HISTOLOGICAL STUDIES ON HOG CHOLERA

III. LESIONS IN THE VARIOUS ORGANS

BY O. SEIFRIED, V.M.D., AND C. B. CAIN, D.V.M.

(From the Department of Animal and Plant Pathology of The Rockefeller Institute for Medical Research, Princeton, N. J.)

PLATES 23 TO 25

(Received for publication, April 22, 1932)

In the preceding paper we have described the changes in the blood vessels of swine infected with hog cholera virus and have stated that these lesions are the principal feature in the histopathology of this disease. In the present paper we propose to discuss in detail the histological changes in the lymph nodes, kidney, spleen, and liver.

A. Blood-Forming Organs

1. Lymph Nodes

The gross lesions in these organs are well known. Three types can be distinguished, (1) swelling and hyperemia, (2) hemorrhagic infiltration especially marked at the periphery, and (3) dense infiltration with red blood corpuscles, indicated by the dark red color of the lymph node parenchyma.

These three types of lesions are usually present in varying degrees in individual cases. In some cases the first type predominates, in others the second and third are more pronounced. Certain groups of lymph nodes are more severely affected than others. In our material there was a general lymphadenitis with the earliest and most characteristic changes in the cervical and thoracic lymph nodes. Although in general the edema and swelling are more frequent in early stages and the foci of necrosis and dark purple color of the lymph nodes usually appear in later ones, there is no rule in this respect. In very acute cases even the reverse may be true.

Papers published during the progress of our work indicated that there are various opinions with regard to the fundamental histological findings of the lymph nodes in hog cholera. In peracute cases of hog cholera Bel (1) saw a lymphatic
hyperplasia and hypertrophy of the follicles and hyperemia of capillaries from which he considered the hemorrhages in the parenchyma to be derived. In acute and subacute cases there was a pronounced hyperplasia in the lymph nodes which he thought resulted from a proliferation of small lymphocytes and macrophages. Nieberle (2) pointed out that, contrary to the common belief, acute cases of hog cholera are not associated with a hemorrhagic lymphadenitis. He holds the opinion that the red blood corpuscles, found in the lymph nodes, originate in other parts of the body and are carried by the lymph stream into the lymph nodes. Roehrer (3), on the contrary, concludes from the study of his material that the hemorrhages and necrotic foci in the various parts of the lymph nodes are due to lesions in the blood vessels.

Normal Histology of Swine Lymph Nodes.—For an understanding of the lymph nodes in hog cholera it is necessary to consider the normal histological structure. Details will be found in papers by Richter (4) and Trautmann (5); the principal points are brought out in the diagrammatic sketch (Text-fig. 1). The arrangement of the swine lymph node is almost the reverse of that found in other mammals. The lymphoid tissue with its follicles and germinal centers is situated centrally, while the cell-poor substance, which corresponds to the medulla in the lymph nodes of other mammals, is located peripherally but extends in the form of cords into the lymphoid tissue. This cell-poor substance consists of a syncytial network containing numerous capillaries. The connective tissue framework is represented by trabeculae that are rarely connected with the capsule. In the trabeculae are found blood and lymph vessels. There are two sinus systems, one around the trabeculae and the other under the capsule.

The afferent lymph vessels, according to Trautmann (5), enter the node at the connective tissue plate, run through the trabeculae, and open into the peritrabecular sinuses. The lymph only reaches the cortical sinus after passing through the cell-poor substance, except in those rare instances in which the trabeculae come into contact with the cortex.

Lesions in the Lymph Node, Type 1.—There are only slight lesions in the parenchyma. They consist mainly of a separation of cellular and fibrillar elements caused partly by edema, partly, as mitotic figures indicate, by a multiplication of reticulum cells. The edema is most pronounced in the cell-poor substance, especially that immediately surrounding the blood vessels. In a few cases fibrin can be demonstrated in small amounts within the edematous areas. Other changes, occurring irregularly, are: slight perivascular infiltrations in the cell-poor substance, perivascular necrosis of various degrees, swelling and degeneration of reticulum cells, increase of eosinophilic leucocytes, local hyperplasia of lymphoid tissue. Follicles and germinal centers are usually enlarged in size but decreased in number. Peritracubular and cortical sinuses are entirely free from lesions, except for a slight endothelial desquamation, which may be normal. Trabeculae and capsule are edematous and in some areas show perivascula infiltration with lymphocytes and histiocytes. Perivascular hemorrhages and marked foci of necrosis are not seen in this stage.
Lesions in the Lymph Node, Type 2.—The most outstanding characteristic is the presence of hemorrhages in the cell-poor substance which usually lies in contact with the cortical and peritrabecular sinuses and is also found in cords within the lymphoid tissue (Text-fig. 1). In the latter tissue hemorrhages are not so pronounced. This peculiar distribution of the hemorrhages in the parenchyma explains the marbled gross appearance of such nodes. In fresh hemorrhages the erythrocytes are well stained, while in older ones they show degenerative changes and appear as cell shadows. In larger hemorrhagic areas with dense accumulations of erythrocytes the structures are often indistinguishable. The frequent
perivascular arrangement of smaller hemorrhages around changed capillaries and smaller arteries indicates that erythrocytes must escape from these blood vessels. In some instances, however, these vessels show only swelling and proliferation of endothelial cells. Hemorrhages are seldom seen around larger blood vessels even when pronounced lesions are present in their walls. It is remarkable that red blood corpuscles are not found in the peritrabecular and cortical sinuses in these stages even when present in the cell-poor substance in great numbers. In only a few cases do they contain a limited number of erythrocytes either free or phagocytized in sinus endothelium or reticulum cells. In addition to these hemorrhages, more or less marked necrotic foci originating from changed blood vessels may be present in an individual lymph node. These foci may be small, but sometimes, by fusing together, they become so large as to occupy considerable areas of the parenchyma and may be so extensive as to be seen with the naked eye. The distribution of the necrotic areas resembles closely that of the hemorrhages. Only occasionally does the necrotic process affect the sinus walls; as a rule, a narrow zone of normal tissue separates necrotic areas and sinuses (Fig. 1). Progressive necrosis involving trabeculae, capsule, and sinuses has been observed in only one case in which secondarily invading bacteria were present. No reactive segregation of necrotic tissue has been seen.

The changes of the remaining structures of the parenchyma correspond to those described in the lesions of Type 1. In the hemorrhagic areas there is a marked hemosiderosis and fatty degeneration of the reticulum cells, but not a striking increase in their number. In necrotic areas or in their immediate surroundings these cells likewise show fatty degeneration or are filled with phagocytized nuclear fragments. Focal hyperplasia of the lymphoid tissue is a rare finding; hyperplasia is found in the majority of cases. Follicles and germinal centers may be reduced in size and number or may be entirely lacking. The changes in the trabeculae and the capsule consist of edema, perivascular cell infiltration, slight hemorrhages, and small foci of necrosis associated with blood vessel lesions.

Lesions in the Lymph Node, Type 3.—Histologically these nodes show an advanced or final stage of the hemorrhagic infiltration found in the lesions of Type 2. Red blood corpuscles may be present in such numbers as to occupy almost the entire cell-poor substance as well as part of the lymphoid tissue. It is remarkable that even in such an advanced stage the peritrabecular and cortical sinuses may sometimes remain entirely free from red blood corpuscles. As a rule, however, the sinuses contain erythrocytes, often in such numbers as to distend the sinuses and rupture the reticular fibers. The presence of red blood corpuscles may cause atrophy of the lymphoid tissue to such an extent that only small islands remain.

These histological findings in the lymph nodes in hog cholera do not support Nieberle’s (2) theory of resorption as a complete explanation for the lesions found in these structures.
We feel that the blood vessel lesions (see Paper II of this series) especially those found in the cell-poor substance in the lymph nodes, must be considered the source of edema, hemorrhages, and progressive necrosis in various parts of the lymph nodes.

These findings are in agreement with those recently described by Roehrer (3). An explanation is required for the fact that the hemorrhages are more pronounced in the cell-poor substance than in other parts of the parenchyma. The discovery of Trautmann (5) that the cell-poor substance is a special channel for the passage of the lymph between the peritrabecular and cortical sinuses offers a satisfactory explanation. As soon as they have left the changed capillaries in the cell-poor substance the erythrocytes are carried along with the lymph stream and are distributed in the manner described (Text-fig. 1). When present in great numbers they may enter the sinuses and lymphoid tissue.

2. Spleen

Out of thirty autopsies, the spleen showed no lesions in eleven cases and in seven it exhibited hyperplasia which was not different from hyperplasia in other infectious diseases. In the remaining twelve cases anemic infarcts were present.

Recently David and Schwarz (6) emphasized the diagnostic significance of these infarcts. Shortly before our investigations were concluded, Roehrer (7) described histological details of these lesions.

Macroscopically these infarcts appear as dark red, sharply outlined, irregularly shaped foci distinctly protruding above the cut surface of the organ. Sometimes they are a quarter of an inch or more in diameter and they are usually located in clusters on the margin of the spleen. On cross-section they are sharply demarcated from the normal tissue and appear in various forms, the most usual being a wedge shape, the apex of which is orientated toward the hilus (Fig. 2). In addition to these marginal foci there are, in a number of cases, smaller areas of various sizes in the parenchyma similar to the marginal infarcts and likewise surrounded by a hemorrhagic zone.

The histological examination of a great number of these infarcts indicates that they are based on the typical blood vessel lesions, described in Paper II of this series. The most pronounced lesions are in the follicular arteries, especially at the apex of the wedge-shaped infarcts (Figs. 2, 3). Frequently the swelling and hyalinization of blood vessel walls is so enormous as to lead to more or less complete occlusion of their lumen. In some cases thrombotic material is also attached.
to the endothelium of such blood vessels. In other parts of the infarcts the blood vessels show exactly the same type of lesions. The parenchyma in their immediate neighborhood is found in various degrees of coagulation necrosis (Figs. 2, 3). In the early stages this necrotic process may be restricted to a single follicle but as a rule it extends to the entire infarct including pulpa, follicles, and trabeculae. Fibrin is missing. Hemosiderin is found in the changed blood vessel walls. Towards the hemorrhagic zone of the infarcts the necrosis of the parenchyma is less pronounced. In this area the reticulum contains numerous red blood corpuscles which form an intermediate zone between necrotic tissue and the peripheral hemorrhagic zone. However, this intermediate zone is sometimes entirely missing and in this case the necrotic tissue is immediately surrounded by a dense zone of erythrocytes which is most pronounced immediately beneath the capsule and which is often undergoing retrogressive changes. This explains the pronounced protrusion of the capsule in these areas as well as the destruction of the subcapsular parenchyma and sinuses.

The capsule itself shows in the early stages a slight thickening with a few hemorrhages while in later stages it may, in the infarct areas, become entirely necrotic.

The same infarcts are found in the parenchyma. Often only small microscopic necrotic foci are found. These extend from necrotic blood vessels, especially follicle arteries. In the parenchyma which is free from infarcts, and in spleens which show no gross lesions, slight blood vessel lesions of the type previously described can be demonstrated. They may be associated with perivascular hemorrhages or with slight perivascular necrosis. The most pronounced changes are: a more or less striking increase of pulpa cells, perifollicular hyperemia and hemorrhages of various degrees, infiltration of the Schweigger-Seidel's capillary tubes and trabeculae with red blood corpuscles, and striking aplasia of the spleen follicles.

To sum up it must be emphasized that the infarcts in the spleen in acute cases of hog cholera are caused by primary lesions of the follicular arteries leading to a more or less complete blocking of the circulation in the corresponding areas.

**B. Urinary Organs**

Although the gross anatomical appearance of the urinary organs, particularly the kidneys, in typical cases of hog cholera is well known, detailed histological information concerning the lesions in these organs is lacking.

According to Proescher and coworkers (8, 9), the lesions in the kidneys correspond to an acute hemorrhagic glomerular nephritis, combined with a tubular nephritis. In peracute hog cholera cases, Bel (1) has described lesions of con-
gestive nephritis with interstitial hemorrhages, changes in the glomeruli and convoluted tubules, proliferation of the endothelial cells and infiltration with mononuclear phagocytes, and scarcity of polymorphonuclear leucocytes. In acute and subacute cases he observed inflammatory reactions in the glomeruli, degeneration of the uriniferous tubules, perivascular infiltration, degenerative processes in the epithelial cells, and cuffs of mononuclear cells around the vessels. Littschwager (10) found microscopical hemorrhages in cases that did not show typical gross lesions in the kidneys.

Macroscopically, petechial and ecchymotic hemorrhages are found quite regularly under the capsule and rarely in the medulla and pelvis. However, in some cases there are so few hemorrhages that diagnosis from macroscopic examination alone is difficult if not impossible.

The ureter, bladder, and urethra often show subserous hemorrhages or hemorrhages on their mucous surfaces, but the gross lesions in these organs are far less common than in the kidneys.

**Interstitial Tissue.**—The small hemorrhages scattered through the cortex and through other parts of the kidneys in practically all cases are regularly associated with the changes in the walls of the affected capillaries. However, the extent of the hemorrhages does not always correspond to the extent of blood vessel injuries. The fact that they frequently occur near the point of entrance of small blood vessels into renal glomeruli (Fig. 4) and that they are often limited to such a distribution in early cases where other changes are not recognizable, suggests that primary injuries occur in the walls of small vessels at these points. Small subcapsular accumulations of blood have a tendency to spread laterally under the capsule so that in cases accompanied by severe hemorrhages a number of these combine to form large subcapsular effusions of blood. Numerous small hemorrhages occurring in the cortex infiltrate interstitial tissue masses of scarcely greater dimensions than glomeruli. Sometimes they are extensive and greatly diffused. Dense accumulations of red blood corpuscles frequently cause the tubules to be widely separated (Fig. 4) and in some areas to be compressed or even collapsed. In more extreme cases the normal structures of the kidneys are obscured by the predominance of erythrocytes. Edema is imperceptible in most cases though it is occasionally present. When present it is more pronounced around affected blood vessels, mainly in the medulla and adjacent cortex.

Not only edema and hemorrhages but also perivascular infiltrations with macrophages (histiocytes) and lymphocytes are seen in the more advanced stages of the disease (Fig. 5). The infiltrating cells, frequently showing degenerative changes, sometimes become so numerous and widespread as to obscure other structures. Necrosis of the interstitial tissues is often continuous with that of blood vessel walls, but necrosis as a result of infarct formation is not found. Proliferation of interstitial connective tissues, occasionally seen, appears to be an extension of the process taking place in the adventitia of the blood vessels. In general the capsule of the kidney shows no significant changes.
Renal Glomeruli.—Capillaries in the renal glomeruli often show the same degenerative changes in their walls as do capillaries in other parts of the kidneys. Hemorrhages in the renal glomeruli occur frequently even in the early stages of the disease process (Fig. 4). Proliferation of the glomerular epithelium is seldom observed. In two cases the renal glomeruli and other structures showed amyloid degeneration. Bowman's capsules exhibit hemorrhages much less frequently than one would expect. Sometimes degenerative changes in the renal glomeruli extend to and include the walls of the corresponding Bowman’s capsules. On the other hand, retrogressive changes of the cells lining Bowman’s capsules are observed where there are no appreciable changes in the corresponding renal glomeruli.

Tubules.—The tubular epithelium shows varying retrogressive changes in a great many cases (Figs. 4, 5). In a few instances the tubules contain red blood corpuscles and fragments of corpuscles. These may have been caused by hemorrhages in the renal glomeruli or, in advanced stages of tubular degeneration, by the extension of interstitial hemorrhages into the tubules (Fig. 5). In some areas the degenerative lesions of the tubules are so pronounced that the structures are no longer distinguishable in the homogeneous necrotic masses.

Ureters, Bladder, and Urethra.—In the few cases examined the walls of the ureters, bladder, and urethra showed lesions of the blood vessels, perivascular hemorrhages, and accumulations of round cells similar to those observed in the kidneys and in the lymph nodes.

C. Digestive Organs

1. Liver

In twenty-three cases examined fifteen showed vascular lesions some of which were associated with hemorrhages. Although these hemorrhages were noticed especially around the capillaries the structure of the liver frequently makes it difficult to define the boundaries of hemorrhagic areas or to associate them with definite blood vessel lesions. In addition, the necrotic process in the blood vessel walls extends into the surrounding structures including the parenchymatous tissue and produces lesions very similar to those found in the other organs. In only one case was the necrosis found to extend from the central vein to include up to one-half of the affected lobule (Fig. 6).

In a number of cases infiltration of the interlobular connective tissue with mononuclear cells or connective tissue proliferation was observed, especially around certain bile ducts and blood vessels, as described by Eberbeck (11). Their occurrence is not constant enough to indicate the action of the hog cholera virus in this organ.
2. Intestinal Tract

The intestinal tract was studied only in the early stages of the disease process and the same blood vessel lesions were found in the mucosa and, rarely, in the submucosa of the large intestine. Hemorrhages associated with them are as frequently observed as in other organs but foci of necrosis are seldom seen in the early stages of the disease. Hemorrhages are also found around blood vessels and capillaries that show no visible changes. Frequently the capillaries between the glands in the mucosa are enormously dilated and filled with red blood corpuscles. In addition to these lesions there are slight degenerative changes in the epithelial cells, slight edema in the connective tissue, and frequently an accumulation of round cells around the blood vessels in the mucosa, less frequently in the submucosa. In a few cases leucocytes are present in great numbers in the ducts of the glands. Necrosis which sometimes is present extends from changed blood vessels and seems to lead to the formation of ulcers. The study of typical larger ulcers in the intestinal tract is not included in this work.

D. Remaining Organs

The remaining organs, notably the lungs, heart muscle, endocrine glands, and skin, were not included in routine examination because in general they are not the site of typical lesions in this disease. However, in a number of cases in which these organs were studied the same blood vessel lesions were found. Hemorrhages in the skin are not always associated with visible blood vessel lesions. Bronchopneumonic areas in the lungs were seldom present in our material.

DISCUSSION

From this study it is evident that the blood vessel lesions described in the previous paper of this series are responsible in great part for the characteristic pathological picture of this disease. Not only the hemorrhages but also the foci of necrosis in the various organs and the anemic infarcts in the spleen find a logical explanation on this basis. The various organic lesions described in this paper are essentially the result of the more or less pronounced hemorrhages. Frequently inflammatory processes in various degrees, as found in the lymph nodes and kidneys, have complicated the histological picture. It must
be admitted, however, that frequently hemorrhages are found around blood vessels that do not show visible changes. On the other hand, even pronounced blood vessel lesions are not always associated with perivascular hemorrhages.

It is important to note that the duration of the disease in general does not determine the type of lesions found in the various organs. Often the course of the disease is so rapid that very severe lesions are found at earlier stages than one would expect. Roehrer (7) believes that the occurrence of splenic infarcts decreases with the length of the disease. However, this observation is not in accordance with our experience. No fundamental difference can be distinguished between the histological lesions in cases of hog cholera produced by virus alone and those complicated by secondarily invading bacteria. While we feel, in agreement with Roehrer (3, 7), that the number and the necrotic character of the lesions in the various organs are not dependent on the presence of secondarily invading bacteria, nevertheless, they are influenced to a certain degree by these organisms. This holds true especially for the lymph nodes, spleen, kidneys, and intestinal tract. In addition, the degree of degenerative changes, especially in the lymph nodes and kidneys, is evidently influenced by compression resulting from large accumulations of red blood corpuscles and round cells. Marked atrophy of the lymphoid tissue in the lymph nodes and spleen frequently seems to be due to the same cause. On the other hand the decrease of lymphoid cells and atrophy of follicles and germinal centers is often present in cases in which hemorrhages are not pronounced. These lesions in the lymph nodes and spleen seem to account for the lymphopenia which is almost always present in virus hog cholera. We are under the impression that the hog cholera virus is able to paralyze the lymphopoiesis in the early stages of the disease, hyperplasia of the lymph nodes and spleen being found very rarely and only in the early stages.

In connection with postmortem diagnosis, the following new observations in the histopathology of acute hog cholera demand consideration: first, the hog cholera encephalitis (see Paper I of this series), and second, the vascular lesions and the lesions in the various organs resulting from them. Waldmann, Roehrer, and Eberbeck (12) emphasize the presence of the encephalitis. We believe, however,
that the diagnostic value of hog cholera encephalitis is a limited one because it occurs in only 60 to 80 per cent of the cases and because it is still questionable whether it is strictly specific for this disease. As we have shown, there is the possibility of confusing hog cholera encephalitis and meningitis with the brain lesions occurring in swine influenza and with similar inflammatory processes of unknown nature as described by Ehrlich (13), Fekete (14), Doyle (15), Bendinger (16), and others. According to our present experience, the diagnosis of hog cholera cannot be based on the presence of an encephalitis alone. We feel that the vascular lesions and the changes resulting from them (especially in the lymph nodes, kidneys, and spleen) are far more important since they are almost invariably present. When present the splenic infarcts are of diagnostic value; but they are found in only 40 to 60 per cent of the cases.

In our work the histology in the various organs was very helpful in establishing a diagnosis in a number of cases in which the nature of the disease was doubtful from the gross anatomical lesions. Further investigation must show whether or not these changes can be relied upon in making a diagnosis of hog cholera.

SUMMARY AND CONCLUSIONS

1. The hemorrhages, foci of necrosis, and anemic infarcts met with in the various organs in virus hog cholera, result primarily from the vascular lesions described in a previous paper of this series. Although they are not dependent on the presence of secondarily invading bacteria, their severity is influenced by these organisms.

2. The lesions in the lymph nodes, spleen, kidneys, and central nervous system seem to be of special diagnostic value in questionable cases of hog cholera. The presence of an encephalitis alone does not justify the diagnosis of hog cholera because in the central nervous system of swine similar inflammatory lesions occur in other diseases.

REFERENCES


EXPLANATION OF PLATES

PLATE 23

Fig. 1. Necrotic blood vessels and large necrotic areas in the cell-poor substance of a lymph node. The sinus and peritrabecular tissue is not affected by the necrosis. Hematoxylin-eosin. × 220.

Fig. 2. Necrotic marginal spleen infarct with peripheral hemorrhagic zone. Atrophy of lymphoid tissue in the other parts of the spleen. Hematoxylin-eosin. × 12.

PLATE 24

Fig. 3. Apex of necrotic spleen infarct with occluded lumen of a small artery. Hematoxylin-eosin. × 245.

Fig. 4. Hemorrhages in a renal glomeruli and in the interstitial tissues, and degenerative changes of the tubules. Hematoxylin-eosin. × 220.

PLATE 25

Fig. 5. Perivascular infiltration with macrophages and lymphocytes in the kidney. Hematoxylin-eosin. × 260.

Fig. 6. Extensive necrosis in the neighborhood of a central vein in the liver. Hematoxylin-eosin. × 300.
(Seifried and Cain: Histological studies on hog cholera. III)
(Seifried and Cain: Histological studies on hog cholera. III)