions in the vessel walls. (2) He has not hitherto found lesions of a hæmorrhagic type in the brain as described by Jarisch. (3) He has not observed any lesions of proliferative endovasculitis as described by Bauer. (4) Polymorphonuclear leucocytes may take part in the formation of inflammatory foci and are often observed in small numbers in the neighbourhood of an area of encephalitis associated with necrobiotic changes in the corresponding capillaries.

Again, Wolbach and Todd, after pointing out that the cutaneous lesions of Mexican typhus are similar to those described in Europe, state that the condition consists essentially in a proliferative reaction of the vascular endothelium, quickly followed by an infiltration of polymorphs into the endothelial lining of the vessels. The small vessels (precapillary arterioles of Fraenkel) and the capillaries are completely occluded by the cells, and the larger vessels in their

turn become blocked by fibrinous and cellular thrombi. They speak of a perivascular infiltration of mononuclears, which they believe to be of endothelial origin, and which in the later stages of the disease is very marked. Mononuclear cells with feebly stained cytoplasm are present together with polymorphs. Nowhere, however, do Wolbach and Todd mention the occurrence of actual necrosis of the endothelial cells.

It is interesting to note that some of the authors already cited have observed the presence of these vascular lesions in a certain proportion of infected guinea-pigs. They do not seem to occur in rabbits infected with the virus of typhus.

Apart from the nodules, other histo-pathological changes have been noted, for example, the diffuse inflammation of the brain substance and meninges with perivascular cell accumulations described by Grzywo-Dabrowski, who also mentions the occurrence of cerebral hæmorrhages and proliferation of the neuroglia cells. The same observer records a phagocytosis of red cells in the spleen and the presence of much pigment in the splenic cells. The heart, liver, and kidney are said to exhibit infiltration of lymphocytes and plasma cells and a proliferation of the adventitia cells of vessels. Cardiac hyperæmia is frequently seen and renal hæmorrhages are common. Grzywo-Dabrowski has noticed in the testes, spinal cord, corpora cavernosa, and sometimes in the kidneys, a perivascular aggregation of cells like that seen in brain sections. He has also observed small yellowish thickenings on the lining of the aorta due to proliferation of the cells of the intima.

Possibly the most detailed account of the subject is that by Herzog, and it seems advisable to quote from his paper the findings he and others have encountered in the internal organs.

Brain.—There is proliferation of the glia cells, especially those in the inflammatory foci. The cells when free from the glia network cannot readily be distinguished from other wandering cells. Accumulation of the nuclei of glia cells occurs in the later stages, chiefly close to the small vessels. Typical corpora amylacea are encountered, many partly destroyed but now and then occurring in circumscribed masses, chiefly in the sub-ependymal areas. Occasionally large sausage-like forms are present.

In such areas the nerve fibrils appear to be thinned out, thus presenting a broken appearance; the glia network is loosened and amongst it migrating cells with long nuclei are seen. Not infrequently these cells are filled with sudanophil granular material. Here and there the blood-vessels are sheathed by granular cells. The macrophages in the area of the ganglion cells are frequently enlarged, and the ganglion cells themselves show necrotic changes, a sieve-like vacuolation being not infrequently observed.

The vessel changes are equally well seen in the white matter. In particular there is as a rule marked cellular infiltration, consisting of large pigmented elements, plasma cells, small basophilic lymphocytes, large uninucleated phagocytes containing red cells and small lymphoid cells.

Heart.—In all cases there are marked changes. As in the brain, so also in the myocardium, the vessel changes, *i.e.*, necrosis and thrombosis, are seen together with cell accumulations which, in cases dying late, are numerous and bulky and occur spread diffusely between the muscle fibres. Scattered foci of cell development are sometimes seen, the lymphocyte elements preponderating and numerous mitoses being present.

Cell accumulations similar to those seen in the brain and consisting chiefly of plasma cells, lymphoblastic forms and non-basophilic lymphocytes occur, principally along the vessels. The cell proliferations are in great part accompanied by a multiplication of the capillaries and endothelial cells.

Other cell forms seen are of the megalokaryocyte type with clear, irregular nuclei and basophilic forms resembling plasma cells. Mast cells are often

demonstrable in the inflammatory infiltration. As a rule a considerable fragmentation of the cardiac muscle is present.

The inflammatory changes in the heart are chiefly localised in the papillary muscles.

The changes in the myocardium doubtless account in large measure for the severe cardiac weakness, which has been wrongly attributed to the effects of the cerebral state. Clinically the condition suggests what is met with in diphtheria.

Aorta.—Three cases were examined. Newly formed vessels are seen in the adventitia and, in cases dying on the thirteenth and fourteenth day, in the media. These vessels are like those found in syphilitic aortitis. An inflammatory cell proliferation containing basophilic and non-basophilic cells is also present. Here and there clumps of mitotic lymphocytes are observed in the intima just under the endothelial coat. Similar conditions were seen in the adventitia and intima of the coronary arteries in a 16-day case.

Kidneys.—Here again are found the usual lymphocytic proliferations either in small circumscribed foci or more widespread and accompanied by infiltrating plasma cells, which frequently exhibit mitosis. The cell proliferations also occur at the junction of the small vessels of the cortex, with a predilection for the hilus of the glomerulus. They also extend along the interlobular arteries and veins, chiefly in the limiting layer along the *vasa recta* and near the apex of the papilla. Parenchymatous changes lead to the presence of granular and hyaline casts and occasionally of areas of circumscribed epithelial necrosis.

Suprarenals.—Similar inflammatory changes and accumulations of plasma cells occur.

Alimentary Canal.—Cell proliferations resembling those above described are now and then seen in the stomach and intestine, being present in the mucosa, submucosa, muscular and serous layers. They are also encountered in the *thyroid, pancreas, and testicle.*

Lungs.—The most characteristic finding is the presence of lymphoblastic elements, plasma cells and small lymphocytes in the alveolar septa, along the line of the vessels in the walls of the bronchi and in the alveolar spaces. Megalokaryocyte forms are also in evidence. The alveolar epithelium is much swollen and contains many multi-nucleated bodies. Pus corpuscles are found in the alveoli.

The lung picture indeed suggests the type of pneumonia seen in measles, and it is difficult to distinguish changes due to typhus from those produced by a secondary lobar pneumonia.

Liver.—In the early stage small foci of proliferating endothelial cells can be demonstrated in the region of the intra-acinous blood capillaries. In many places thrombotic masses, nuclear *débris* and leucocytes with lobular nuclei are interposed between them. Older foci may preponderate, composed of small, non-basophilic, lymphoid cells with long or round nuclei. Occasionally the cell foci are extensive, extending over several zones of liver cells which themselves may present a necrotic aspect. Degenerated hepatic cells are not uncommon. Here and there the liver cells may contain mitotic figures.

Changes are seen in the endothelial cells of the intra-acinous blood capillaries. They are markedly swollen and may contain red blood cells and small lymphoid elements. Their nuclei are often disintegrated and mitotic division may be present, especially in the earlier stages.

The lymphogenic changes seen in other organs are occasionally found both in the capillaries of the acini and between the liver cell zone and the capillary walls. Round-celled infiltrations of plasma, lymphoblastic and lymphoid cells into the

periportal connective tissue are frequently seen, together with proliferation of the endothelial cells of the vessels.

Spleen.—The changes here are of special interest. The splenomegaly is due to cell proliferations localised essentially in the pulp. This leads to a compression of the splenic sinuses. In the earlier stages cell proliferations occur in the splenic trabeculae. These consist chiefly of small, non-basophilic lymphoid cells, lymphoblasts and plasma cells, which in the main are attached to the small blood vessels, arterics, and capillaries, and are occasionally associated with endothelial cell proliferation. In the earlier cases the above-mentioned lymphoblastic forms are numerous and often show mitosis. Together with plasma cells they are widely distributed in the pulp, often forming small accumulations. In cases dying from the thirteenth to the nineteenth day these accumulations are so marked that the splenomegaly can with justice be attributed to their presence.

Between these lymphocytic accumulations examination even under a low power will show cell foci round the small arteries and capillaries consisting of smaller, non-basophilic lymphoid elements with some basophilic forms.

Leucocytes with lobed nuclei are also present. Here and there necrotic areas and small hæmorrhages are in evidence. Phagocytes containing red cells and at times cells full of pigment are found deeper in the pulp. The outline of the follicles, as a rule, persists, but their tissue also undergoes the usual cell invasions.

Lymph Glands.—Here the conditions closely resemble those found in the spleen. The lymph sinuses, however, are usually very distended, exhibit a swollen endothelium and contain red cells, leucocytes, phagocytes, small lymphocytes, large lymphoblasts, often showing mitotic figures and plasma cells.

Bone-Marrow.—New cell formation marked.

Muscles.—Areas of inflammatory change are noticeable, particularly in the diaphragm.

SUMMARY.—The changes are of an inflammatory nature and three distinct reactions can be recognised—vascular, lymphogenic, histiogenic.

Vascular—acute inflammation—local injury of vessel wall with hyperæmia, exudation, and emigration of leucocytes—is only of slight extent and short duration.

Lymphogenic.—Accompanying this are reactive tissue processes which in fatal cases are chiefly seen in the internal organs. These consist particularly in the production of uni-nucleated migratory cells, which traverse the primary vessel foci, and in the specially rich development of basophile lymphocytes in the production of which the very numerous mitoses of the lymphoblastic elements are concerned. With the absorption and organisation of the foci this reaction disappears.

Histiogenic.—Prominence is accorded to the vessel changes and those in the blood-forming organs, notably the spleen and lymph glands, especially as regards the presence of lymphoblasts and plasma cells.

The post-mortem examination and the histological changes in the organs are sufficient to establish a diagnosis of typhus, the characteristic appearances being best marked in the brain and notably in the region of the fourth ventricle. In some circumstances the examination of a *single* organ is not sufficient to enable a diagnosis to be made. There is a marked correlation of clinical symptoms and pathological findings, the stress of the disease falling on the brain and the heart. As regards the important vessel changes, the small pre-capillaries are chiefly affected in the internal organs, not those vessels with

definite middle coats. As the causative agent circulates in the blood, the veins may also sometimes be affected. The vessel changes usually proceed from within outwards and occasionally there is perivascular extension.

The histo-pathology of the disease has been studied by Nicolle and his co-workers (1910-20¹⁶⁻²⁰), Neill (1917¹⁴), and others in monkeys and guinea-pigs, but it is scarcely necessary to refer to their findings in this paper. We give the references for those who wish to pursue the matter further.

(B) Turning now to (b) we find several references to the presence of Rickettsia or Rickettsia-like bodies in the tissues of patients dead of typhus fever. It is important to obtain a clear conception of the appearance of the small coccal-like bodies which are regarded as true Rickettsia, for the accounts vary, and it is probable that different structures have been described under the generic name.

They are tiny cocco-bacilli varying in size from 0.3μ to 0.9μ . According to Arkwright, Bacot, and Duncan (1919¹), who have devoted special attention to them in lice, the usual measurements are 0.2 to 0.3μ in the shorter diameter and 0.3 to 0.5μ in length. They are thus distinctly smaller than *B. influenzae* or *M. melitensis* taken from young cultures. The bodies found by Ricketts and Wilder (1910²³), which Rocha-Lima (1916-19²⁴) regards as true Rickettsia, are approximately 2μ by 0.65μ .

Possibly slight discrepancies in the accounts regarding size may be due to differences in technique, but there seems undoubtedly to be considerable variation both in size and shape, for there is a gradation from short elliptical coccus-like bodies to definite rods. The latter frequently have a bipolar appearance or exhibit a beaded aspect, like cocci arranged in a chain within a feebly-staining envelope. The most successful staining method appears to be that with Giemsa, though Löffler's flagellar stain and carbol gentian violet are effective. Rickettsia do not retain the stain in Gram's method.

The presence of these curious bodies, which Rocha-Lima regards as *Strongyloplasmata* and classifies as *Chlamydozoa*, in the typhus nodules has been signalled by several observers, notably by Kuczynski, who found them occurring in groups in the Kupffer cells of the liver capillaries. His paper contains some remarkable but rather diagrammatic illustrations, and Jaffé states that he has been able to confirm Kuczynski's work, yet he is obviously a little doubtful regarding it.

No one else seems to have encountered such well-marked appearances, but Wolbach and Todd in their paper on typhus in Mexico describe and figure clumps of a tiny Rickettsia-like organism, for which they propose the name *Dermacentroxenus typhi*, and which is found in the vessel lesions.

Ficai (1920⁶) has found both in lice and in the tissues of patients dead of typhus certain round bodies, the nature of which he has not so far been able to determine. He describes them as occurring in the cytoplasm of large nerve-cells of the cerebral cortex, and elsewhere in the brain, and has met with them both outside and within the capillaries. They vary in size, the larger being 6 to 8μ in diameter, and containing what he terms secondary bodies. Occasionally also he encountered very large forms 12 to 15μ , which in his opinion resembled Negri bodies. It is clear that these findings bear no relation to Rickettsia. Their possible nature will be discussed in the consideration of the material which we have examined.

EXAMINATION OF TISSUES.

As stated, the tissues from five cases were available for examination:—

CASE I.—G. R., aged 38. Uncomplicated. Died eighth day of disease.

CASE II.—M. Z. (Indian), aged 35. Uncomplicated. Died eighth day of disease.

CASE III.—S. S., aged 36. Uncomplicated. Died twelfth day of disease.

CASE IV.—H. A., aged 33. Uncomplicated. Died fourteenth day of disease.

CASE V.—C. E., aged 36. Reported as complicated with pneumonia. Died sixteenth day of disease.

From all of them there were available cerebrum, cerebellum, aorta, lung, spleen, liver, pancreas, kidney, and suprarenal. In addition, from four there were trachea and cardiac muscle. From three, specimens of small and large intestine were forthcoming, from two there were lymphatic glands, and from one portions of stomach, duodenum, and skin. Sections of the tissue were cut and stained with Mayer's acid hæmalum and acid fuchsin or by Giemsa.

It seems advisable to consider the findings in each type of tissue, making reference, where necessary, to any special case, and dealing in the first instance solely with histological changes.

Cerebrum.

In Cases I., II., III., dying at an early date, the contents of the vessels show a peculiar appearance suggestive of the blood serum having coagulated next the walls, while leaving a central clear channel in which the red blood corpuscles are present (Plate XII., Figs. 1 and 2). Occasionally this condition, which is probably of a thrombotic nature, is limited to certain areas of the vessel wall, and in the masses wandering leucocytes can sometimes be found, occasionally in great numbers. When this is the case an appearance suggestive of the so-called typhus nodule is produced.

Another vascular change is the infiltration of the extra-muscular coats of the vessel wall. This varies from a few scattered leucocytes, mononuclear in type, in the adventitia to a continuous single layer either partially or completely surrounding the vessel (Plate XII., Fig. 3). This annular arrangement of the leucocytes was best seen in Cases II. and IV., but as it is very local in its occurrence it is possible it was present in other portions of the brain than those cut in the remaining cases.

Pigment occurred in the walls of the vessels (Plate XII., Figs. 1 and 2) in the majority of cases, and was also seen in the nerve cells in Case I. This pigment is yellowish when unstained and stained with hæmalum, but becomes a bright greenish-blue with Giemsa. The granules vary in size from $0.5\ \mu$ to $6\ \mu$.

The changes in the nervous elements are not very striking. A few of the ganglion cells tend to be vacuolated, and sometimes in these cells the nuclei show signs of degeneration. In Cases III. and V. there are small areas of softening with infiltration of leucocytes into the necrotic areas.

Cerebellum.

In this part of the brain the changes are slight and observed only in Cases I., IV., V., and then only in the vessels of the pia mater between the laminae, where there was some infiltration of the vessel walls.

Aorta.

No typical changes are observed, unless an apparent loosening of the tissue layer between the intima and the media can be so described. This is noted in Cases I., III., IV. In III. and IV. there is some calcification of the media, and in II. and IV. there was atheroma, very marked in the latter case.

Heart.

In all the cases there is excess of yellow pigment around the nuclei of the muscle cells, and in Cases I., II., IV., infiltration of leucocytes amongst the bundle fibres and round the vessels. This latter is most marked in Case II., where a few megalokaryocytes are also seen. In this case also one vessel was found almost occluded by a mass of cells apparently of endothelial origin. Case IV. shows a peculiar fragmented appearance of the red cells.

Lung.

In all cases there is evidence of a broncho-pneumonia, though it is variable in degree. It is most marked in Cases II., III., and least so in Case I., where the patches are smaller but characterised by hæmorrhages into the alveoli and the presence of numerous free pigmented endothelial cells in the same situation. In the other four cases hæmorrhages occur more generally, and are also present in the sub-mucous coat of the small bronchi. In these, too, the exudate into the alveoli is fibrinous in some places, and in others consists of a mass of polymorphonuclears, many of which show phagocytosis of organisms. Amongst these a few megalokaryocytes and other cells can be found. These masses of polymorphonuclears are also found in the small bronchi. The organisms are mainly of two types: (a) a Gram-staining organism resembling pneumococcus, and (b) a much smaller Gram-negative diplococcus in small clumps. In Case II. some of the vessels show masses of cells attached to their inner walls resembling the "typhus nodule," with some degeneration of the vascular walls, mostly in the sub-endothelial and muscular layers.

Trachea.

All that need be noted is the presence of congestion and submucous hæmorrhages, the former being present in all four cases examined, the latter only in Case II., which also shows some general round-celled infiltration of the submucous tissue.

Spleen.

The vascular changes are better marked than in any other organ except the brain and the lungs. They consist chiefly of a sub-endothelial infiltration of highly granular cells staining readily with acid dyes (Plate XII., Figs. 4 and 5). In addition, accumulations of cells of a similar type are found in the lumen of the vessels, practically occluding them. There are also swelling and degeneration of the muscular coats. These changes were best seen in Cases III. and IV. The cells of the spleen pulp show marked phagocytosis of blood elements. In Case II. the pulp contained many small bodies resembling blood platelets, both free and in the phagocytes. The amount of engorgement of the spleen varied greatly, Case IV. showing very little blood, while in Case V. there was much engorgement. The amount of pigment in the splenic cells was fairly large, but in Case II. much of it was malarial in character.

Liver.

Infiltration of leucocytes into the portal canals, swelling up of and much phagocytosis (both of red blood corpuscles and other elements) by the endothelial cells (Plate XIII., Fig. 7) are the most constant changes observed. Degenerated areas associated with hæmorrhage into them are seen in Case II., while in Case III. there is a suppurative condition, the pus apparently tracking along the portal canals. The pus and many of the leucocytes surrounding the suppurative areas contain acicular crystals. Fatty degeneration was only seen to a very limited extent, and only in small areas. It is mainly sub-capsular. Generally scattered through the section individual liver cells are seen to be degenerate, the condition rather resembling the hyaline and acidophilic appearance met with in cases of yellow fever. Case IV. showed this well. No marked vascular changes.

Pancreas.

A certain amount of cellular degeneration is present in all cases, but it is difficult to say how much is due to post-mortem change. In Case V. some single cells show a degeneration closely resembling that in the liver, the cells looking hyaline and being acidophilic.

Suprarenals.

In all cases the appearance is normal. There is no noticeable cell infiltration or loss of lipoid substance.

Kidney.

Case I. stands out from the others, as it was the only one showing marked changes. These consist of hæmorrhages into the tubules, the presence there of casts of various sorts, and some areas of small cell infiltration between the tubules. In Cases I. and III. there is also a considerable amount of brownish pigment in the cells of the straight tubules. The other three cases appear normal.

Lymphatic Glands.

Unfortunately we do not know from what areas in Cases II. and III. these glands came. In both glands the spaces of the areolar network seem larger than usual, and there is a marked deficiency of lymphocytes. There is some leucocytic infiltration of the vessel wall in both cases, and this is very marked in one vessel in Case III., where a mass of acidophilic cells with drawn-out nuclei can be seen between the endothelium and the other coats (Plate XIII., Fig. 6). In Case II. a vessel contains masses of bodies resembling blood platelets.

Intestinal Tract.

All the tissues show signs of post-mortem change in varying degree, so we disregard the appearances that may be due to this cause. Tissue from the stomach was available only from Case I., and this showed great engorgement of the vessels in certain spots, with small hæmorrhages into the mucosa and a small superficial ulcer. In the small intestine, Cases II., IV., V., there was patchy vascular engorgement in II. and V., while nothing was observed in IV. Specimens of large intestine were obtained from Cases II., III., V. Case II. shows much hæmorrhage into the inter-glandular tissue. Case III. shows a well-marked ulcer involving the muscular coat and with overhanging edges. Many of the endothelial cells of the lymph spaces around the ulcer contain crystals similar to those seen in the liver of the same case. Case V. merely showed much congestion of the vessels.

Skin.

Presence of irregularly distributed pigment is noted in the deep layers of the epidermis (result of freckling?). A certain amount of perivascular leucocytic infiltration is present, and there are a few small hæmorrhages. The condition of the specimen prevented a satisfactory study of the condition of the vessels.

DISCUSSION.

If we now draw a comparison between our results on this small number of cases and those recorded by other observers, and more especially by Herzog, it is apparent that, so far as the brain is concerned, there is a general agreement. Little attention, however, has hitherto been directed to *the single layer of mononuclear cells which we have found in most cases surrounding the vessels*, this appearance being limited to certain areas. It is very striking, and almost resembles a layer of cubical epithelium (Plate XII., Fig. 3). In a case from a different locality, and fixed in a different manner, it was even better marked than in the present series. It appears to be a fairly late phenomenon, and is probably identical with Herzog's sheathing layer of granular cells. The cerebral changes are said to be best seen in the floor of the fourth ventricle, and unfortunately tissue from this region was not available. We do not consider the presence of the pigment granules in the vessels of much import as we have observed a similar condition in several cases of cerebral malaria, and in one case of death by accident in this country. It is possible, however, that in the typhus cases the pigment is in greater quantity. It is also possible that these deposits of pigment are identical with the peculiar bodies described by Ficaï, as they apparently stain in a similar manner and appear to correspond in dimensions.

In the case of the *aorta* we found none of the cellular proliferation described by Herzog.

The *cardiac* changes noted by us closely correspond to those previously recorded, save that we were unable to demonstrate any marked degeneration of muscle fibres. This, however, may be due to the fact that the papillary muscles, in which such changes are said to be most evident, were not available for examination.

The *lung* condition in every case suggested pneumonic processes and closely resembled what Herzog and other authors have described.

It is very doubtful if Case V., which was recorded as complicated by pneumonia, really suffered from a pneumonic condition separate and distinct from that induced by the typhus infection, as, apart from the question of severity, there appeared to be no difference between the lung state in this case and that in the other four cases.

As regards the *spleen* we confess we were unable to study the changes so closely as Herzog has done. Nor does it seem altogether necessary, for the German author enters into very minute details concerning the type of cells; these do not throw much light on the pathological condition, while Herzog does not lay much stress on the important vascular changes which were the chief feature in most of our cases.

Apart from the fact that in our cases the described small-celled infiltration into and between the lobules was not much in evidence,

the *liver* changes were practically identical with those previously recorded.

In the *pancreas* we did not see the cell proliferations which have been described.

Where *renal* changes were noted at all they conformed to the type recorded by Herzog. The presence of casts was very noticeable, and in one case hæmorrhages into the tubules were observed. In this connection it is interesting to note that Aschoff, Schminke (1916²⁵), and Herzog have recorded the presence of hæmoglobin casts. The last named found them in one case only.

The appearances of the *lymphatic glands* in our cases do not coincide with those recorded by Herzog. Indeed, instead of a cellular increase, the cells, or at least the lymphocytes, appeared to be diminished in number (Plate XIII., Fig. 6).

In no instance have we in any organ observed in the masses of small cell infiltration the mitotic divisions to which Herzog so frequently refers, nor do we believe that there is any primary necrosis in the endothelium of the precapillaries. Such degeneration as occurs appears to us to be a late phenomenon and to start under the endothelium.

Turning now to the question of the demonstration of Rickettsia or Rickettsia-like bodies, we think it is unnecessary to consider each case in detail, and will content ourselves with a short general account of the appearances noted in certain organs.

In various tissues we have found small diplococcal forms measuring about $1\ \mu$ in length, each moiety of the diplococcus being spherical and under $0.5\ \mu$ in diameter. Bodies of this size and appearance stain both with basic and acid dyes.

Brain.—In the vacuolated, multipolar nerve cells of the cerebrum these diplococcal forms occur. In this situation, if the specimen be stained with Giemsa, the bodies assume a very dark blue colour, while, if with hæmalum and acid fuchsin, bodies morphologically the same are found stained bright red (Plate XIII., Figs. 9, 10, 11, 12). In the walls of some of the precapillaries and larger vessels in Giemsa-stained sections small blue-staining granules, occasionally diplococcal in form, can be demonstrated.

Lung.—Many of the polymorphs of the alveolar and bronchial exudation contain masses of organisms, some obviously pneumococci, but others of a size and appearance suggesting the Rickettsia type.

In the walls of the larger vessels of the lung, usually in the endothelial cells or in the sub-endothelial layer, there are masses of diplococcal granules staining dark blue with Giemsa, the whole picture closely resembling the appearance depicted by Wolbach in Plates XI. and XIX. of his paper on the *Dermacentrozenus rickettsi*, which he regards as the causative organism of Rocky Mountain spotted fever (Plate XIV., Fig. 13).

Spleen.—In the phagocytic cells of the pulp small groups of granules staining deep red with Giemsa occur. These masses bear a great similarity to blood platelets. In some of the vessels there are clumps of bluish-staining granules corresponding to the granule groups figured by Wolbach and Todd in their paper on Mexican typhus (Plate XIV., Fig. 14).

Liver.—The liver cells show in many instances isolated or grouped granules lying in small vacuoles. These stain bright red both with Giemsa and with acid fuchsin (Plate XIII., Fig. 8). In the Kupffer cells the platelet-like bodies seen in the spleen have been demonstrated (Plate XIII., Fig. 7).

Pancreas.—Granules similar to those seen in the liver cells occur in the pancreatic cells.

Kidney.—A few similar granules have been seen.

Small Intestine.—The above type of granule has also been found in the epithelium of the glands.

There can be little doubt that the greater number of these granules is of a secretory nature, especially those found in the parenchymatous cells of the secreting organs. They are, however, much smaller than the easily recognised secretion granules of the pancreatic cells.

The only granules which can be considered as possibly Rickettsia are those seen in the nerve cells of the cerebrum, the vessels of the brain and lung, the cells and vessels of the splenic pulp and the Kupffer cells of the liver. So far as the brain is concerned a complication arises, owing to the presence both in the nerve cells and the vessel walls of the pigment to which reference has been made, and which, as it stains dark blue to greenish blue with Giemsa, and is often in the form of tiny granules, is difficult to distinguish from any micro-organism which may be present (Plate XII., Figs. 1 and 2).

We are unable to differentiate the bodies found in the lung from the appearances regarded as Rickettsia. Although we have never found in the Kupffer cells of the liver the large aggregations of Rickettsia bodies described by Kuczynski, it is possible that the platelet-like bodies above mentioned are really of this nature. Here, as also in the spleen, they stain with Giemsa in the same way as do the Rickettsia of Kuczynski, taking on a red colour. Hence they present a contrast to the bodies found in the brain and lung. Too much stress, however, must not be laid on the mere colour reaction, as there can be little doubt that in section-staining the results given by the Giemsa stain are variable, even when to all appearance the same technique has been employed.

Mention may also be made of some granules of diplococcal form seen in the cell masses projecting into the lumina of the splenic vessels. These granules (Plate XII., Fig. 5), which conform to the usual size of Rickettsia bodies, stain quite definitely with hæmalum, but cannot be definitely recognised in sections of the same tissue stained by Giemsa.

Their position is suggestive but we cannot form any opinion regarding their true nature.

We do not think the time has yet come to draw any definite conclusions on the latter part of this typhus work, despite the recent advances which have been made in our knowledge of Rickettsia. A study of the literature and of specimens we have seen at various times induces us to keep an open mind on the question. So many different species of Rickettsia have been found that, despite Kuczynski's statement as regards their successful cultivation, we confess to having doubt as to their exact nature, let alone their pathological significance. This may be considered a somewhat heretical utterance at the present moment when Rickettsia are so much to the fore, but it would appear advisable to adopt an Asquithian attitude until further investigations have thrown more light on what is undoubtedly a difficult question.

REFERENCES.

1. ARKWRIGHT, J. A., BACOT, A., AND DUNCAN, F. M. "The Minute Bodies (Rickettsia) found in Association with Trench Fever, Typhus Fever, and Rocky Mountain Spotted Fever," *Trans. Soc. Trop. Med. and Hyg.*, 1919, vol. xii. p. 61.
2. ASCHOFF, L. "Ueber anatomische Befunde bei Fleckfieber," *Med. Klinik*, 1915, Jahrg. xi. S. 798.
3. BAUER, E. "Zur Anatomie und Histologie des Flecktyphus," *München. med. Wchnschr.*, 1916, Jahrg. lxiii. S. 541.
4. CELEN "Histologische Befunde bei Fleckfieber," *Berl. klin. Wchnschr.*, 1916, Jahrg. liii. S. 530.
5. DOERR, R., AND KIRSCHNER, L. "Beitrag zur Diagnose der Fleckfieberinfektion beim Meerschweinchen," *Med. Klinik*, 1919, Jahrg. xv. S. 894.
6. FICAI, G. "Reperto di speciali corpuscoli nel tifo esantematico," *Il Policlinico*, 1920, vol. xxvii. p. 133.
7. FRAENKEL, E. "Ueber Fleckfieber und Roseola," *München. med. Wchnschr.*, 1914, Jahrg. lxi. S. 57.
8. " " " " "Zur Fleckfieberdiagnose," *München. med. Wchnschr.*, 1915, Jahrg. lxii. S. 805.
9. GRZYWO-DABROWSKI, W. . "Untersuchungen über die pathologische Anatomie des Fleckfiebers," *Virchow's Arch.*, 1918, Bd. ccxxv. S. 299. (Ref. in *Medical Supplement, Daily Review of the Foreign Press*, 1919, vol. ii. p. 123.)
10. HERZOG, G. "Zur Pathologie des Fleckfiebers," *Centralbl. f. allg. Path. u. path. Anat.*, Jena, 1918, Bd. xxix. S. 97.
11. JAFFÉ, R. (1) "Zur pathologischen Anatomie des Fleckfiebers. I. Die makroskopische Diagnosestellung," *Med. Klinik*, 1918, Jahrg. xiv. S. 210.

11. JAFFÉ, R.—*continued* . (2) II. "Mikroskopische Untersuchungen mit besonderer Berücksichtigung der Frage der Diagnosestellung," *Ibid.*, S. 540.
(3) III. "Mikroskopische Untersuchungen mit besonderer Berücksichtigung ganz frischer und ganz alter Fälle," *Ibid.*, S. 564.
(4) IV. "Zur Pathogenese des Fleckfieberknötchens," *Ibid.*, S. 1209.
12. JARISCH, A. "Zur Kenntnis der Gehirnveränderungen bei Fleckfieber," *Deutsches Arch. f. klin. Med.*, Leipzig, 1918, Bd. cxxvi. S. 270.
13. KUCZYNSKI, M. H. . . . (1) "Ueber histologisch-bakteriologische Befunde beim Fleckfieber," *Centralbl. f. allg. Path. u. path. Anat.*, Jena, 1918, Bd. xxix. S. 279.
(2) Die Kultur der Rickettsia Prowazeki aus dem fleckfieberkranken Meerschweinchen," *Med. Klinik*, 1920, Jahrg. xvi. SS. 706, 733, and 759. (Cited in *International Journal of Public Health*, 1920, vol. i. p. 357.)
14. NEILL, M. H. "Experimental Typhus Fever in Guinea-Pigs. A Description of a Scrotal Lesion in Guinea-Pigs infected with Mexican Typhus," *U.S. Public Health Reports*, 1917, vol. xxxii. p. 1105.
15. NICOL, KURT "Pathologisch-anatomische Studien bei Fleckfieber," *Beiträge zur path. Anat. u. z. allg. Path.* 1919, Bd. lxxv. S. 120.
16. NICOLLE, CH. "État de nos connaissances expérimentales sur le typhus exanthématique. (Exposé des méthodes suivies et des problèmes qui restent à résoudre)," *Bull. de l'Inst. Pasteur*, 1920 tome xviii. pp. 1 and 49.
17. NICOLLE, CH., AND BLAIZOT, L. (1) "Nouvelles recherches sur le typhus exanthématique. (Conservation et siège du virus. Typhus du lapin, etc.)," *Compt. rend. Acad. d. Sc.*, Paris, 1915, tome clxi. p. 646.
(2) "Recherches expérimentales sur le typhus exanthématique pratiquées à l'Institut Pasteur de Tunis pendant l'année 1915," *Arch. de l'Inst. Pasteur de Tunis*, 1916, tome ix. p. 127.
18. NICOLLE, CH., BLANC, G., AND CONSEIL, E. "Quelques points de l'étude expérimentale du typhus exanthématique," *Compt. rend. Acad. d. Sc.*, Paris, 1914, tome clx. p. 661.
19. NICOLLE, CH., AND CONSEIL, E. (1) "Données expérimentales nouvelles sur le typhus exanthématique," *Ibid.*, 1910, tome cli. p. 454.
(2) "Propriétés du sérum des malades convalescents et des animaux guéris de typhus exanthématique," *Ibid.* p. 598.
20. NICOLLE, CH., AND LE-BAILLY, C. "Les infections expérimentales inapparentes. Exemples tirés de l'étude du typhus exanthématique," *Arch. de l'Inst. Pasteur de Tunis*, 1919, tome xi. p. 1.

21. OTTO, R., AND DIETRICH . "Beiträge zur 'Rickettsien'-Frage," *Deutsche Med. Wchnschr.*, Leipzig, 1917, Bd. xliii. S. 577.
22. PARODI, U. "Note istologiche sulle alterazioni encephaliche nel tifo esantematico," *Pathologica*, 1919, vol. xi. p. 377.
23. RICKETTS, H. T., AND (1) "The Typhus Fever of Mexico (Tabardillo). Preliminary Observations," *Journ. Amer. Med. Assocn.*, 1910, vol. liv. p. 463.
WILDER, R. M. (2) "The Transmission of the Typhus Fever of Mexico (Tabardillo) by Means of the Louse (*Pediculus vestimenti*)," *Ibid.*, p. 1304.
(3) "The Etiology of the Typhus Fever (Tabardillo) of Mexico City. A further Preliminary Report," *Ibid.*, p. 1373.
24. ROCHA-LIMA, H. DA . . (1) "Zur Aetiologie des Fleckfiebers," *Deutsche med. Wchnschr.*, Leipzig, 1916, Jahrg. xlii. S. 1353.
(2) "Untersuchungen über Fleckfieber," *München. med. Wchnschr.*, 1916, Jahrg. lxiii. S. 1381.
(3) "Beobachtungen bei Flecktyphusläusen," *Arch. f. Schiffs- und Tropenhyg.*, 1916, Bd. xx. S. 17.
(4) "Zur Aetiologie des Fleckfiebers," *Berl. klin. Wchnschr.*, 1916, Jahrg. liii. S. 567.
(5) "Zum Nachweis der *Rickettsia prowazeki* bei Fleckfieberkranken," *München. med. Wchnschr.*, 1917, Jahrg. lxiv. S. 33.
(6) "Die Uebertragung des Rückfallfiebers und des Fleckfiebers. Bemerkungen zur Rickettsiafrage," *Deutsche med. Wchnschr.*, Leipzig, 1919, Jahrg. xlv. S. 732.
25. SCHMINKE "Zur Aetiologie des Fleckfiebers. (Diskussionsbemerkungen; Tagung der Kriegspathologen, Berlin, April 26 and 27, 1916)," *Deutsche med. Wchnschr.*, Leipzig, 1916, Jahrg. xlii. S. 899.
26. WOLBACH, S. B. "Studies on Rocky Mountain Spotted Fever," *Journ. Med. Res.*, 1919, vol. xli. p. 1.
27. WOLBACH, S. B., AND TODD, "Note sur l'étiologie et l'anatomie pathologique du typhus exanthématique au Mexique," *Ann. de l'Inst. Pasteur*, Paris, 1920, tome xxxiv. p. 153.
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DESCRIPTION OF PLATES XII-XIV.

These figures are photographic reproductions of original water-colour drawings by A. C. S., outlines drawn by camera lucida at known magnifications.

- FIG. 1.—Small vessel in cerebrum showing some degeneration of wall, serous clot, and pigment in cells in wall. Stain Giemsa. ($\times 500$)
- FIG. 2.—Vessel in cerebrum showing serous clot lining vessel and infiltrated by leucocytes. The serous clot is represented by the clear area between the vessel wall and the mass of red blood corpuscles. Leucocytes also present in wall of vessel together with pigment. Stain Giemsa. ($\times 500$)

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- FIG. 3.—Small vessel in cerebrum showing annular infiltration of wall by leucocytes. Stain Giemsa. ($\times 500$.)
- FIG. 4.—Small vessel in spleen showing infiltration of leucocytes between endothelial and muscular layers. Stain hæmalum and acid fuchsin. ($\times 500$.)
- FIG. 5.—Vessel in spleen showing infiltration of leucocytes beneath endothelium and degeneration of muscular coat. Small granules darkly staining with hæmalum are seen in the area of infiltration. Stain hæmalum and acid fuchsin. ($\times 500$.)
- FIG. 6.—Section of vessel in lymphatic gland showing under endothelium mass of acidophilic cells with irregularly drawn-out nuclei. Note apparent looseness and small number of lymphocytes. Stain hæmalum and acid fuchsin. ($\times 500$.)
- FIG. 7.—Endothelial (Kupffer) cell in liver containing small masses of red-staining granules resembling blood platelets. There is also phagocytosis of red cells. Stain Giemsa. ($\times 1500$.)
- FIG. 8.—Section of liver showing the presence of granules staining strongly with acid fuchsin in parenchymatous cells. These granules also stain bright red with Giemsa. Stain hæmalum and acid fuchsin. ($\times 1500$.)
- FIGS. 9, 10, 11, 12.—Four nerve-cells from cerebrum showing vacuolation of cell and presence of small dark-blue-staining granules diplococcal in character. (*Rickettsia*?) Stain Giemsa. ($\times 1500$.)
- FIG. 13.—Section of vessel in lung showing numbers of blue-staining granules (*Rickettsia*?) in endothelial coat. Stain Giemsa. ($\times 1500$.)
- FIG. 14.—Endothelial cell of vessel in spleen showing a large number of granules, many diplococcal in character, staining bluish with Giemsa. Stain Giemsa. ($\times 1500$.)