

XII. THE PATHOLOGICAL HISTOLOGY OF THE SPLEEN
AND LIVER IN SPONTANEOUS RAT-PLAGUE, WITH
OBSERVATIONS ON THE EXPERIMENTAL INFECTION.

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(PLATES VIII AND IX.)

The pathological histology of plague in man and experimental plague in animals has already been the subject of several researches, notably those of Aoyama (1896), Yamagiwa (1897), Albrecht and Gohn (1897), Dürck (1904) and Hamdi (1904) in the case of human plague, and of van der Stricht (1897), Honl (1897), Lustig and Zardo (1897), Babes and Livadite (1897), Albrecht and Gohn (1900) and Sata (1900) in the case of experimental plague.

The guinea-pig and rat have been mainly employed as experimental animals owing to their great susceptibility to infection, but in view of the natural occurrence of plague in the latter animal and the important part it plays in the propagation of human plague, it is highly essential that we should have all details regarding the histology of the natural rat infection even though the differences between such and the experimental form may be presumably insignificant.

The pathological histology of natural plague infection in rats has been referred to only by Albrecht and Gohn (1900) who gave brief histological details of the organs of five rats which had died of plague in Bombay. Ogata (1897) also contributed a few observations on the subject.

It is to fill up this lacuna in our knowledge of spontaneous rat plague that the following histological examinations have been made from material collected in Bombay by the Plague Commission. The primary cause, however, of this inquiry was the elucidation of the peculiar characteristic post-mortem appearances of the spleen and liver,

to which reference has been made in another article in this number. For this purpose, therefore, only the spleens and livers from the various cases were forwarded.

It was felt, moreover, that a more minute investigation of the histological changes might throw some light on the conditions leading up to the chronic form of rat plague which is associated with the presence, in the spleen particularly, of encapsulated abscesses.

To add completeness to the work and for purposes of comparison the organs of several rats which had been inoculated in Bombay with virulent plague, were submitted to detailed examination by similar methods. Finally one or two cases of chronic experimental plague in vaccinated rats were investigated histologically. The results obtained in these experimental cases will be discussed in Part II of this paper.

PART I.

Spontaneous Rat Plague.

The very brief histological details recorded by Albrecht and Gohn may be here summarised :—

Rat I. *Spleen* :—Numerous haemorrhages were present in the pulp. Necroses had also commenced especially at the periphery of the nodes. Bacilli were scarce. *Liver* :—Showed cloudy swelling. Bacilli scarce.

Rat II. *Spleen* :—Pulp was haemorrhagic and infiltrated with polynuclear leucocytes. The nodes were surrounded by a fine or coarse network of connective tissue. Bacilli were numerous. *Liver* :—Liver cells showed karyorrhetic nuclei in many cases. The capillaries contained enormous masses of bacilli.

Rat III. *Spleen* :—Pulp contained large amounts of nuclear debris especially in the vicinity of the nodes. *Liver* :—Showed degeneration of parenchyma. Capillaries were full of bacilli.

Rat IV. *Spleen* :—Pulp presented commencing necroses. Bacilli numerous.

Rat V. *Spleen* :—Numerous haemorrhages and necroses in the pulp. The peripheral portions of the nodes and the adjoining pulp-tissue were transformed into a coarse network staining intensely with eosin.

Rat VI. *Spleen* :—Showed haemorrhages and nuclear disintegration. Bacilli very numerous. *Liver* :—Liver cells showed fatty degeneration. Bacilli very abundant in the capillaries.

Ogata (1897), during the epidemic of plague in Formosa, obtained six rats which had died of plague. Referring to the condition of the organs he merely remarks that the spleen was much swollen and the liver congested. Small haemorrhages were also present in the liver and bacilli were numerous, as also in the spleen and glands.

From the above summary, it will be evident that the grosser lesions only have been recorded, possibly owing to the difficulty of procuring material fresh enough for detailed histological examination. The organs at my disposal were the spleens and livers of thirteen cases of rat plague. These had been fixed in Orth's fluid and sent to this country in spirit. The tissues were embedded in paraffin and the stains chiefly employed were Unna-Pappenheim's methyl-green-pyronin and Ehrlich's haematoxylin and orange-rubin. The former stain proved eminently satisfactory for the demonstration of plague bacilli and plasma cells.

Rat I. *Protocol*:—Primary bubo—left axillary. Congestion of spleen and subcutaneous tissues. Bacilli present in bubo, heart blood and spleen.

Spleen:—Capsule: shows no pathological changes.—Nodes: The nodes are few in number but regular in outline. Karyorrhexis of the lymphoid cells of the node is a marked feature and a large amount of nuclear detritus is lying either free or included in large endothelioid phagocytic cells. Some of these particles show their cytoplasmic origin by taking up the pyronin stain. Large mononuclear cells of endothelioid type are abundant throughout the node, many of them presenting mitotic figures (see Plate VIII, Fig. 2). The protoplasm of these cells stains a deep red, the nucleus being rather vesicular. No bacilli were detected within the node though a specially rich zone of them was present in the perinodal lymph sinus.—Pulp: Extravasation of red cells was very marked and plague bacilli were fairly uniformly distributed and in large numbers. No necrotic foci were present. Rows of plasma cells, many showing mitosis, were arranged in the sheaths of the trabecular vessels. *Liver*:—The protoplasm of the liver cells was coarsely vacuolated. Necrotic foci, which are the outstanding feature of plague livers, were in this case few in number and of very small size, in some cases only two or three liver cells being involved. Within these necrotic areas were a few vesicular nuclei and occasionally a small group of bacilli lying in what remained of the intraacinar capillaries. Enormous numbers of bacilli were present in the liver capillaries. Many of the liver cell-nuclei showed karyorrhexis.

Rat II. *Protocol*:—Primary bubo—left submaxillary. Spleen, lungs, and subcutaneous tissues congested. The surface of the liver had a mottled appearance. Bacilli in spleen and bubo.

Spleen:—Subcapsular haemorrhage was considerable.—Nodes: These were greatly diminished in number. Large mononuclear endothelioid cells were numerous, the small lymphoid cells showing extreme karyorrhexis. In some nodes were small necrotic foci containing large endothelioid cells and nuclear detritus, similar to those described in the diphtheritic spleen (see Waschkeiwitsch *Virch. Archiv*, Bd. 159, 1900).—Pulp: There was great congestion of the pulp sinuses accompanied with red cell extravasation. Around the trabecular vessels were many plasma cells showing extreme karyorrhexis and pyknosis (see Plate VIII, Fig. 5). The cells of the spleen pulp presented as a whole only a slight degree of karyorrhexis and no actual necrotic foci were observed. Bacilli occurred in swarms throughout the pulp especially in the areas of blood extravasation. *Liver*:—The protoplasm of the

EXPLANATION OF PLATES VIII AND IX.

Plate VIII. Fig. 1. Portion of necrotic focus of liver (natural rat plague). *a*=Blood in capillaries. *b*=Remains of liver-acini. *c*=Liver cell showing vacuolar honeycomb degeneration. *d*=Mononuclear cell in capillary.

Fig. 2. Portion of malpighian body (natural rat plague) showing large mononuclear endothelioid cells. *a*=Mitosis of the same. A degenerated endothelial cell containing nuclear detritus is also seen.

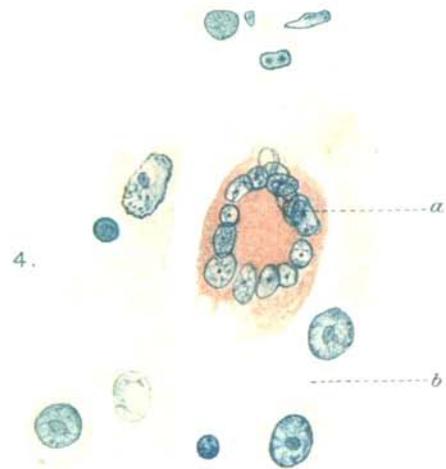
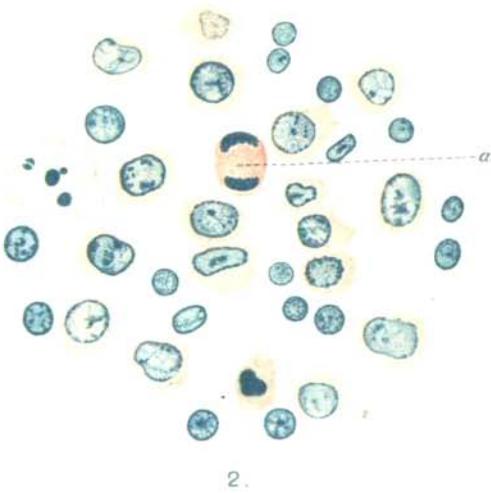
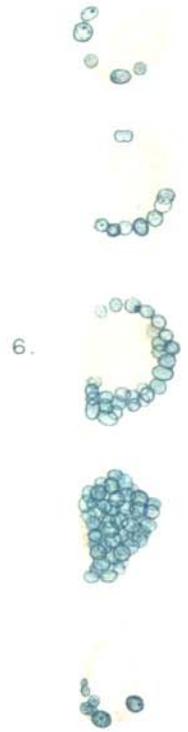
Fig. 3. Portion of spleen in chronic experimental rat plague. *a*=Giant-cell (of tubercular type). *g*=Commencing agglomeration of nuclei to form giant-cell. *b*=Megakaryocyte. *d*=Granulation spindle cell. *c*=Rows of plasma cells. *f*=Leucocytic debris round bacilli. *e*=Degenerated bacilli.

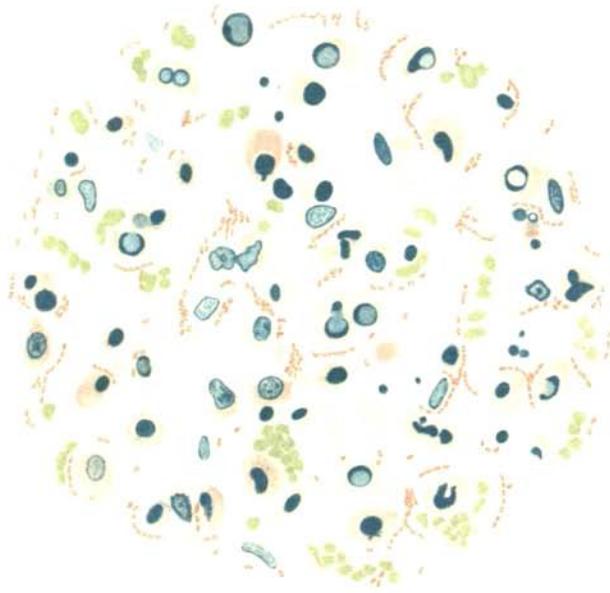
Fig. 4. Portion of liver (natural rat plague). *a*=Megakaryocyte in capillary. *b*=Liver-acinus.

Fig. 5. Portion of spleen-pulp (natural rat plague) showing bacilli and pyknotic plasma cells of all types, and effused red cells.

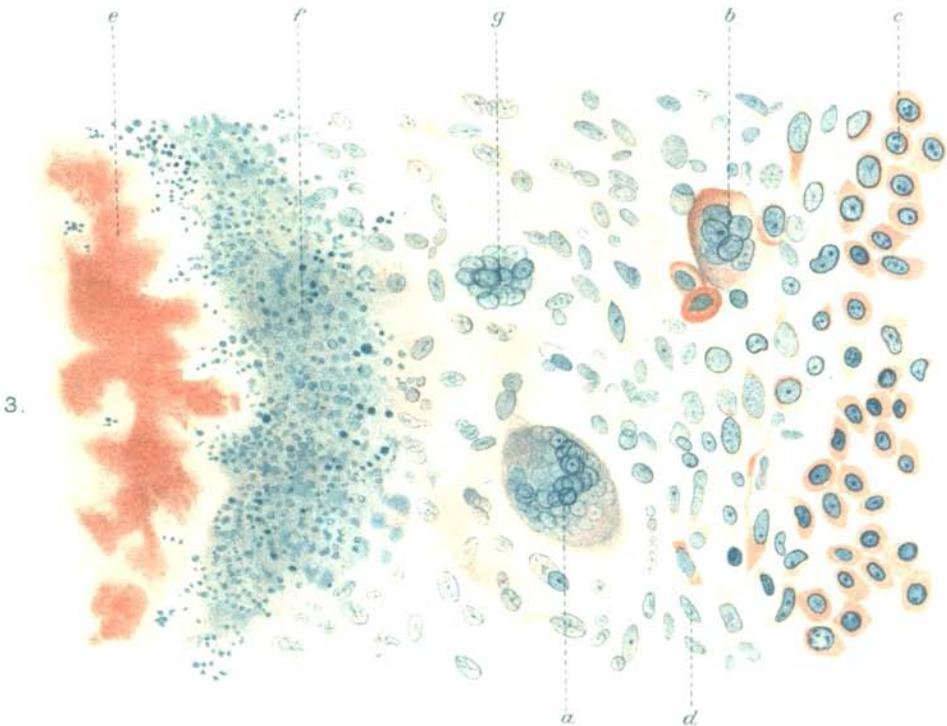
Fig. 6. Giant-cell (of Langhans' type) from periphery of malpighian body (experimental rat-plague). The drawings are made from five successive sections through the same cell. Note the grape-like nuclear agglomeration in the 4th drawing.

Plate IX. Photomicrograph of liver necroses (natural rat-plague).



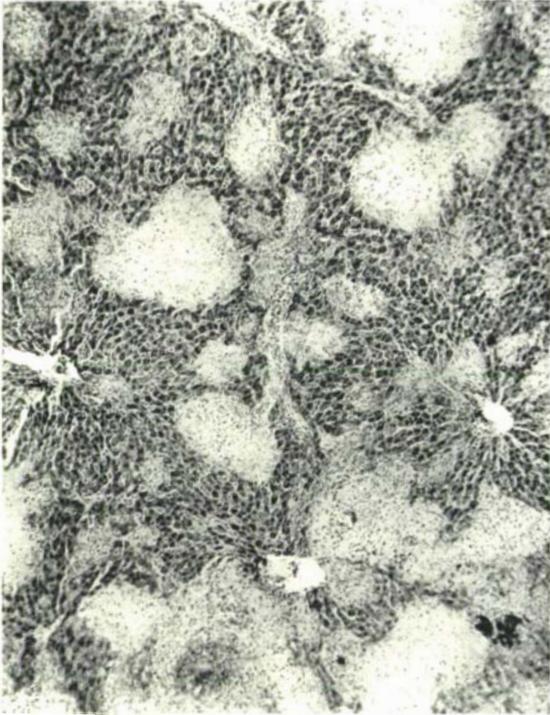


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liver cells was finely vacuolated but not fatty. Acinar necroses were few in number and of very irregular contour. In the capillaries of the necrotic area, bacilli were still present. The portal vessels and intraacinar capillaries were extremely congested and contained large numbers of bacilli.

Rat III. *Protocol*:—Primary bubo—right submaxillary. The liver had a granular appearance and presented minute haemorrhages on the serosa. Bacilli present in heart blood, spleen and bubo.

Spleen:—The capsule presented no marked changes.—Nodes: These were few and of irregular shape and size and showed the characteristic endothelioid proliferation with numerous mitoses. At the periphery of the node plasma cells were abundant. A marked feature was the presence of a reticular zone encircling each node. The few pulp cells remaining in this zone showed extreme karyolysis and bacilli were specially abundant.—Pulp: The pulp showed great congestion with haemorrhages and polynuclear infiltration. No definite necrotic foci were seen although bacilli occurred in swarms. Plasma cells were numerous in the sheaths of the vessels and there was a very pronounced catarrh of the vascular endothelial cells. *Liver*:—Focal liver cell necroses were fairly numerous especially in the subcapsular area. They were apparently of recent origin and contained many extravasated red blood corpuscles with bacilli still lying in the capillaries. The liver cells showed fine vacuolation of their cytoplasm. Bacilli were not quite so numerous in the vascular system of the liver as in the previous cases.

Rat IV. *Protocol*:—Primary bubo—right submaxillary. The serosa of spleen and liver had a granular appearance. Bacilli few in heart blood, spleen and bubo.

Spleen:—The capsule was markedly thickened and oedematous, the subcapsular lymph space showing extreme endothelial catarrh.—Nodes: The nodes were greatly diminished in number and in some cases contained rounded areas with vacuolated endothelial cells and nuclear debris. Many lymphoid cells had undergone karyorrhexis.—Pulp: Even with low magnification large clumps of bacilli could be seen throughout the pulp, each surrounded by a zone of karyorrhctic nuclei. The condition was thus one of multiple small abscess formation. Around the nodes and vessel-sheaths plasma cells and vesicular epithelioid cells abounded. The karyorrhctic focus was immediately surrounded by a zone of vesicular epithelioid nuclei and this again by a barrier of plasma cells. These epithelioid cells showed a slight tendency to nuclear grouping but no fully formed giant-cells of tubercular type were met with. *Liver*:—Liver cell necroses were present in enormous numbers and in fact little healthy liver tissue was left (see Plate VIII, Fig. 1 and Plate IX). Some foci contained only red blood corpuscles, with no traces of bacilli remaining, while others contained a central clump of bacilli surrounded by karyorrhctic nuclei or proliferating epithelioid cells. The production of some necroses by vascular bacillary emboli was quite patent though in others such a connexion could not be traced. Among the vesicular nuclei surrounding one focus a fully formed giant-cell of tubercular type was detected. In the healthy liver capillaries, bacilli were scarce and evidently degenerated, their remains being taken up by the endothelial cells of the vessel wall. A very interesting feature was the presence in the dilated capillaries of great numbers of epithelioid cells some of which were undergoing mitosis. An occasional giant-cell of the splenic megakaryocyte type was detected in the capillary lumen. Round the portal vessels in Glisson's capsule small lymphomata were sometimes met with.

Rat V. *Protocol*:—Congestion of subcutaneous tissue, lungs and spleen.—Liver fatty and granular. No bacilli in heart blood, spleen or liver.

Spleen:—The capsule is very oedematous.—Nodes: There is no diminution in the number of malpighian bodies, each containing many endothelioid cells with plasma cells at the periphery. Among the latter, very many mitotic forms were observed. A perinodal zone of reticular tissue with few nuclei was a constant feature, forming a species of capsule for the node.—Pulp: The pulp was extremely congested but only a few bacilli were detected in small groups lying among the extravasated red blood corpuscles. Many necrotic foci were present. These at times consisted of karyorrhetic nuclei and detritus or of vesicular epithelioid cells. The plasma cell reaction was very conspicuous. Pigment cells containing haemosiderin and catarrhal endothelial cells occurred in fairly large numbers. *Liver*:—Very numerous sharply demarcated necroses were present in all stages of development. In some of them, red blood corpuscles were the predominant elements, while in others the endothelial cells of the capillaries showed a marked proliferation. A few bacilli could still be detected in these foci. Elsewhere, the capillaries of the liver contained here and there small bunches of bacilli which appeared to have undergone degenerative changes. The phagocytic endothelial cells frequently contained such bacillary débris.

Rat VI. *Protocol*:—Double pelvic bubo containing swarms of bacilli. No bacilli in heart blood or spleen.—Liver coarsely granular and spleen congested.

Spleen:—The capsule was oedematous and the subcapsular area very much congested, the endothelial cells actively proliferating.—Nodes: These were much diminished in number but presented only slight pathological changes.—Pulp: The pulp was greatly congested. There were no definite areas showing karyorrhexis of the pulp cells but here and there could be seen foci in which the nuclei had disappeared or had become vesicular. Pyknotic plasma cells were present in moderate numbers. No bacilli could be demonstrated. *Liver*:—The liver cells looked fairly healthy. Focal necroses were moderate in number, a few remains of bacilli being still apparent in them. The portal vessels were extremely congested. Free bacilli were never seen in the capillaries but the endothelial cells contained here and there what appeared to be bacillary remains.

Rat VII. *Protocol*:—Primary bubo unknown. Liver fatty and granular.—Spleen granular. Many bacilli in spleen.

Spleen:—The capsule was oedematous and infiltrated with red cells, the superficial endothelium being catarrhal.—Nodes: These showed no important changes. No bacilli were detected in them.—Pulp: Large irregular necrotic areas were present showing no very definite boundary and frequently lying alongside a malpighian body. At the margins of these areas or inside them were wisps of bacilli. In one case, a vein leading to such a focus was completely blocked by plague bacilli for a considerable distance. Extraordinary numbers of bacilli were present in the pulp among the extravasated red cells and polynuclear infiltrates. Karyorrhetic and pyknotic plasma cells and catarrhal endothelial cells were specially numerous. *Liver*:—The liver cells throughout the lobule showed large protoplasmic vacuoles due to fat. Focal liver cell necroses were very numerous and sharply demarcated from the healthy liver substance. Some foci contained very few nuclei, while others contained numerous vesicular nuclei tending at times to coalesce. The contents of

the capillaries were polynuclear cells, red cells and occasional degenerated bacilli. A few small lymphoid nodes were observed around the portal vessels in the large trabeculae. Large mononuclear endothelioid cells showing mitoses could be seen in these small lymphomata as in the splenic nodes.

Rat VIII. *Protocol* :—Primary bubo—left axillary. Liver fatty and granular.—Spleen faintly granular.—No bacilli in heart blood or spleen.

Spleen :—The chief feature was the presence of numerous pulp necroses in which only a few vesicular nuclei remained. These areas were invariably perinodal. Outside these areas the pulp cells showed slight karyorrhesis. Pyknotic plasma cells occurred in enormous numbers. Bacilli were exceedingly scarce and confined to the necrotic foci. *Liver* :—Cell necroses were very numerous and contained nuclear debris and vesicular epithelioid cells. Sometimes a few degenerated bacilli could be seen in them. Elsewhere, the liver capillaries contained numerous degenerated endothelial cells and karyorrhetic nuclei. Bacilli were very scarce and only in phagocytic endothelial cells. There was marked congestion throughout.

Rat IX. *Protocol* :—Primary bubo—left submaxillary. Liver fatty and granular.—Spleen granular.—No bacilli in heart blood, spleen or bubo.

Spleen :—In this case the areas of pulp degeneration were very numerous and extensive. The malpighian bodies were encroached upon and very little normal splenic tissue remained. In the degenerated areas were enormous masses of nuclear detritus with occasional degenerated bacillary clumps in the centre. Bounding these areas were rows of plasma cells in active division and catarrhal endothelial cells. Signs were already present of the replacement of these foci by spindle-shaped granulation cells formed from the actively dividing plasma cells. *Liver* :—Necroses were few but of all sizes. Some bacilli still remained in the capillaries of the necrotic area along with red cells. Throughout the liver substance, the capillaries were greatly dilated with red cells, desquamated endothelial cells containing nuclear detritus and large mononuclear cells suggesting a splenic origin. Typical giant cells of megakaryocyte type were also met with not infrequently lying in the capillary lumen (see Plate VIII, Fig. 4). It seems most probable that these cells, along with many of the types filling up the liver capillaries, have found their way to this organ from the spleen. Babes and Livadite (1897) noted the presence of similar giant cells in the guinea-pig's liver (in experimental plague), but apparently assigned to them a different origin. They write "Sehr bemerkenswerth ist das Auftreten von Riesenzellen mit gelappten Kern wohl auf Kosten gewisser Endothelien." Only a very few bacilli were present in the capillaries.

Rat X. *Protocol* :—No primary bubo. Liver fatty and granular.—Spleen congested.—No bacilli in heart blood, spleen or liver.

Spleen :—Not available for histological examination. *Liver* :—Liver cell necroses were few and of small size. The subcapsular region was mainly the site of these foci and there also bacilli were most frequent. The capillaries of the necrotic area were blocked by bacilli in many cases. Throughout the liver substance the capillaries were dilated with red cells and splenic elements as in the previous case. Megakaryocytes were also occasionally detected. Bacilli as a rule were scarce and many were included in the endothelial phagocytes.

Rat XI. *Protocol* :—Primary bubo—left axillary. Liver and spleen congested. Many bacilli in spleen and bubo.

Spleen :—The lymphoid tissue was greatly diminished. Large mononuclear endothelioid cells in active division were present in the nodes. Necrotic areas containing vesicular nuclei and bacillary débris were distributed throughout the pulp. Megakaryocytes, pyknotic plasma cells and catarrhal endothelial cells were specially abundant. An interesting feature was the presence of a large number of eosinophile cells. *Liver* :—Necroses were few but of all sizes. The capillaries were dilated as in the previous cases with splenic elements. Plasma cells were also numerous. A slight degree of perivascular lymphoid infiltration was noted in the portal spaces.

Rat XII. *Protocol* :—Liver coarsely granular and fatty, spleen finely granular.—Subcutaneous and pulmonary haemorrhages.—No bacilli in heart blood, few clumps in spleen.

Spleen :—The nodes were few in number and badly differentiated from the surrounding pulp.—Pulp : Small irregular necrotic foci were distributed throughout the pulp. The centre of each focus was occupied by swarms of bacilli and the periphery by vesicular nuclei, detritus and blood-pigment-carrying cells. The subcapsular area was infiltrated with red cells and polynuclear leucocytes. Megakaryocytes were exceedingly numerous especially in the neighbourhood of the necrotic foci. *Liver* :—Fatty infiltration of the liver cell-protoplasm was far advanced. Many nuclei also exhibited karyorrhexis. Only a few small necrotic foci were noted. The intraacinar capillaries were greatly dilated, their lumina being filled with small and large mononuclear cells and endothelial phagocytes.

Rat XIII. *Protocol* :—Lungs both consolidated. Gray hepatisation of upper and middle lobes of right lung.—Liver has a mottled appearance.—Spleen congested.—Swarms of bacilli in heart blood, spleen and bubo.

Spleen :—Malpighian bodies were numerous and of irregular form and size. Many karyorrhectic nuclei were present in the nodes along with large endothelial cells containing nuclear detritus.—Pulp : A few clumps of degenerated bacilli were seen here and there but no necrotic foci were in evidence. The cell types met with in the pulp were very varied, small and large mononuclear cells, endothelial cells, megakaryocytes and nucleated red cells. An interesting feature was the great abundance of coarsely granular eosinophile cells many of which showed mitotic figures. They occurred in greatest numbers in the subcapsular area. A few clumps of mast cells were also noted. Plasma cells were very scarce. In this case the pneumonia was evidently the main plague-lesion, while the spleen presented none of the characteristic changes observed in the foregoing cases. The splenic picture, in fact, was that associated with an actively functioning haemopoietic organ. *Liver* :—Unsuitable for histological examination.

Survey of the above cases.

The cases may be divided into two main groups :—

1. Those in which bacteriaemia of the spleen and liver is at a maximum and has been of recent development.
2. Those in which bacteriaemia is less prominent or is rapidly disappearing as a result of reactive tissue changes.

In the first group, the incursion of bacillary swarms into the spleen and liver has been accompanied by extensive haemorrhages and congestion of the pulp sinuses and liver capillaries. Definite abscess formation in the spleen has not had time to develop and focal liver cell-necroses are few in number, the latter being very largely confined to the sub-capsular region.

In the second group, definite abscess formation in the spleen is far more frequent and is accompanied by extensive reactive changes on the part of the plasma cells. The reduction in the amount of lymphoid tissue is due in great measure to the perinodal distribution of degenerated pulp areas. A barricade of plasma cells separates the lymphoid tissue of the node from the necrotic zone. Proliferation of the large mononuclear endothelioid cells of the node is a noteworthy feature. Dürck (1904) has described a similar change in the splenic nodes in human plague.

In the liver, focal necroses may be so numerous that little healthy liver tissue remains. The demonstration of bacilli in the central capillaries of these foci was made in nearly every case and frequently actual bacillary embolism was noted. The formation of giant-cells of Langhans' type in the neighbourhood of necrotic foci is also of great importance, although in some of the cases these cells had not reached their full development. It can readily be conceived how, providing the animal lives long enough, the reaction of the fixed tissue cells may proceed to complete encapsulation of abscess areas and so bring about a more or less chronic condition. So far I have had no opportunity of examining histologically such cases of chronic spontaneous rat plague, but it is hoped that suitable material of this kind may soon be available. The chronic experimental case, which will be described later, gives however a very clear notion of the later stages in this process of abscess-encapsulation.

Frequent mention has been made in the protocols of a granular and mottled appearance of the liver. The spleen has also been described as granular in some cases. In the case of the liver such changes are readily accounted for by the distribution of the haemorrhages and the focal necroses together with the fatty changes in the liver cells. It must be understood, however, that a peculiar, honeycomb-like vacuolar degeneration of the liver cell protoplasm was far more frequent than an actual coarse fatty infiltration. The granular appearance of the spleen is due partly to endothelial catarrh and partly to subcapsular changes.

With regard to the disappearance of bacilli from the intraacinar capillaries of the liver it appears that phagocytosis by endothelial cells is largely responsible. Indeed in some cases no free bacilli were demonstrable. The presence of large giant-cells of megakaryocyte type in the liver capillaries of some cases is highly interesting: in such cases the capillaries generally contained so many extraneous cell elements that one is forced to assign to them a splenic origin.

Finally, with regard to the distribution of plague bacilli in the spleen, it was exceedingly rare to find the organisms in the interior of the nodes. Yet, though bacilli were absent, karyorrhexis of the nodal cells was frequently far advanced. Toxaemia must then be largely responsible for the alterations in the nodes, as we know that analogous changes take place in the malpighian bodies after the inoculation, for instance, of diphtheria toxin.

PART II.

Experimental Rat Plague.

The following is a brief *résumé* of our knowledge regarding the histology of the spleen and liver in experimental plague.

Spleen. In the guinea-pig van der Stricht (1897) noted a diminution in the size of the malpighian bodies with dilatation of the capillaries of the node, leading to actual rupture. Abscesses occurred in the pulp but did not affect the nodes. The splenic megakaryocytes were very numerous and the capsule of the organ was infiltrated with white corpuscles. Honl (1897), working with the same animal, found an enlargement of the follicles and extreme congestion of the pulp. Bacilli occurred in "zoogloal" groups round which were numerous fragmented cell elements. Lustig and Zardo (1897) working with rats, mice, guinea-pigs and rabbits noted that the periphery of the follicle was the seat par excellence of the necrotic foci. The trabeculae had a hyaline appearance and the arteries were dilated. Haemorrhage into the pulp was a constant feature. Plague bacilli were numerous throughout the pulp and might occur inside the nodes. Babes and Livadite (1897) recorded in guinea-pigs and mice the presence of large numbers of giant-cells of megakaryocyte type, especially in the vicinity of the necrotic areas. Blood-corpuscle-containing cells and pigment cells were scarce in spite of extensive pulp haemorrhages.

Albrecht and Gohn (1900) found a great similarity in the main

splenic lesions in experimental rat plague by whatever method the inoculation was performed. The nodes were as a rule much diminished and necrotic pulp-foci were of constant occurrence.

Sata (1900) gives a fairly detailed description of the histology of experimental rat plague and lays great stress on the variations met with as regards the distribution of plague bacilli in the organs. Subcapsular haemorrhage was a frequent feature in the spleen and bacilli might be very numerous, very scarce or not demonstrable at all in sections.

Liver. Van der Stricht observed areas of fatty degeneration of the liver cells and also a fine vacuolated condition of the liver cell protoplasm. In one animal small necrotic areas due to capillary emboli were noted.

Honl noted focal necroses surrounded by a zone of leucocytes. Groups of bacilli arranged in zoogloal masses were present in these foci. Babes and Livadite recorded the presence in the liver capillaries of "Riesenzellen mit gelappten Kern" which have been already alluded to.

Fatty degeneration of the liver cells was noted both by Albrecht and Gohn and Sata. The latter also demonstrated fibrin in the larger vessels. The occurrence of bacilli in the liver capillaries was found to be a very variable factor.

The material of the following six cases was obtained from rats inoculated by the cutaneous method in Bombay. For Rat No. VII of chronic experimental plague I am indebted to Capt. S. R. Douglas.

Rat I. Spleen :—Serous endothelium swollen, capsule oedematous with effusion of red cells into it. The endothelial cells of serosa contained red cell debris. There was marked subcapsular haemorrhage.—*Nodes* : The lymphoid tissue was increased in amount. At the periphery of each node was a circular zone of necrotic cells with bacillary clumps in the neighbourhood. Near the margin of one node was a typical Langhans' giant-cell. The appearance of this cell in five serial sections is indicated in Plate VIII, Fig. 6. In one cross section the constituent nuclei are seen to fill practically the whole cell leaving only a faint rim of protoplasm. The pulp was much congested and numerous zoogloal bacillary masses were noted. Plasma cells were abundant. The pulp cells showed a slight degree of karyorrhexis. No bacilli were seen in the nodes. *Liver* :—The liver cells were generally healthy apart from the necrotic areas which were numerous. Each focus contained small heaps of bacilli and a good deal of haemorrhage was present at the periphery. Endothelial catarrh of the capillaries was a marked feature. Bacilli were distributed in clumps and many of them were noted inside phagocytic endothelial cells. Fibrin was also observed in the capillaries, along with numerous red cells.

Rat II. Spleen :—Marked catarrh of the serous endothelium with subcapsular haemorrhage. The lymphoid tissue was increased and irregularly distributed. Numerous actively dividing large mononuclear endothelial cells were observed in the

nodes. A zone of karyorrhctic pulp cells with detritus forms a sort of capsule to each node. Bacilli occurred in clumps surrounded occasionally by necrotic pulp cells. Pyknotic plasma cells were very abundant. In the haemorrhagic areas, fibrin was present in large amount and blood-corpuscle-containing cells were numerous. *Liver* :—Liver cells were not fatty. Marked subcapsular haemorrhage. Necroses were few and small and most of them contained bacillary clumps, surrounded by karyorrhctic nuclei. Bacilli were very numerous in the capillaries and the endothelial cells frequently contained ingested bacilli.

Rat III. *Spleen* :—Capsule swollen and subcapsular haemorrhage. The malpighian bodies were swollen but regular in contour. Round each was a zone of thickened reticulum containing few cells. For the first time, a node was seen whose central artery contained a fibrin thrombus with bacilli. In the pulp, enormous numbers of bacilli were present along with red cells and fibrin. Polynuclear cells, pyknotic plasma cells and endothelial cells were abundant. Haemosiderin cells also occurred frequently. *Liver* :—The liver cells were markedly fatty. Their nuclei also frequently presented karyorrhhexis. Necroses were fairly numerous and often of large size. Capillaries containing bacillary emboli were noted in these foci. In the capillaries of the healthy liver substance were enormous numbers of bacilli generally clinging to the walls of the vessels. Round the portal vessels were lymphoid and plasma cell infiltration.

Rat IV. *Spleen* :—Large numbers of bacilli surrounded each node but in only one case were bacilli seen in the follicular artery. The large mononuclear endothelioid cells were abundant in the node and showed signs of active division. Also small necrotic areas containing large endothelial phagocytes and detritus sometimes appeared inside the node. The pulp showed extensive haemorrhages with polynuclear infiltrates and haemosiderin cells. No necrotic foci were present but here and there were small areas in which the cell-nuclei were vesicular. *Liver* :—The liver cells were fatty. Only one or two minute necroses were seen each containing bacilli in its central capillary with effusion of red cells at the periphery. The capillaries throughout the liver substance were quite filled with bacilli and many polynuclear cells were present. Colonies of plasma cells were seen in the sheaths of the large portal vessels in the Glisson's space.

Rat V. *Spleen* :—Capsule thickened, trabeculae increased, and marked subcapsular haemorrhage. The nodes were greatly diminished and irregular in contour. They contained numerous large mononuclear cells of endothelioid type, many of which were dividing. The spleen pulp was greatly congested and bacilli occurred in swarms especially in the large trabecular sinuses. Polynuclear cells, haemosiderin pigment cells and blood-corpuscle-containing cells were abundant in the areas of red cell extravasation. Plasma cells were very numerous and were in active division. No actual pulp necroses were observed. *Liver* :—Only a very few minute necrotic foci were observed in the subcapsular region, involving individual liver cells or a few adjacent ones. Bacilli were also most numerous in this region, lying in clumps in the capillary vessels. The intraacinar capillaries throughout the organ were filled with red cells, infiltrating cells of polynuclear type, and catarrhal endothelial cells.

Rat VI. *Spleen* :—Marked subcapsular haemorrhage and great reduction in the amount of lymphoid tissue. Many of the nodes showed a hyaline thrombosis of the central artery, the lymphoid cells in the neighbourhood being karyorrhctic.

Many endothelial phagocytic cells were present, containing nuclear detritus in their interior. A perinodal zone of karyorrhectic pulp cells was a conspicuous feature. Vesicular epithelioid cells and plasma cells invariably bounded this zone. The pulp was greatly congested with extravasated red cells and polynuclear leucocytes. Bacilli occurred in enormous numbers. Haemosiderin cells and megakaryocytes were also very abundant. *Liver*:—Necroses were few in number. Bacilli were generally to be found in the central capillaries of the focus with effused red cells at the periphery. The large portal sinuses and the intraacinar capillaries throughout the organ were extremely congested and contained enormous numbers of bacilli and polynuclear leucocytes.

Rat VII. *Chronic experimental rat plague.*

The rats in which these chronic plague lesions were found had been inoculated with virulent plague ten days after a partial immunisation with plague vaccine. Those which survived were killed on the eleventh day following the inoculation with the virulent culture.

Protocol:—Spleen much enlarged and contained large grayish caseous-looking areas.—Liver also showed a few grayish nodules.

Spleen:—Microscopical examination (Unna-Pappenheim's stain). No differentiation of the splenic tissue into nodes and pulp was possible. In fact the organ was transformed into a veritable plasma-cell granuloma with abscesses interspersed here and there. A large clump of degenerated bacilli occupied the centre of each necrotic area and all around were broken down polynuclear cells. Bounding this zone of degenerated cells was a band of epithelioid cells, spindle cells and numerous giant-cells of tubercular type. Megakaryocytes also appeared in this zone. Enclosing the whole was a barricade of plasma cells in active division, and transition forms were readily demonstrable between these latter cells and the spindle cells from which the granulation zone surrounding the abscess was being developed (see Plate VIII, Fig. 3). The presence of giant-cells of Langhans' type was especially interesting as confirming the view that the small agglomerations of nuclei above referred to in some of the cases of spontaneous plague were really developing giant-cells. Fully formed cells of this type have been already noted in the liver of Rat IV, Part I. *Liver*:—A section through one of the small subcapsular nodules showed that nothing remained of the original abscess. The nodule consisted solely of spindle cells and fine connective tissue fibres with a boundary zone of actively proliferating plasma cells.

Survey of the experimental cases.

The changes met with in the experimental cases present far more points of resemblance with those of group I of the spontaneous cases than with those of group II.

Extreme bacteriaemia is the rule and the infiltrating cells are found to belong mainly to the polynuclear type. In the spontaneous cases the latter feature was not so prominent.

Focal necroses of the liver cells were invariably scanty. The vessels were all greatly congested and contained large deposits of fibrin.

In the spleen, a noteworthy feature in two cases was the occurrence of thrombosis of the follicular artery accompanied by bacillary incursion and the production of karyorrhctic changes in the nodal cells. Giant-cell formation (of Langhans' type) had evidently not proceeded to any extent, but the discovery of a typical cell of this nature at the periphery of one follicle and bordering a necrotic patch shows that, even in acute experimental cases, the tendency to giant-cell development is at least not in entire abeyance.

The importance of Rat VII, as showing the later stages of the pathological processes already at work in the more acute cases, has been sufficiently alluded to at the close of the histological summary.

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