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SYSTEMS OF CATTLE AFFECTED WITH
MUCOSAL DISEASE.

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PATHOLOGY OF THE BLOOD-VASCULAR AND
LYMPHATIC SYSTEMS OF CATTLE AFFECTED WITH MUCOSAL DISEASE

by

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A Dissertation Submitted to the
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1960

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INTRODUCTION*

In 1953 Ramsey and Chivers reported an apparently new disease syndrome in Iowa cattle. They proposed the name "mucosal disease" for this syndrome because the most striking gross lesions were confined to the mucosa of the alimentary canal.

Reports of similar disease conditions have been recorded previously and many reports have appeared since that time. In a majority of these reports there seemed to be considerable variation in the lesions observed while the signs were somewhat more constant. A severe diarrhea has been the most prominent sign observed in many of the reported conditions.

In the past few years there has been a tendency to apply the name "mucosal disease complex" or more loosely, simply "mucosal disease" to this group of diseases.

A partial list of the most important members of the mucosal disease complex follows:

X-disease of cattle-Saskatchewan. (Childs, 1946)

Virus diarrhea-New York. (Olafson et al. 1946)

Mucosal disease-Iowa. (Ramsey and Chivers, 1953)

Virus diarrhea-Indiana. (Pritchard et al. 1956)

Muzzle disease. (Hollister et al. 1956 and Scheidy et al. 1956)

Infectious bovine ulcerative stomatitis. (Pritchard et al. 1958)

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A study of the clinical signs and gross lesions makes it apparent that this group of diseases is very similar to the dreaded foreign disease, rinderpest. Yet it has been shown that these diseases are not forms of rinderpest (United States Agricultural Research Service, 1956). However, the possibility that rinderpest could be introduced and widely disseminated in this country before an absolute differential diagnosis could be made should be borne in mind.

Mucosal disease as described by Ramsey (1956) is the syndrome of the so-called mucosal disease complex which is most similar to rinderpest. The similarity, particularly of gross lesions observed, is striking. It has been said by some authorities on "old world diseases" that "mucosal disease looks more like rinderpest than rinderpest itself."

The specific cause of mucosal disease has not been unequivocally established. It is thought by many research workers to be a virus. Other workers suggest the possibility that it might be a manifestation of a stress reaction or a combination of stress and a viral agent or agents.

It is known that rinderpest is caused by a virus and that the virus has a specific affinity for epithelial and lymphoid tissue. Severe destruction of lymphoid tissue has been reported in rinderpest affected cattle. There is also a severe leukopenia resulting primarily from a lymphopenia.

Ramsey (1956) observed that changes of a variable severity occur in the lymphatic tissue of the small intestine

and mesenteric lymph nodes in animals affected with mucosal disease. He also noted degenerative changes in the vascular system of some animals. His work, although extensive, did not include a detailed study of the blood-vascular and lymphatic systems.

It was therefore felt that a critical study of the blood-vascular and lymphatic systems of Iowa mucosal disease might serve as an aid in the differentiation of the members of the mucosal disease complex and rinderpest. Further, this study should lead to a better concept of the pathogenesis of Iowa mucosal disease.

REVIEW OF LITERATURE

Childs (1946) reported on X-disease of cattle in Saskatchewan. Only gross lesions were described and were very similar to those observed by Ramsey (1953 and 1956). Ramsey (1956) concluded that mucosal disease in cattle in Iowa and X-disease of cattle in Saskatchewan were probably the same disease.

Childs (1946) described the lymph nodes as being mildly swollen, pale in color and granular on section. A slight hemorrhagic streaking was noted in the lymph nodes draining the areas of the alimentary mucosa which were most severely affected. The spleen was noted to have an area one by three inches in its center which was markedly thickened and quite dark in color. Childs felt that this was an area of thrombosis. He also noted an apparent decrease in blood volume, even falling as low as twenty percent of the normal. The blood was bright red in color and had a rapid clotting time.

A severe diarrhea was the most prominent and consistent sign observed by Childs.

Olafson et al. (1946) and Olafson and Rickard (1947) described an apparently new transmissible disease of cattle which was characterized clinically by a severe diarrhea, rapid loss of condition and a severe drop in milk production. It was noted that abortions commonly occurred following an outbreak of this disease. Olafson and Rickard (1947) named this condition virus diarrhea. Since that time, this condition

has become widely known as virus diarrhea-New York. Prominent gross lesions observed were marked dehydration and ulcerations on the dental pad, palate, lateral surfaces of the tongue, around the incisor teeth and on the inside of the cheeks.

Less consistent lesions included ulcerations or diffuse necrosis of the pharyngeal mucosa, in some cases necrotic areas in the larynx, irregular, shallow, punched out ulcers or necrotic foci in the esophagus and a diffuse reddening or petechial hemorrhages and a few ulcers in the abomasum.

Olafson et al. (1946) also noted that the mucosa of the small intestine might be diffusely reddened but, "In general, the intestinal lesions are less severe than one would expect from the symptoms." Petechiae and small ulcers were present in the cecum. There was no report of the histopathology on this group of cases.

Olafson et al. (1946) observed a severe leukopenia in some animals in the affected herds. The total leukocyte counts in some cases being as low as 450 cells per cubic millimeter.

Hedstrom and Isaksson (1951) described an epizootic enteritis in cattle in Sweden and suggested that it might be related to virus diarrhea-New York. The authors stated that "besides acute catarrhal enteritis no remarkable changes were found on post-mortem examination." It was believed by Ramsey (1956) that this was not mucosal disease.

Mucosal disease was the name applied to a disease syndrome

described by Ramsey and Chivers (1953) and Ramsey (1954 and 1956). These reports described in detail the history, clinical signs and gross and microscopic lesions observed in numerous cases. The gross and microscopic lesions will be reviewed here for the purpose of comparison with the lesions observed in other reports.

Erosions and ulcers occurred on the muzzle, lips, tongue, gingivae, pharyngeal mucosa, hard palate, buccal mucosa, esophagus, rumen and omasum. Erosions and ulcers were not present in the same locations in all animals. Ramsey (1956) described the approximate frequency of erosions and, or, ulcers in the various locations as 80 percent in muzzle and nares, 66 percent in the mucosa of the oral cavity, over 90 percent in the esophagus, frequently on the rumen pillars but throughout the rumen mucosa in only 10 percent, many times in the omasum and regularly in the abomasum.

Ramsey (1956) stated that gross lesions were consistently present in the small intestine, cecum and colon. Lymph nodes showed no gross lesions or were only slightly edematous. In some cases the mesenteric, retropharyngeal and cervical lymph nodes were slightly to moderately swollen and hyperemic. Gross observation of the hemal nodes and spleen revealed no striking changes.

Microscopic study of the stratified squamous epithelium of the upper digestive tract showed that most of the lesions were of a similar nature. Degenerative changes occurred in

all layers of the epithelium. In some cases the necrosis extended from the surface to the basal layers of the epithelium, while in other cases, necrosis of basal layers was observed without surface involvement. Ramsey (1956) pointed out that the latter observation may be a false impression due to the plane at which the lesion was sectioned.

Vacuolization of cell cytoplasm was observed primarily in the stratum spinosum but occurred to some extent in the stratum germinativum. A breakdown of intercellular bridges appeared to be the initial change. Later, increased cytoplasmic fluid caused the cells to enlarge and form small vesicles. The vesicles coalesced and the surface epithelium became detached which left superficial or deep erosions. In some cases secondary bacterial invasion took place and ulcers were formed. Inflammatory reaction was generally minimal but did occur when bacteria were present.

Microscopic examination of the abomasum showed that many of the lesions which appeared to be ulcers on gross examination were actually atrophic cystic glands. These glands were filled with desquamated epithelial cells and leukocytes. In some instances ulcers were observed. Marked edema of the lamina propria and submucosa with some leukocytic infiltration, increased numbers of leukocytes in some blood vessels, hyperemia and hemorrhage were also observed on microscopic examination.

Histopathological alterations of the intestinal mucosa

were congestion, hemorrhage, defects of the epithelial lining and degenerative changes of the lymphoid tissue. Ramsey stated that Peyer's patches consistently exhibited lesions varying from complete disappearance of lymphocytes to varying degrees of necrosis of lymphoid tissue. Large amounts of mucus occurred in many of the crypts, often causing pressure atrophy of the glands and being most marked in the mucosa over Peyer's patches. This confirms the gross observations of excessive accumulations of mucus in the regions of Peyer's patches noted in some animals.

In numerous cases lymphoid tissue necrosis was observed in the submucosa immediately underlying some intestinal glands. Beginning ulcers were often noted at the bases of the crypts. Lesions in the large intestine were similar to those described for the small intestine.

Numerous pathological alterations were noted in the lymph nodes. These included a decrease in mononuclear cells of the cortex, the presence of cellular debris and phagocytosed blood pigments in the medulla of many lymph nodes, coagulative necrosis of lymph nodules and the presence of excessive numbers of neutrophilic leukocytes in blood vessels and lymph sinuses in some mesenteric nodes. Occasional infiltration by eosinophilic leukocytes was sometimes observed.

Ramsey (1956) stated that the hemolymph nodes showed no marked changes.

A consistent marked decrease of lymphocytes and irregular

necrotic foci were noted in the spleens of many cases. In these foci karyorrhex had occurred with the nuclear debris being phagocytosed by macrophages. Occasionally a distinct, focal eccentric coagulative necrosis of some of the Malpighian corpuscles was observed.

Subepicardial and subendocardial petechial and ecchymotic hemorrhages were seen in some animals. Uneven staining and difficulty in discerning cross striations in cardiac muscle were the lesions observed microscopically.

Segmental degeneration of the media in some arteries, a focal periarteritis and a diffuse arteritis were noted.

Hyperemia, hemorrhage and edema in the lamina propria of the abomasum and intestine, with thrombosis of vessels noted in the submucosa of areas where ulceration had occurred, were also reported. Hyaline-like emboli of small arterioles of the abomasum and intestine were seen in some cases.

Hematologic studies made by Ramsey (1956) indicated that increased erythrocyte counts were common especially in the later stages of the disease after pronounced dehydration had taken place. Total leukocyte counts were low in many animals but a pronounced leukocytosis was observed in numerous animals at the height of clinical signs. Ramsey (1956) stated that "differential leukocyte counts indicated a decided neutropenia." Blood urea nitrogen levels of 100 to 300 milligrams percent were observed in the terminal stages of the disease and were thought to be associated

with the hemoconcentration and dehydration.

Nielson et al. (1955) described a mucosal disease of cattle in Ontario, Canada. Only gross pathology is discussed and the lesions that they observed were variable. In some of the animals they noted a rather prolonged course and it was in these animals that intestinal lesions were not observed. Erosions in the mucous membrane of the oral cavity and esophagus were seen in all cases. Enlarged lymph nodes were observed in some animals. The authors state that in the first cases observed they had made a diagnosis of virus diarrhea but had changed it to mucosal disease because of morbidity rates and transmissibility.

Nielson et al. noted that hematological examinations indicated that a leukocytosis was present even though blood samples were taken in the early stages of the disease. Total white blood cell counts ranged from 14,450 to 24,600 per cubic millimeter.

Schipper et al. (1955) described a mucosal disease of cattle in North Dakota. Erosions and ulcers on the tongue, hard and soft palates, esophagus and in some instances in the rumen were noted. They stated that a catarrhal or fibrino-necrotic enteritis was always present with lesions being particularly evident in the pyloric, ileocecal and rectal areas. Erosions, ulcerations and various degrees of hemorrhage throughout the intestinal tract were seen. The lymph nodes were described as being soft and edematous and the hemal nodes

were usually enlarged and dark red.

Schipper et al. (1955) noted other gross lesions that were not reported by Ramsey, Nielson or Childs. They were enlargement of the gall bladder with a thickening of the wall, cholecystitis and cholangitis, in some instances fibrinous tracheitis, and frequently a pneumonia. Another interesting observation by Schipper et al. (1955) on impression smears of the brain was the presence of inclusion bodies "similar to those observed in rabies specimens." They also state that large numbers of coccidial oocysts and ova from several species of nematodes were present in the feces of all cases.

Histopathological studies were not reported by Schipper et al. (1955). The presence of large numbers of coccidia reported and the pseudomembranes in the trachea tend to make one wonder if some of the cases may have been coccidiosis or malignant catarrhal fever.

Pritchard (1955) described and compared some of the members of the mucosal disease complex. His description of mucosal disease is very similar to that of Ramsey and Chivers (1953) and Ramsey (1954 and 1956). He states that "a characteristic pathological change is ulceration which occurs in the intestinal mucosa over Peyer's patches." The presence of a large quantity of mucus adhering to the intestinal mucosa was noted. Subepicardial hemorrhages and edema and hemorrhages of the lymph nodes were observed.

Hematological studies (Pritchard, 1955) revealed that

leukopenia was present early in the course of the disease, but when clinical signs were marked many animals had developed a leukocytosis. No striking change was noticed in differential leukocyte counts. A marked hemoconcentration was seen in the later stages of the disease.

Pritchard (1954-1955) and Pritchard et al. (1956) described a disease syndrome of Indiana cattle that was clinically similar to virus diarrhea-New York. Because of this similarity the condition was named virus diarrhea-Indiana. The clinical signs noted were fever, nasal discharge, cough, erosions of the oral mucosa, lameness and a severe diarrhea.

Erosions of the oral mucosa and lameness were observed in about ten percent of the cases. The morbidity rate approached 100 percent in most herds and the mortality rate varied from two to fifty percent. The characteristic hematological findings included a severe leukopenia with the development of a relative lymphocytosis during the later stages of the leukopenia. It was reported that no alteration occurred in the sedimentation rate (Pritchard, 1954-1955).

The gross lesions observed by Pritchard et al. (1955) and Pritchard et al. (1956) and Carlson et al. (1957) in field cases were very similar to those which occurred in experimental cases. Congestion, hemorrhages and erosions of the mucosa of the digestive tract were the usual gross lesions encountered, but all portions of the digestive tract were not involved to the same extent in all animals. Erosions were

noted in the oral mucosa, pharynx and esophagus in about fifty percent of experimental cases and about ten percent of the field cases. Grossly visible erosions were observed in the abomasum of less than fifty percent of the experimental cases and in only some of the field cases. Congestion, hemorrhage and edema of variable degrees were noted in the abomasums of all acute and chronic cases. Almost all animals exhibited a catarrhal enteritis which was most severe in the duodenum. Congestion, hemorrhage and edema of the mucosa and necrosis of the tips of the villi were common findings. Edema of the Peyer's patches was frequently encountered as evidenced by their visibility through the serosal surface of the ileum.

Palpable lymph nodes were enlarged in about fifty percent of the cases, while Peyer's patches and lymph nodes of the abdominal viscera were enlarged in about ninety percent of the acutely affected animals. In an occasional animal with a natural case of virus diarrhea-Indiana hemorrhage and congestion of the lymph nodes of the abdominal viscera were noted. The spleen and hematopoietic system were normal according to gross observation.

The principal lesions of the heart were subepicardial and subendocardial hemorrhage and atony of the myocardium.

The changes observed in the respiratory tract, primarily in field cases, consisted of congestion of the nasal cavity, larynx and trachea. At times, edema around the larynx and

of the trachea were observed.

Consistent, significant changes were not found in the urogenital, nervous, endocrine, skeletal or integumentary systems.

Carlson et al. (1957) reported that histopathological changes of the mucosa of the digestive tract seemed to be of the same general nature. In the stratified squamous epithelium the changes consisted of necrosis and sloughing of the more superficial layers. Initial necrosis of cells immediately above the germinal layer did occur and this was similar to changes observed in rinderpest (Maurer et al. 1955). Microscopic lesions in the abomasum and the large and small intestines were reported to be of a very similar nature. They consisted of an edema of the mucosa with loss of surface epithelium. In the small intestine a pronounced widening of lymph spaces and an edema between the epithelium and stroma of the villi appeared.

Carlson et al. (1957) reported that histological examination of lymph nodes from acutely affected experimental animals revealed that lymphoid "exhaustion" and edema were present in sixty percent of the cases. In some instances, a majority of the lymphoid follicles were depleted while in other cases, only a few of the follicles were affected. The spleen also exhibited a depletion of cells in the germinal centers. Occasionally, necrotic foci were observed in both the spleen and lymph nodes. The foci were reported to be associated

with, but did not appear to involve an entire germinal center.

Carlson et al. (1957), in comparing the lesions of virus diarrhea-Indiana to field cases of mucosal disease, stated that the changes seen in virus diarrhea-Indiana were of a much milder nature than those observed in mucosal disease. The histopathological and gross changes reported were essentially the same as those described by Ramsey (1956).

These findings of Carlson et al. (1957) support the earlier statement made by Pritchard (1955) that the differences in the three conditions, mucosal disease, virus diarrhea-New York and virus diarrhea-Indiana, were differences of degree rather than differences in kinds of signs and lesions.

Dow, Jarrett and McIntyre (1956) and Jarrett (1958) have described a disease syndrome in Britain which resembled the virus diarrhea--mucosal disease complex. Lesions were reported to be quite variable in severity and extent. Buccal ulcerations were seen in all cases. Erosions and ulcers of the esophagus and rumen were also common findings. Ulceration of the abomasum was frequently observed.

In animals that died after a prolonged diarrhea, enteritis was usually noted at necropsy. The degree of enteritis ranged from irregular superficial erosions which occurred every six to seven inches along the small intestine, to intense congestion and desquamation of the necrotic mucous membrane. It was stated that the latter process appeared to start in the Peyer's patches. In many animals the intestine appeared

normal. The alimentary lymph nodes were moderately enlarged and edematous but this was not a constant finding. Histological examination of lymph nodes revealed a non-specific cortical lymphocytolysis.

A persistent leukopenia affecting all types of leukocytes was observed in some animals, but this was not constant.

Erosions, papules and ulcers were frequently observed in the interdigital cleft. Abortions were seen on two occasions.

This condition resembles virus diarrhea-New York more closely than it does mucosal disease as described by Ramsey (1956).

Swope and Luedke (1956) reported a so-called mucosal disease in cattle in Pennsylvania. Changes of the stratified squamous epithelium consisted of hypertrophy, vacuolation, and degeneration. On the tongue papillary projections of the epithelium into the underlying connective tissue were observed. Some of the vacuolated epithelial cells in the esophagus were reported to contain acidophilic inclusion bodies. The abomasum exhibited glandular hyperplasia and dilatation of the crypts of gastric glands. Cystic dilatation of the glands of Lieberkuehn and Brunner occurred in the duodenum. The kidney presented a picture of cystic dilatation of the collecting tubules and interstitial fibrosis. The mucosal glands of the gall bladder and the maxillary sinus also showed cystic dilatation. Fibrosis of the liver was noted.

Seibold (1956) described the gross and microscopic lesions

of the alimentary canal of nine animals affected with mucosal disease in Alabama. He observed that the lesions appeared to be particularly severe in the mucosa covering Peyer's patches of the ileum. On histological examination he noted that the intestinal glands were destroyed and "atrophy" of the lymphoid tissue of Peyer's patches had taken place. No mention was made of other lymphoid tissue or the vascular system. The changes of the various portions of the digestive tract were the same as those reported by Ramsey (1956).

Hollister et al. (1956) and Scheidy et al. (1956) reported the occurrence of "muzzle disease" in Pennsylvania. The conditions described by the two groups were very similar and probably should be considered as a single disease.

Gross lesions consisted of erosions of the epithelium of the external nares, muzzle, dental pad, gums, dorsal surface of the tongue, esophagus, skin of the underline, teats, scrotum or vulva and at the coronary band. Petechial hemorrhages, erosions and, at times, ulcers were scattered throughout the small and large intestines. These lesions were reported to be the most consistent and the most severe in the cecum and first part of the colon.

Hollister et al. (1956) stated that diarrhea was "an infrequent sign" but was seen in fatal cases. They also reported that the hematological findings were within the normal range except in animals which had extensive purulent discharges. In these cases a neutrophilia and a leukocytosis

occurred.

This condition resembles very much so called "mycotic stomatitis." (Hutyra and Marek, 1926).

Richards et al. (1956) observed a "mucosal disease" of deer in North Dakota. It was stated that "the term mucosal disease as it relates to deer is used in the broad sense and may include any of those new cattle diseases that affect the mucosae of the body." In the deer, erosions, ulcerations or hemorrhages of the tongue, dental pad, palates and lips were conspicuously absent.

The respiratory tract appeared to be normal in most cases.

Severe gastritis was observed in most cases, but ulcerations were not seen in several animals. Varying degrees of catarrhal enteritis were present in all deer examined. Small ulcerations were scattered throughout the small intestine in severe cases. Hemorrhage and necrosis were most severe in the duodenum and jejunum and decreased in severity in the ileum, cecum, colon and rectum. Epicardial hemorrhages were noted in a few cases. A mild to severe cystitis was present in all cases. Mild to severe coccidial infections were noted in many cases.

No report of the histopathology was available. This report was the only one in which "mucosal disease" has been recognized in any species other than the bovine.

Hoag et al. (1956) and Rooney (1957) reported a mucosal-

type disease in cattle in Virginia. The gross lesions were somewhat different than those described by Ramsey (1956), in that Peyer's patches were not involved, liver lesions were present in ninety percent of the cases and interdigital erosions were present in all cases of the disease observed.

The histopathology of the lesions in the stratified squamous epithelium was not markedly different than that observed by Ramsey (1956). Lesions consisting mainly of hyperemia, hemorrhage and edema in the abomasum, small intestine and colon were reported to be mild, scattered and focal in nature. Necrosis of the epithelial lining of the abomasum was regularly found. Crypt abscesses were noted in both the abomasum and small intestine. Rooney stated that significant lymphorrhexis was observed in one Peyer's patch in one animal. Fatty degeneration of the liver was noted in all but one of the animals. The distribution of fat in the lobule followed no specific pattern.

The kidneys showing gross lesions presented the histological picture of anoxic or lower nephron nephrosis.

The spleen presented a highly variable histological picture although no gross lesions were found. There was usually some lymphocyte depletion and perifollicular hyperemia. Megakaryocytes, neutrophils and hemosiderophages were present in moderate numbers in the perifollicular areas. Significant lesions were observed in only the suprapharyngeal, bronchial and mediastinal lymph nodes. These lymph nodes were affected

only when they were draining necrotic and/or suppurative areas. Edema, the presence of numerous reaction centers and neutrophil packing of the capsular and medullary sinuses were the lesions noted on microscopic examination. The thymus was identified as a remnant in only one animal and microscopically was hyperemic, hemorrhagic and almost devoid of thymocytes. An acute suppurative pneumonia and a bronchitis were observed in many cases.

Microscopic changes were not found in the heart, blood vessels, or in the brain.

Schipper and Eveleth (1957) reported a mucosal disease in North Dakota calves. The disease was seen in calves which were dead at birth and also in calves which died within the first few days of life. The gross lesions consisted primarily of hemorrhages, edema, and necrosis of the alimentary canal. In this report the presence of "an area of necrosis and hemorrhage adjacent to the ileocecal valve" was stressed. No mention was made of localization of lesions in the Peyer's patches of the small intestine. Small foci of necrosis and hemorrhages were found in the mucosa of the gall bladder.

No other reports of the presence of mucosal disease in calves were found in the literature.

Huck (1957) reported the occurrence of a disease of cattle in England which was considered to be a member of the mucosal disease complex. Diarrhea, anorexia, polydipsia and encrustation of the muzzle were the clinical signs most

frequently noted. Gross lesions varied from a mild catarrhal enteritis to a severe hemorrhagic gastroenteritis with ulceration that, at times, extended from the oral cavity to the rectum.

Huck (1957) found erosions and ulcers on the lips, hard palate, tongue, around the base of the teeth and in the esophagus. In some animals discrete hemorrhages and ulcers were found in the abomasum. The lumen of the small intestine commonly contained a thick, tenacious and blood-flecked mucus. Peyer's patches were dark and congested. A "striping" effect caused by hemorrhage was found in the large intestine and rectum. Lymph nodes were enlarged, edematous, and of a cherry red color. He reported that the hemolymph nodes were also prominent. Occasional interdigital ulcerations were the only other lesions found. Histopathologic findings were not reported.

Blood et al. (1957) reported a mucosal disease of cattle in Australia which was very similar if not identical to that described by Ramsey (1956).

Pritchard et al. (1958) reported the occurrence of an apparently new disease of cattle in Indiana. The principal lesions were confined to the oral cavity and esophagus and were of an ulcerative type. The name "infectious bovine ulcerative stomatitis" was applied to this condition. The relationship to the mucosal disease complex is unknown. About the only similarity between infectious bovine ulcerative

stomatitis and the other members of the mucosal disease complex is the presence of ulcerative lesions in the oral cavity. Diarrhea and/or gastrointestinal lesions have not been described in this condition.

Voss (1959) reported a mucosal disease in cattle in Germany. The description of the gross lesions observed was brief and extensive histopathology was not reported.

Erosions and ulcers were noted on the lips, tongue, hard palate and buccal cavity. Hyperemia of the abomasum and a catarrhal enteritis with focal hemorrhagic necrotic duodenitis and jejunitis were found. A severe hyperemia of the nasal mucosa and an excess of cerebrospinal fluid were present. A profuse bloody diarrhea, anorexia, lameness, conjunctivitis, keratitis and panophthalmia were noted. The author stated that the disease belonged to the mucosal disease complex but did not suggest which one of the syndromes it resembled the most.

McCormack et al. (1959) described a disease condition in South Australia which did not closely correspond to either of the viral diarrheas or mucosal disease-Iowa.

In many of the animals, McCormack et al. (1959) observed very few gross changes with the exception of those due to emaciation. Usually erosions and ulcers were present on the buccal mucosa, lips, cheeks, ventral surface of the tongue and the esophagus. Varying degrees of inflammation of the mucosa and edema of the submucosa were observed in the abomasum of

nearly all cases. The degree of inflammation of the small intestine was highly variable. In some cases, apparently normal areas alternated with intensely inflamed areas of two to three inches in length. Occasionally the entire length of the small intestine was severely affected and contained flecks of blood. Microscopically a catarrhal enteritis accompanied by necrosis was the usual feature. Often, very little polymorphonuclear reaction accompanied the necrosis. It was noted that "the excessive mucous secretion and collection of glairy mucus in the intestine as described by Ramsey and seen in the Sydney cases (Blood et al., 1957) was not present in any of our material." Necrosis and other changes in Peyer's patches were not mentioned in this report.

Edema was present in the mesenteric lymph nodes of all cases but the nodes were either normal in size or slightly swollen. Histopathological studies of the mesenteric lymph nodes showed that invariably a "sinus catarrh" and frequently a marked involution had occurred.

The authors felt that, because of the age incidence and mortality rate, this condition did not belong in the viral diarrhea category. They concluded that the condition did not closely correspond to mucosal disease because of the absence of erosions on the dorsum of the tongue, lack of excessive mucous production in the small intestine and differences in infectivity rate and case mortality. It was mentioned that it was not clearly evident whether all of the cases

investigated were the same or different disease entities.

Schulz (1959) described the pathology of a mucosal disease of cattle in Germany. The gross and microscopic lesions were almost identical to those described by Ramsey (1956). It was noteworthy that Schulz consistently found gross and microscopic lesions in Peyer's patches. An involution of the spleen and lymph nodes was observed.

Stöber (1959) worked with the same group of cattle as Schulz and described the symptomatology. He observed that a severe leukopenia did not occur in the animals he studied. He reported a relative lymphocytosis in the early stages of the disease but noted a neutrophilia with a shift to the left as the disease progressed. Stöber (1959) believed that the shift to the left was due to secondary bacterial infection. An increase in the total leukocyte and erythrocyte counts and hemoglobin concentration were found. It was suggested that some of the increases may have been due to the severe dehydration which occurred as the animal approached death. Schulz (1959) and Stöber (1959) concluded that this disease in Germany was the same as mucosal disease described by Ramsey (1956).

MATERIALS AND METHODS

Histological Procedures

It is obvious that much confusion exists in the literature concerning the pathology of a mucosal disease. In the present study materials were collected only from those animals that evidenced the gross lesions described by Ramsey (1956).

The presence of visible lesions in Peyer's patches was the main criterion used in the selection of materials.

Material was collected from the affected animals that were submitted to the Stange Memorial Veterinary Clinic at Iowa State University between January 11, 1957 and December 24, 1959. Materials were collected from four animals before the research project was selected for this study. Comparable tissues from twenty apparently normal cattle were obtained from the Iowa State University meats laboratory and served as controls.

Materials from sixty-four cases of mucosal disease were available for histopathological study. Thirty of the moribund animals were sacrificed by electrocution. Two animals were destroyed in the early stages of the disease. Tissues were collected from thirty-two animals that died during the natural course of mucosal disease. In the latter cases necropsies were performed and tissues were collected within three hours after death with the exception of seven animals that succumbed during the preceding night.

Tissues collected for histopathological study included various portions of the lymphatic and cardio-vascular systems. Representative samplings of the mesenteric lymph nodes and the prescapular, suprapharyngeal, bronchial, prefemoral and parotid lymph nodes were taken from each animal. The internal iliac and the superficial inguinal lymph nodes were also collected from some animals.

Specimens were collected from Peyer's patches, abomasum and spleen in all animals. From many animals portions of the thymus, tonsils and hemal nodes were collected.

The tissues of the cardio-vascular system that were routinely taken included cardiac muscle, thoracic dorsal aorta, abdominal aorta one inch anterior to the origin of the internal iliac arteries, the umbilical, the internal iliac, internal pudic, external iliac, middle uterine, brachial, external maxillary and common carotid arteries. A section of the femoral artery was collected at a point three to four inches distal to its emergence from the femoral canal. The corresponding veins were collected in the cases of peripheral arteries. A portion of the posterior vena cava was collected from the same level as the abdominal aorta. Sternal bone marrow from the first four sternebrae was cut into blocks approximately five to ten millimeters in thickness before fixation.

Tissues from fifty-six of the animals were fixed in ten percent buffered formalin (Armed Forces Institute of Pathology, 1957). Materials from eight animals were fixed in mercury-

formol-saline (Dawson and Friedgood, 1938). In five animals duplicate blocks of lymphoid tissues and bone marrow were fixed in buffered formalin and in Bouin's fluid. In another five animals Zenker's fluid was used instead of Bouin's fixative. The tissues were allowed to fix for a minimum of three days in buffered formalin and mercury-formol-saline. The tissues were fixed for eight to sixteen hours in Bouin's and Zenker's fixatives.

Upon removal from mercury-formol-saline, Zenker's and Bouin's fluids the tissues were washed for eight to twelve hours in running tap water. After removal from either the buffered formalin or the tap water wash all tissues except bone marrow were placed in seventy percent ethyl alcohol and stored until they could be embedded in paraffin. Bone was decalcified after fixation in buffered formalin or after washing in the case of the other fixatives.

The method of decalcification was the one described by Dotti et al. (1951). This method employs the use of thirty percent formic acid and an ammonium salt of sulfonated resin (WIN - 3000).^{*} Decalcification was usually complete in three to five days and was followed by washing in running tap water overnight. The bone was then placed in seventy percent alcohol.

All tissues were dehydrated with seventy percent, ninety-five percent and then absolute ethyl alcohol. They were

^{*}Manufactured by Winthrop Laboratories, 1450 Broadway, New York 18, New York.

cleared in chloroform, infiltrated and embedded in Altman's paraffin-stearin-beeswax mixture.

Sections were cut at six microns and mounted on albuminized slides. Paraffin prepared sections of all tissues were routinely stained with hematoxylin and eosin. Special staining procedures were used on selected tissues. In all cases, unless otherwise noted, the procedures were carried out as suggested by the Armed Forces Institute of Pathology (1957).

Paraffin prepared sections of cardiac muscle were stained with Gomori's one step trichrome stain. Selected sections of lymph nodes, hemal nodes, intestine, bone marrow and spleen were stained with Gomori's reticulum stain and Wolbach's modification of the Giemsa stain. In the Giemsa procedure 0.25 percent acetic acid in seventy percent ethyl alcohol was substituted for the rosin-alcohol used for the differentiation of sections. Gomori's iron reaction was carried out on paraffin sections of lymph nodes, spleen and intestine from a number of cases of mucosal disease and also sections from the normal animals.

Hematological Procedures

Hematological studies were performed on fifty of the sixty-four animals.

Erythrocyte counts, total leukocyte counts and differential leukocyte counts were done according to the methods suggested by Todd et al. (1953). Hemoglobin concentrations

were determined by the acid hematin method (Sahli, 1905) or the alkaline hematin method of Sanford and Sheard (1930). The procedure was either that suggested in the Leitz Photrometer Handbook (Leitz, 1948) or that suggested by Fister (1950). Readings were made on either the Leitz Photrometer* or the Coleman Jr. Spectrophotometer, Model 6A.** Hematocrit readings were made by means of the microhematocrit tubes using an International Hematocrit Centrifuge.*** Blood sugar determinations were made using either the method of Folin and Wu (1920) for total reducing substances with readings being made on the Leitz Photrometer or a modification of Nelson's (1944) and Somogyi's (1945) methods for true dextrose concentration. The procedure of Fister (1950) was followed for true dextrose determinations and the readings were made on a Coleman Jr. Spectrophotometer.

Blood urea nitrogen determinations were made using either the direct nesslerization procedure of Gentzkow (1942) or the diacetyl monoxime reaction first described by Fearon (1939) and modified by Ormsby (1942). The procedure suggested by Fister (1950) was followed in the diacetyl monoxime method and the readings were made on the Coleman Jr. Spectrophotometer.

*Manufactured by E. Leitz, Inc., 468-4th Ave., New York 16, New York.

**Manufactured by Coleman Instruments, Inc., 318 Madison Street, Maywood, Illinois.

***Manufactured by International Equipment Co., 1285 Soldiers Field Road, Boston, Mass.

Sedimentation rates were checked using Westergren tubes and making the readings at 24 hours. Blood platelet counts were made with the diluting fluid of Rees and Ecker (1923) and the technique suggested by Todd et al. (1953). Total blood volume determinations were made on five animals. The T-1824 Evans blue dye method as described by Reynolds (1953) was employed. This method consists of the intravenous injection of a known quantity of dye and calculating the amount of dilution in a plasma sample drawn ten minutes after the injection. A Coleman Jr. Spectrophotometer was used to determine the dye concentration in the plasma sample.

Cerebrospinal fluid was removed from the cisterna magna in seventeen animals. Cell counts, sugar and total protein determinations were made on many of the samples. The cell counts were made according to the method suggested by Hepler (1957). Sugar determinations were done by the same method as the blood sugar determinations (Folin and Wu, 1920). The method of Looney and Walsh (1939) was used for spinal fluid protein determinations.

FINDINGS

Hematopoietic System

Lymphatic system

Lymph nodes In most of the cases, striking gross changes were not observed in the majority of the lymph nodes. The size, color and consistency of the lymph nodes of affected animals did not differ appreciably from the corresponding lymph nodes of normal animals. In other cases, all the lymph nodes of the body contained an excess of fluid which flowed from the incised parenchyma. Hyperemia and hemorrhage were apparent on gross examination of the lymph nodes in a few of the animals.

The microscopic lesions were quite variable between animals and between lymph nodes in the same animal. In general, the microscopic changes were of a similar nature and the differences were variations in degree rather than in type. First will be described certain changes that occurred in all lymph nodes and later the lesions associated with particular lymph nodes.

Generally the most striking microscopic change was a marked depletion in the number of lymphocytes in the cortex of all lymph nodes. The loss in lymphocytes in most instances was diffuse with the germinal centers being most severely affected. In other cases the disappearance of lymphocytes was more focal. Occasionally one half of a primary nodule

would be practically devoid of lymphocytes while the other half would have almost a normal number. In lymph nodes that showed a pronounced diffuse loss of lymphocytes the stroma was more easily demonstrated than in normal lymph nodes. Reticulum stains revealed that the reticular fibers were still intact and more evident than in normal animals (Figures 1 and 3). The condensation of reticular fibers at the periphery of germinal centers, presenting a ring-like pattern, was seen in all lymph nodes from normal animals (Figures 2 and 4), but sections of affected lymph nodes differed in that this ring-like pattern was not evident.

Variable distension of the subcapsular sinus was apparent in most of the lymph nodes from all affected animals (Figures 5 and 6). This space between the capsule and the cortex was often completely devoid of cells or stainable material, but frequently the distended subcapsular sinus was almost completely filled with neutrophils (Figures 7, 8, 9 and 10). Occasionally focal accumulations of neutrophils were observed. In many instances numerous eosinophils were diffusely distributed throughout the subcapsular sinus and intermingled with a few neutrophils. In a few cases edema was noted and rarely an increase in the number of primitive reticular cells was also observed.

Occasionally a marked focal to diffuse infiltration of neutrophils was observed in the outer portion of the cortex. In numerous cases a less pronounced neutrophilic leukocyte

Figure 1. Lymph node from an animal with mucosal disease
demonstrating intact reticulum. X 95.
Gomori's reticulum stain.

(M.D. No. 53B8)

Figure 2. Lymph node from normal animal. X 95.
Note condensation of reticular fibers
around the germinal center.
Gomori's reticulum stain.

(M.D. No. 109C2)



Figure 3. Lymph node from an animal with mucosal disease.
X 495. Compare with Figure 4.
Gomori's reticulum stain.

(M.D. No. 53B8)

Figure 4. Lymph node from normal animal demonstrating
reticular fibers. X 495. Note condensation
of fibers at the periphery of germinal center.
Gomori's reticulum stain.

(M.D. No. 109C2)

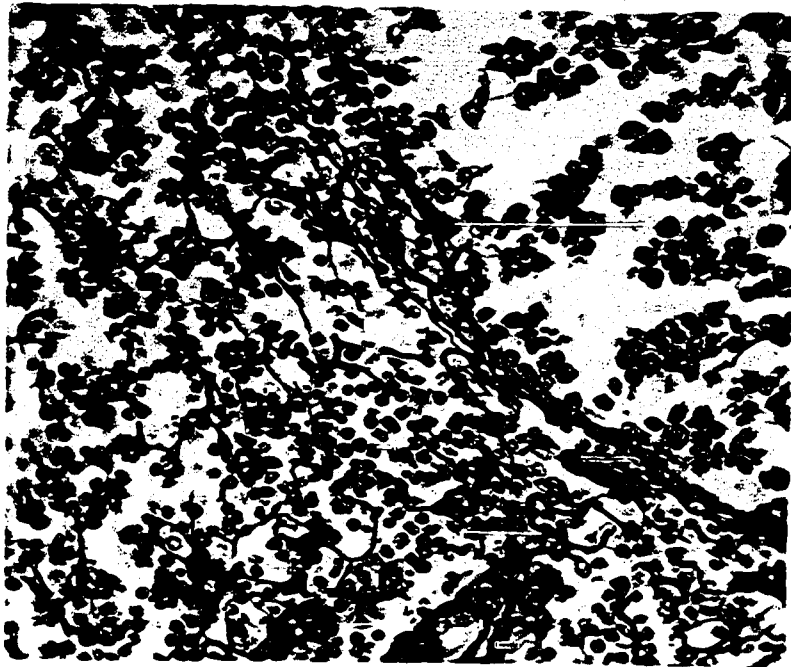


Figure 5. Distension of subcapsular sinus of lymph node
from an animal with mucosal disease. X 95.
Note acellular material in germinal center.
(M.D. No. 40B16)

Figure 6. Lymph node from an animal with mucosal disease
demonstrating lack of stainable material in the
subcapsular sinus. X 95.
(M.D. No. 69G1)

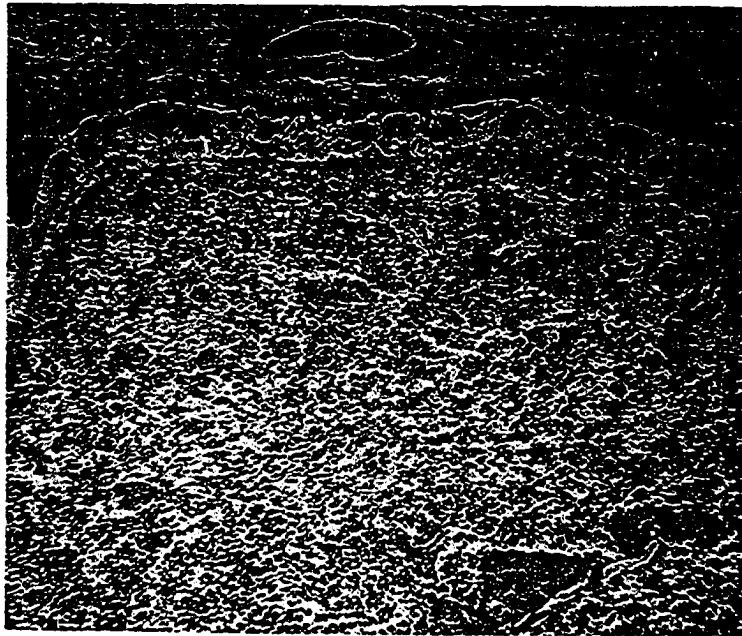
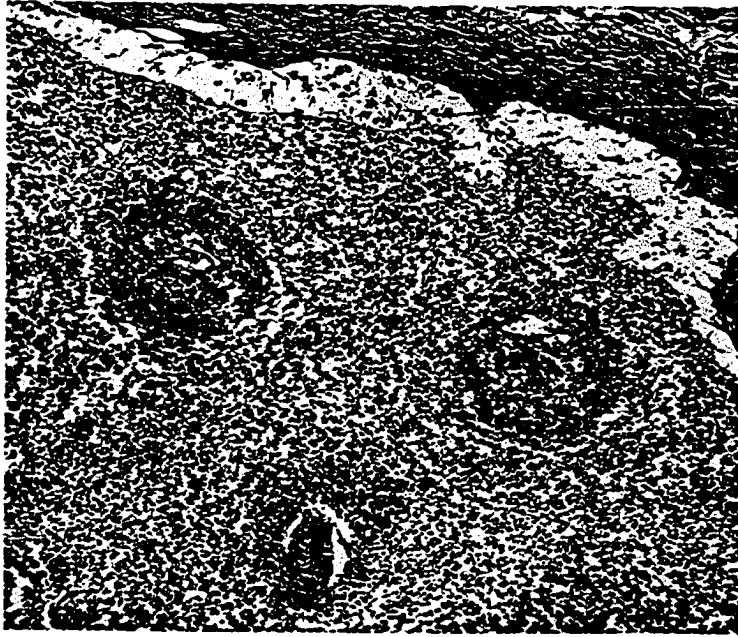


Figure 7. Neutrophils in the subcapsular sinus of lymph node. X 95.

(M.D. No. 92A4)

Figure 8. Higher magnification of subcapsular sinus in Figure 7. X 495.

(M.D. No. 92A4)

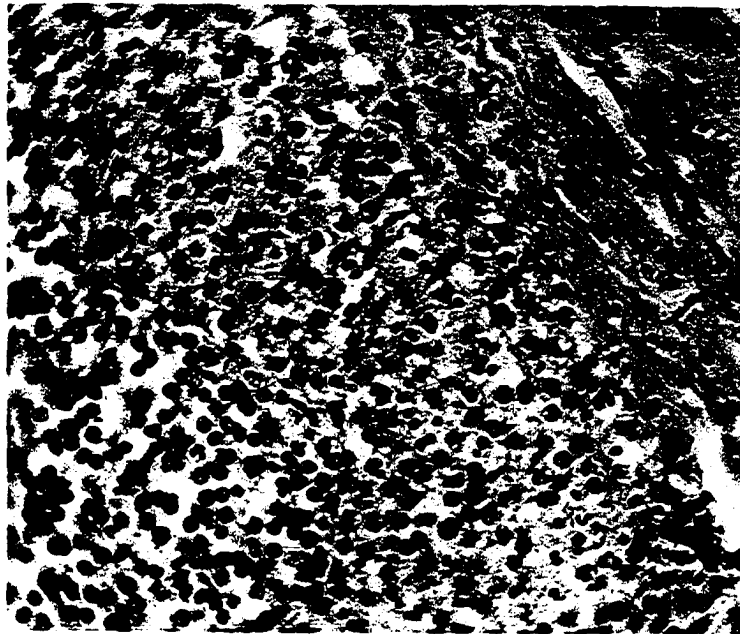
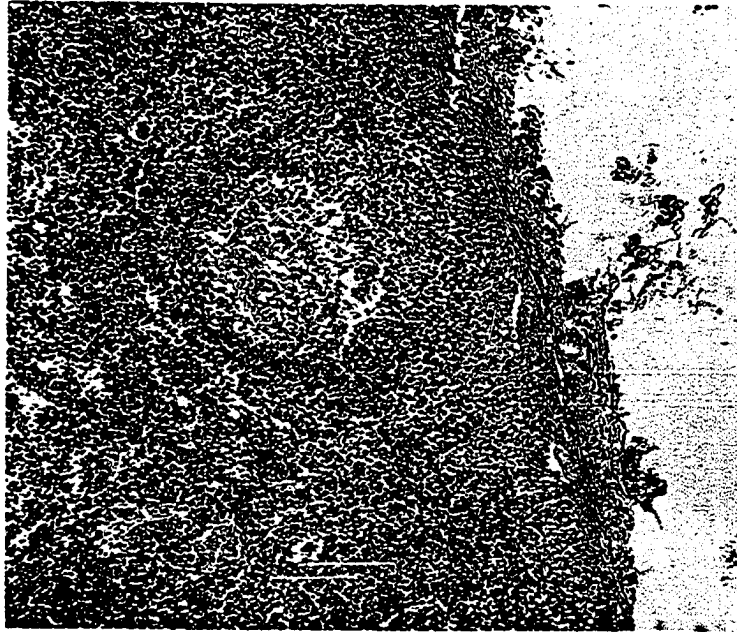
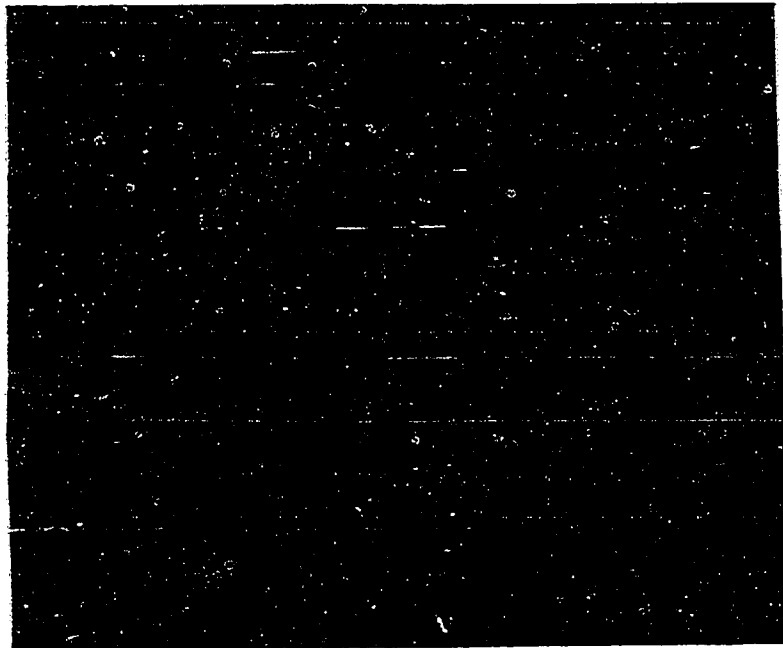
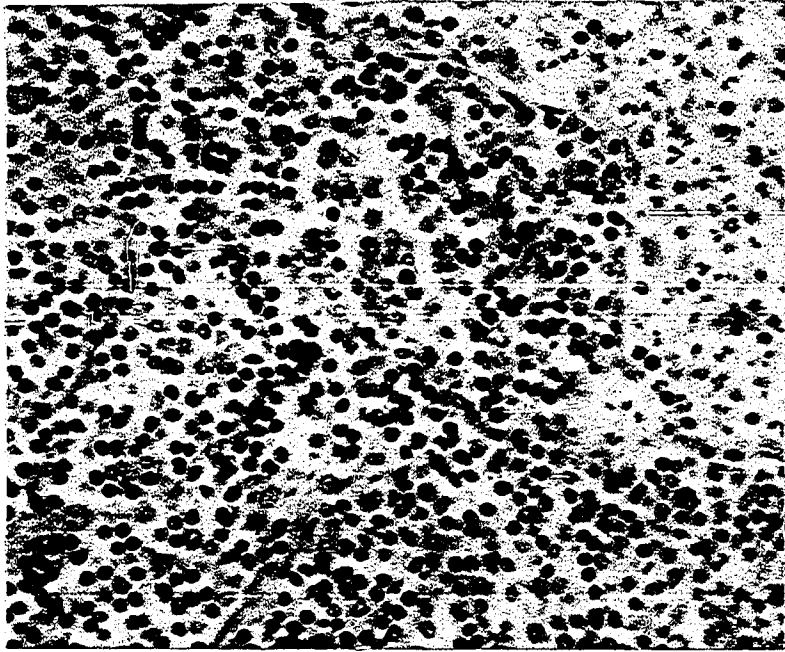


Figure 9. Neutrophils in subcapsular sinus of lymph node. X 495. Giemsa stain.

(M.D. No. 92A4)

Figure 10. Higher magnification of a portion of the field in Figure 9. X 920. Note eosinophils in the outer cortex of lymph node. Giemsa stain.

(M.D. No. 92A4)



infiltration was seen. The infiltrations were generally found in the areas between the lymphatic follicles, but at times neutrophils were noted in the germinal centers. Focal and diffuse infiltrations of eosinophilic leukocytes were encountered more frequently than neutrophils especially in the peripheral lymph nodes. The eosinophils were found in the outer portions of the cortex as a rule (Figures 11 and 12). They were most numerous in lymph nodes that also exhibited areas of coagulative necrosis. At times accumulations of eosinophils were observed in the germinal centers, especially in those that were largely depleted of lymphocytes.

In lymph nodes from 56 of the affected animals accumulations of eosinophilic material were observed in the germinal centers. The material was relatively acellular, strongly eosinophilic and amorphous to finely granular (Figures 13, 14, 15, 16, 17 and 18). Sometimes the entire germinal center was involved while in other cases only a portion of the nodule contained the eosinophilic material. At times there were numerous smaller spherical masses of the material, 10 to 15 microns in diameter, surrounding the larger mass. In most instances nuclear debris was found in and around the fibrinoid-like material in the germinal center.

In the germinal centers that contained this material there were very few small lymphocytes and the predominant cell type was the macrophage. An abundance of plasma cells was also observed in the lymph nodes of some animals in which

Figure 11. Eosinophils in the cortex of a lymph node of an animal with mucosal disease. X 920. Giemsa stain.

(M.D. No. 90A1)

Figure 12. Eosinophils in the cortex of a lymph node from an animal with mucosal disease. X 920. Note edema in subcapsular sinus at upper right. Giemsa stain.

(M.D. No. 90B3)

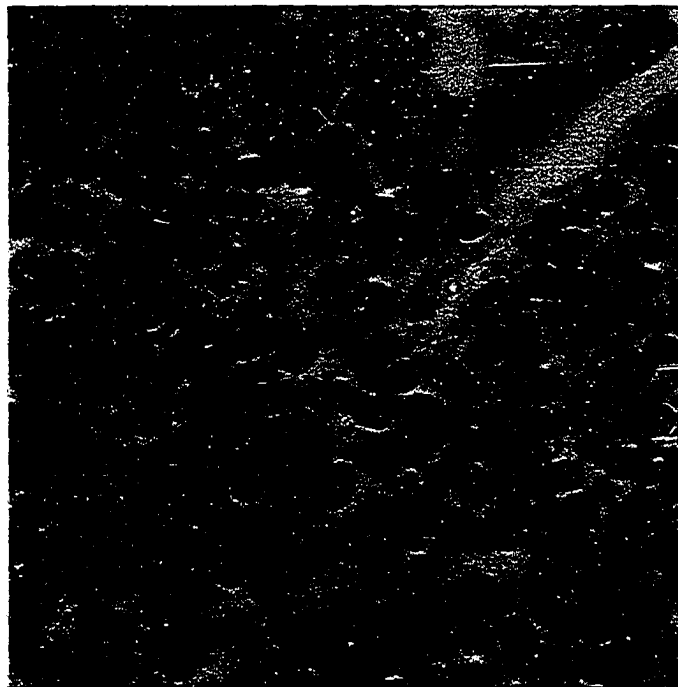


Figure 13. Hyaline-like material in a germinal center of a lymph node. X 95. Note distention of the subcapsular sinus.

(M.D. No. 107A1)

Figure 14. Higher magnification of germinal center area of Figure 13. X 495. Note hyaline-like material and mononuclear cells.

(M.D. No. 107A1)

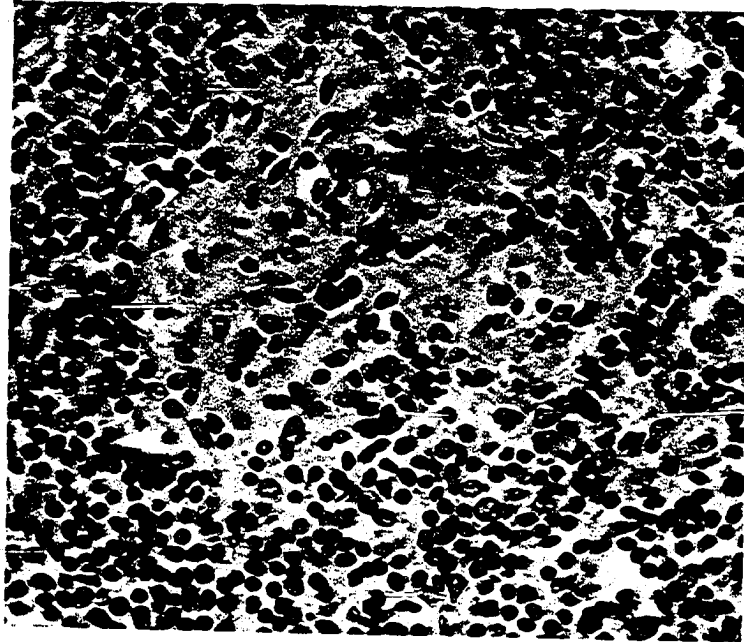


Figure 15. Lymph node of an animal with mucosal disease showing hyaline-like material in a germinal center. X 95.

(M.D. No. 62-50)

Figure 16. Higher magnification of a portion of the field in Figure 15. X 495. Note presence of neutrophils.

(M.D. No. 62-50)

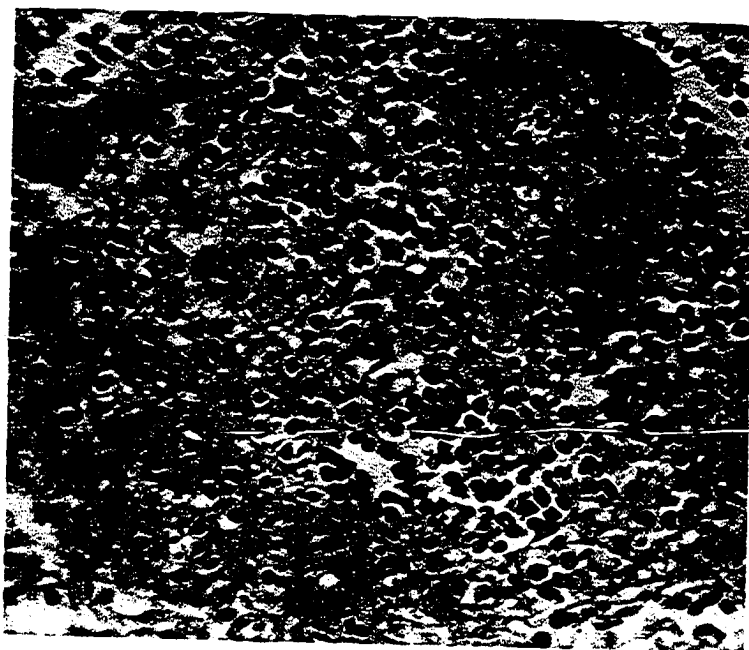
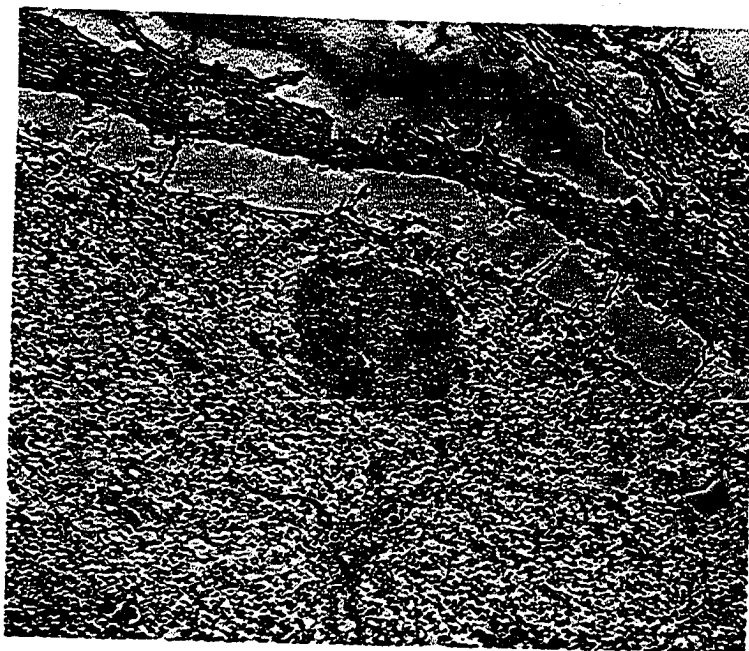
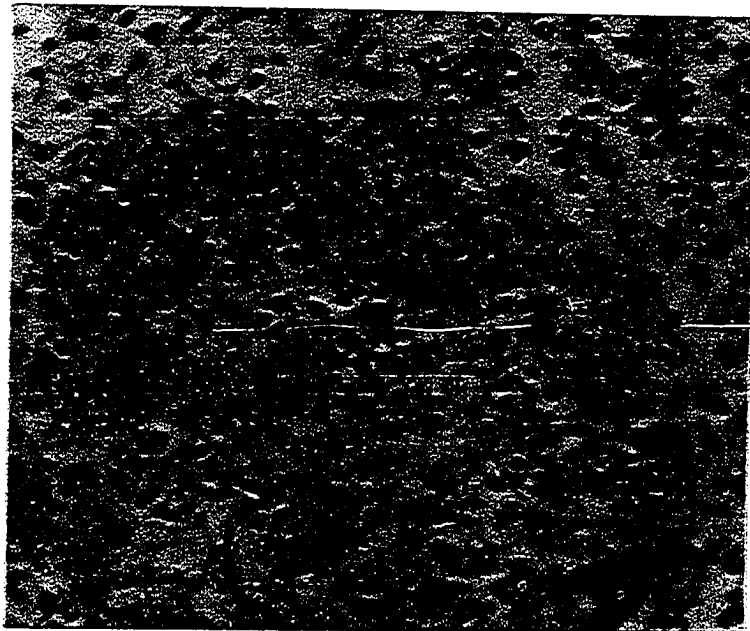
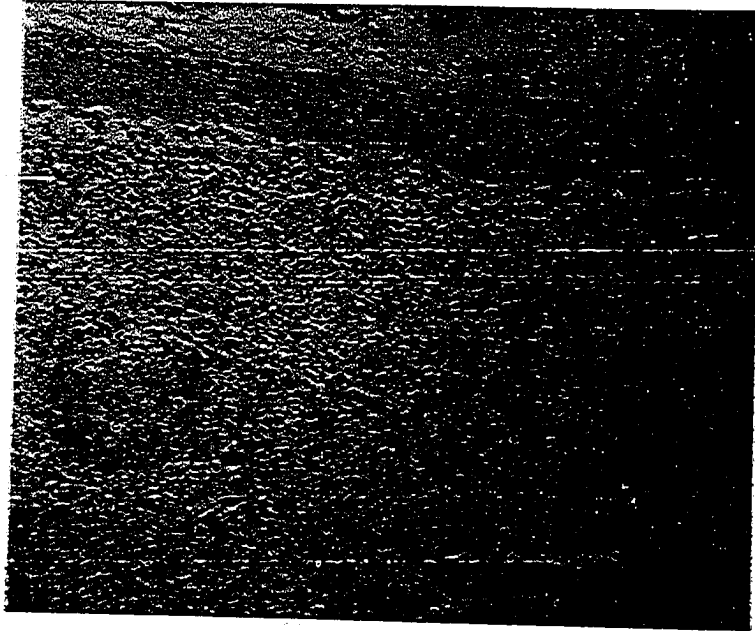


Figure 17. Eosinophilic material in the area of germinal centers of a lymph node in an animal affected with mucosal disease. X 95. Note lack of small lymphocytes in the surrounding cortex. Hematoxylin and eosin stain.

(M.D. 75 E4)

Figure 18. Higher magnification of the germinal center area of Figure 17. X 495. Hematoxylin and eosin stain.

(M.D. 75E4)



this fibrinoid-like material was found.

In a majority of the cases blood vessels of the cortex of some lymph nodes contained large numbers of leukocytes (Figures 19 and 20), and the predominant cells were neutrophils. Enumeration of cells in the distended arterioles revealed that the ratio of neutrophils to lymphocytes was often as great as ten to one. Neutrophil packing usually appeared to be focal in distribution, but in a few cases all the arterioles of a lymph node appeared to contain excessive numbers of these granulocytes.

Hyperemia of blood vessels of the cortex was a consistent finding in nearly all lymph nodes of all animals. Hemorrhages in the cortices of some of the lymph nodes were seen in forty-three animals. In most cases hemorrhages were seen in only one or a few of the lymph nodes in each animal. Generally the hemorrhages were not extensive and involved only a small part of the lymph node. In about half of the cases the hemorrhage accompanied coagulative necrosis of the outer cortex of the lymph nodes (Figures 21 and 22). Hemorrhages were found most commonly in the suprapharyngeal, prescapular and mesenteric lymph nodes.

An increased amount of yellow-brown pigment was observed in and around the germinal centers of some of the lymph nodes from a few animals. In a majority of these cases the material did not contain iron and was therefore thought to be lipofuscin.

Figure 19. Neutrophils in blood vessels of the prescapular lymph node of mucosal disease affected animal.
X 95.

(M.D. 107A1)

Figure 20. Enlargement of a part of the field in Figure 19.
X 495.

(M.D. 107A1)

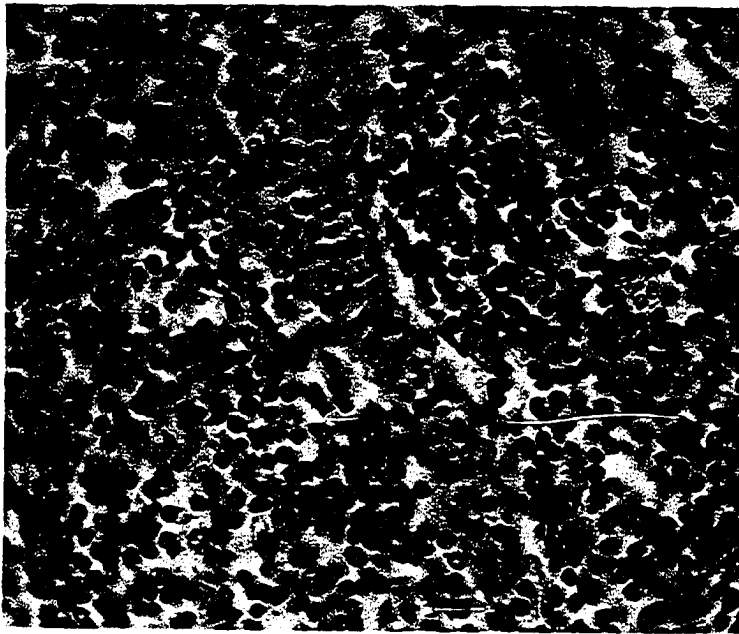
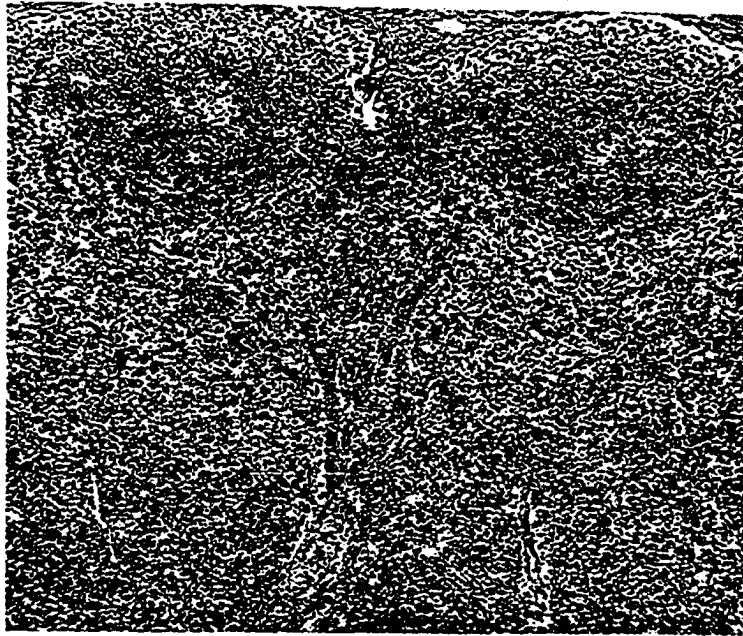
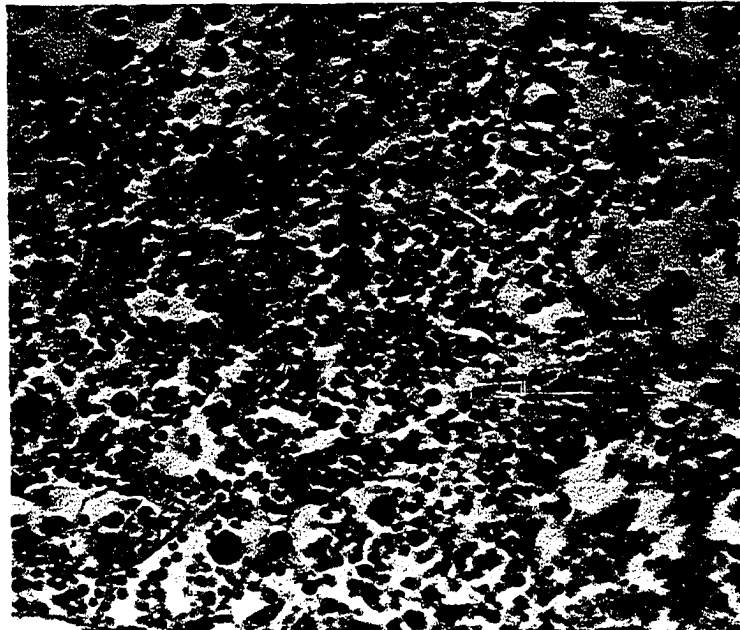


Figure 21. Hyperemia, hemorrhage and decreased numbers of lymphocytes in a lymph node of a mucosal disease affected animal. X 95.

(M.D. 75E10)

Figure 22. Higher magnification of a portion of field shown in Figure 21. X 495. Note lack of small lymphocytes.

(M.D. 75E10)



Mitotic figures were either lacking or very few in number in the germinal centers of all lymph nodes from affected animals. Numerous mitotic figures were observed in the germinal centers of lymph nodes from normal animals.

Histological examination of the medulla of the lymph nodes revealed pathological changes that were variable in severity. The most prominent change was the accumulation of granulocytes scattered throughout the medulla, but they were variable in amount. The neutrophil was the most predominant leukocyte observed. In some cases focal accumulations of large numbers of neutrophils and eosinophils were observed while in other cases they were few in number and widely scattered throughout the medulla.

A limited number of affected cattle exhibited an increased amount of lipofuscin in the medulla of lymph nodes, but this was not a constant finding. The lymph nodes of some affected animals had very little pigment present.

Edema was noted in the medullary sinuses of the lymph nodes of sixteen of the affected cattle. In twelve of the sixteen cases the animals had been electrocuted and other lesions besides the edema in the lymph nodes were obvious.

The number of primitive reticular cells in the medulla of lymph nodes of some of the affected animals was definitely increased but because of the variability in numbers of these cells in normal animals this change was difficult to evaluate.

Comparison of lymph node involvement

The supra-pharyngeal lymph nodes were generally more severely involved than any of the others with the exception of the mesenteric lymph nodes. Depletion of number of lymphocytes was generally of a diffuse nature. In about forty percent of the cases the accumulation of eosinophilic material and almost complete loss of small lymphocytes was noted in at least one of the germinal centers on cross section of the node. Probably the most consistent and most striking changes found in the supra-pharyngeal lymph nodes were the severe congestion of the arterioles and the hemorrhage that was observed in both the medulla and the cortex. Neutrophil packing of the arterioles was occasionally seen and the presence of neutrophils in the subcapsular sinus was a common finding.

In general the changes in the prescapular lymph nodes were less pronounced than those observed in the supra-pharyngeal nodes of the same animal. The most marked difference in the histopathology of the two lymph nodes was the frequency of neutrophil packing of the arterioles. This change occurred more often and was more severe in the prescapular than in the supra-pharyngeal lymph nodes.

The severity of the changes in the bronchial lymph nodes was intermediate between the supra-pharyngeal and the prescapular lymph nodes. Varying degrees of hyperemia, hemorrhage, cortical lymphocytolysis, necrosis of germinal centers or fibrinoid formation, leukocytic infiltration of

the cortex and medulla, distension and neutrophil packing of the subcapsular sinus were observed. The amount of lipofuscin in the bronchial lymph nodes of normal and affected animals appeared to be greater than in the prescapular, supratharyngeal or prefemoral nodes.

The abnormal changes noted in the prefemoral lymph nodes were milder than in any of the other lymph nodes studied. The most consistent findings were a diffuse cortical lymphocytolysis, distension of the subcapsular sinus with or without neutrophilic packing, an increase in the number of neutrophils and eosinophils in the medulla and engorgement of the arterioles of the cortex with neutrophilic leucocytes. At times coagulative necrosis in the region of the germinal centers of the prefemoral lymph nodes was observed. In those cases the animal had usually died during the natural course of mucosal disease and changes were severe in all lymph nodes studied.

The microscopic changes in the parotid lymph nodes were moderately more severe than those in the prefemoral lymph nodes but were of a similar type.

Little difference in the degree of severity of involvement of the mesenteric and colic lymph nodes was detected. The microscopic lesions in these lymph nodes were more severe than in any of the others. Occasionally, in animals which had died, a coagulative necrosis was present and involved up to forty percent of the area of the cortex observed on

cross section of the lymph node. In these instances there was a marked disappearance of small lymphocytes with some hemorrhage, eosinophilic and neutrophilic infiltration and nuclear karyorrhexis and karyoschisis. Mononuclear phagocytes could be seen engulfing the nuclear debris.

A diffuse lymphocytolysis accompanied by the accumulation of eosinophilic material in the germinal centers in the outer cortex of some of the mesenteric lymph nodes was noted in over ninety percent of the animals. Invariably neutrophils and frequently eosinophils were apparent in the outer cortex. In an occasional animal neutrophils and more often eosinophils could be found in the germinal centers of the mesenteric lymph nodes.

There was considerable variation in the severity of the lesions in different sections of the mesenteric lymph nodes of an individual animal. This variation was particularly noticeable in animals that had been electrocuted and in animals with lesions of a mild nature.

In a few cases some of the sections of the mesenteric nodes showed a mild reaction consisting primarily of a diffuse lymphocytolysis and slight neutrophilic infiltration while others showed a severe focal coagulative necrosis accompanied by a marked inflammatory reaction.

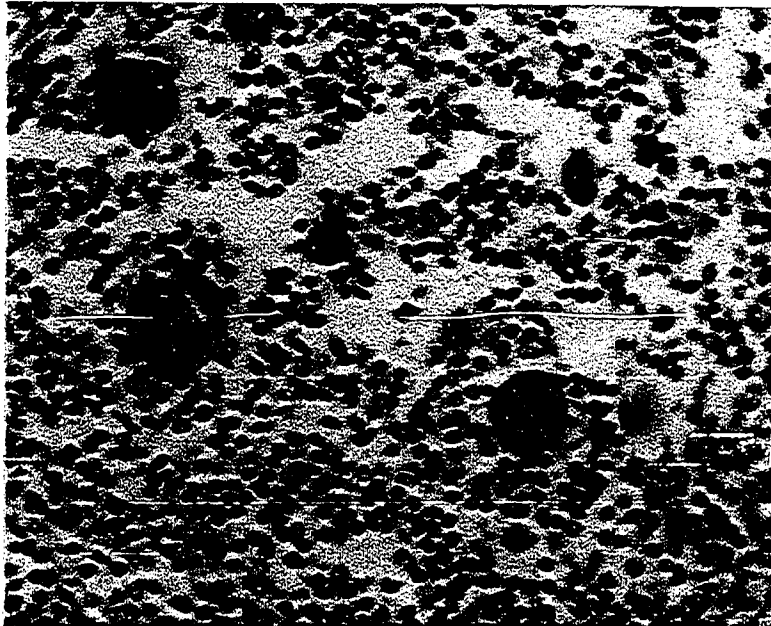
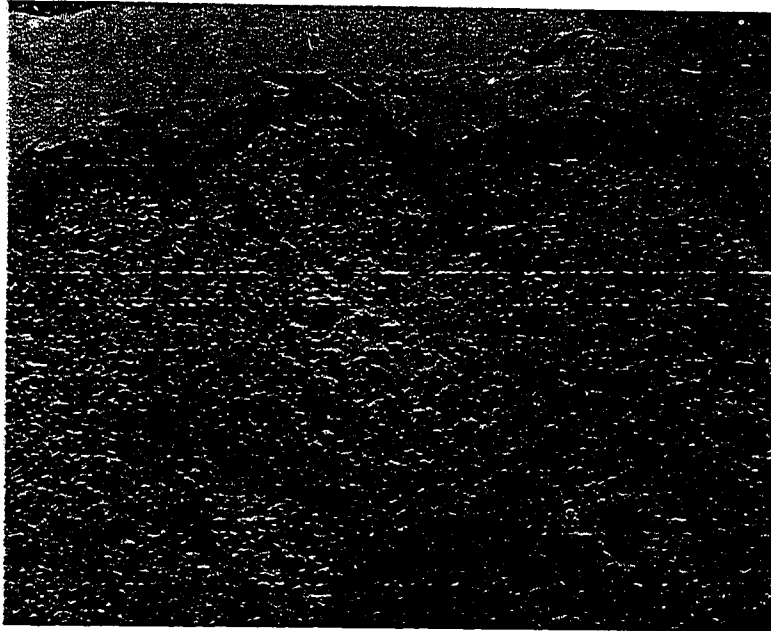
Another interesting observation made on the mesenteric lymph nodes was the presence of circular calcified bodies in the germinal centers (Figures 23 and 24). The appearance of

Figure 23. Mesenteric lymph node from an animal with mucosal disease. X 95. Note spherical bodies in cortex. Hematoxylin and eosin stain.

(M.D. No. 88H5)

Figure 24. An enlargement of a portion of field shown in Figure 23. X 495. Note concentric ringed appearance of some of the spherical bodies. Hematoxylin and eosin stain.

(M.D. No. 88H5)



these objects was similar to the corpora amylacea that are sometimes observed in the mammary and prostate glands. A concentric ringed appearance was noted in some of them. They varied in diameter from 15 to 60 microns. The objects appeared reddish purple with hematoxylin and eosin stain. Histochemical tests performed by Thompson* revealed that these bodies contained calcium carbonate and gave a false positive test for iron. Generally from one to ten of the objects were found in the region of a single germinal center. The bodies were found only in the mesenteric lymph nodes and their location tended to be in the region of the germinal center. They were present in nineteen of the mucosal disease affected animals.

These aggregates of calcium carbonate were also found in the mesenteric lymph nodes of some of the apparently normal cattle obtained from the Meats Laboratory. They have also been observed by the author in the mesenteric lymph nodes of cattle that have died of other disease.

Spleen Careful gross examination of the spleen of mucosal disease affected animals revealed no striking changes, but the microscopic changes resembled very closely those observed in the lymph nodes. The Malpighian corpuscles regularly contained fewer small lymphocytes than did those

*Thompson, Dr. S. W., U.S. Army Medical Research and Nutrition Lab., Fitzsimons Army Hospital, Denver, Colorado. Histochemical studies of mineralized lesions in lymph nodes. Personal communication. 1960.

of the normal animals. In a few instances the loss of lymphocytes was focal in nature and appeared to involve only a part of a Malpighian corpuscle (Figures 25 and 26), giving the latter a vacuolated appearance. More commonly a diffuse lymphocytolysis of the germinal center (Figures 27 and 28) and the white pulp occurred.

In the Malpighian corpuscles that contained few small lymphocytes the large mononuclear cell was the predominant type. Plasma cells were observed in the Malpighian corpuscles in many of the cases. Mitoses were seen only rarely in the lymphatic nodules of the spleen.

The presence of an eosinophilic mass in an eccentric position in the Malpighian corpuscles was observed in approximately twenty percent of the affected animals (Figures 29 and 30). This material had the same appearance as that observed in the lymph nodes. It did not generally obliterate an entire Malpighian corpuscle, whose remainder often contained numerous erythrocytes.

In approximately one half of the cases large numbers of neutrophils and some eosinophils were seen at the periphery of the Malpighian corpuscles (Figures 31 and 32). Less often neutrophils and eosinophils were noted in the Malpighian corpuscles. The presence of these eosinophils and neutrophils was most easily detected in those cases that exhibited a marked decrease in lymphocytes.

Figure 25. Focal disappearance of small lymphocytes from lymphatic nodule in the spleen. X 95. Mucosal disease affected animal.

(M.D. 121F10)

Figure 26. Higher magnification of lymphatic nodule in Figure 26. X 495.

(M.D. 121F10)

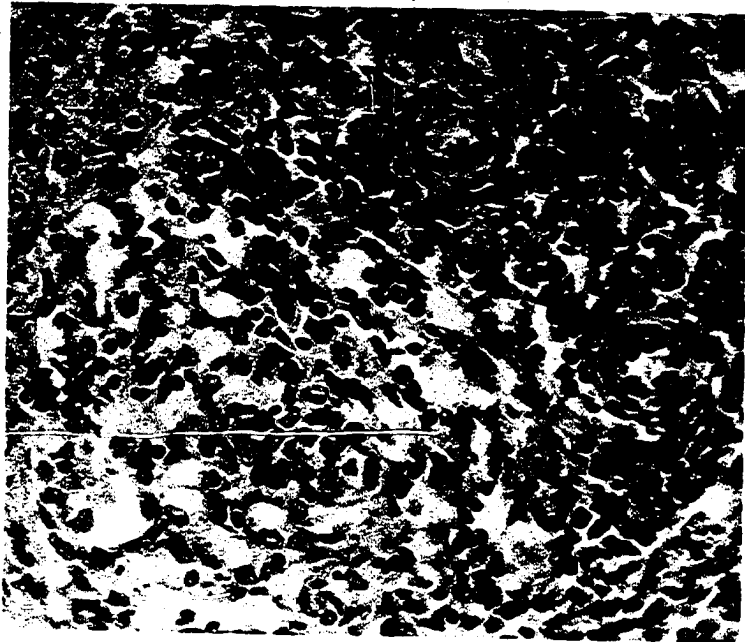


Figure 27. Decrease in number of lymphocytes from lymphatic
nodule of spleen. X 95. Mucosal disease
affected animal.

(M.D. 101A2)

Figure 28. Enlargement of lymphatic nodule in Figure 27.
X 495.

(M.D. 101A2)

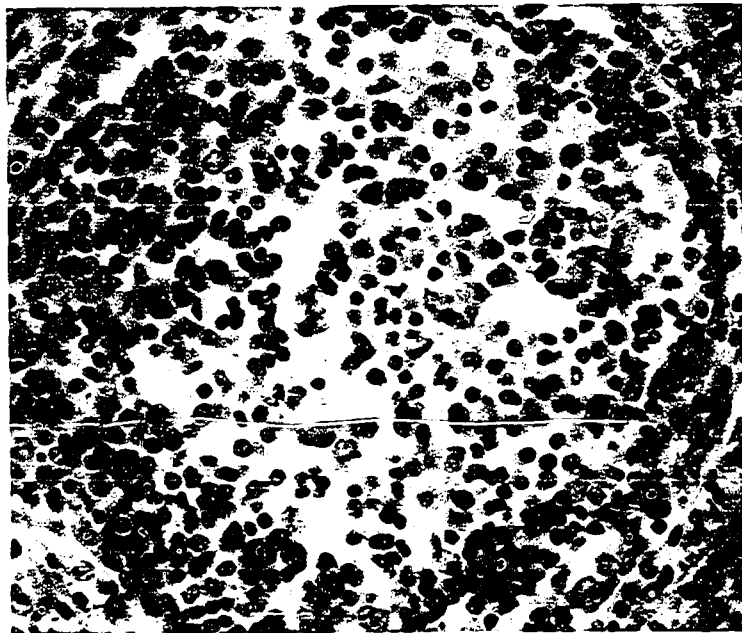
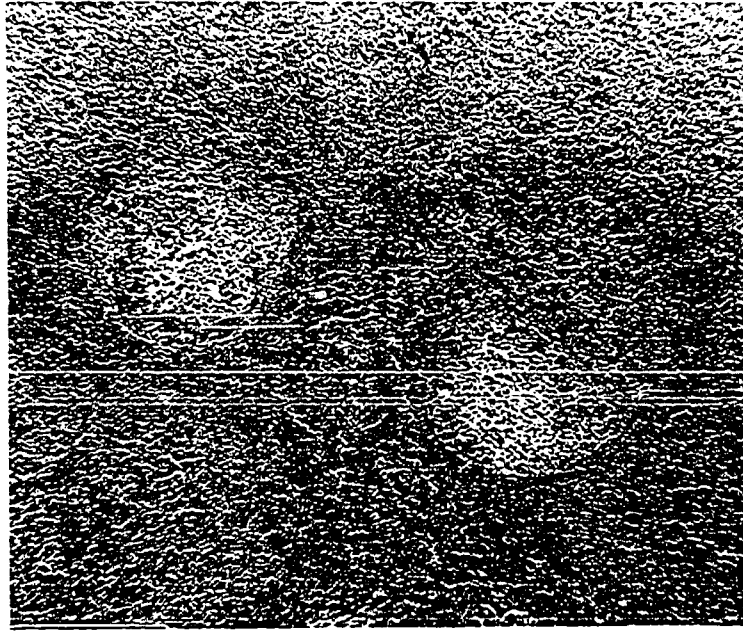


Figure 29. Focal eccentric accumulation of fibrinoid-like material in spleen of mucosal disease affected animal. X 95.

(M.D. 62-28)

Figure 30. Higher magnification of fibrinoid-like material in Figure 29. X 495.

(M.D. 62-28)

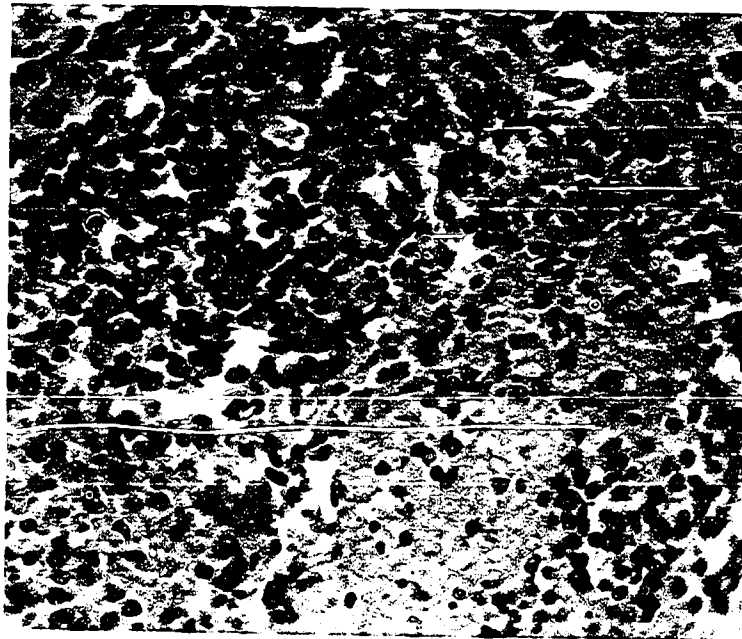
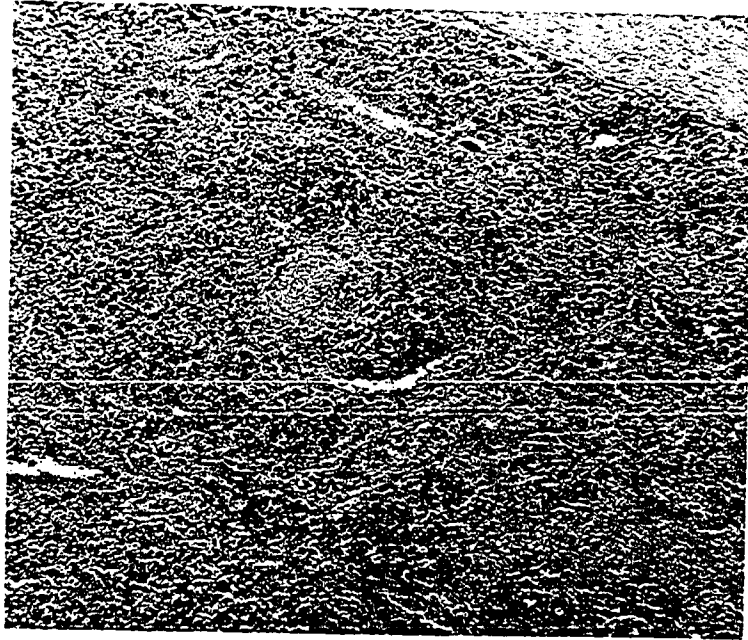
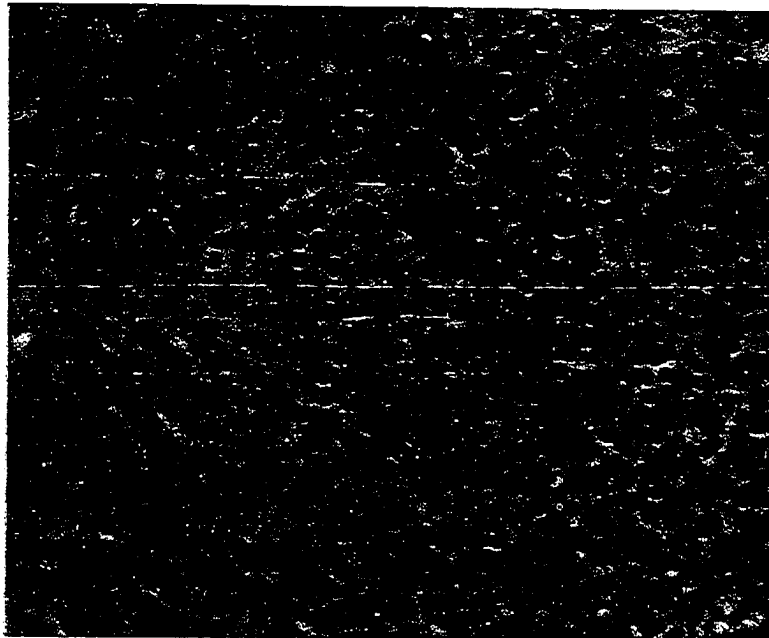
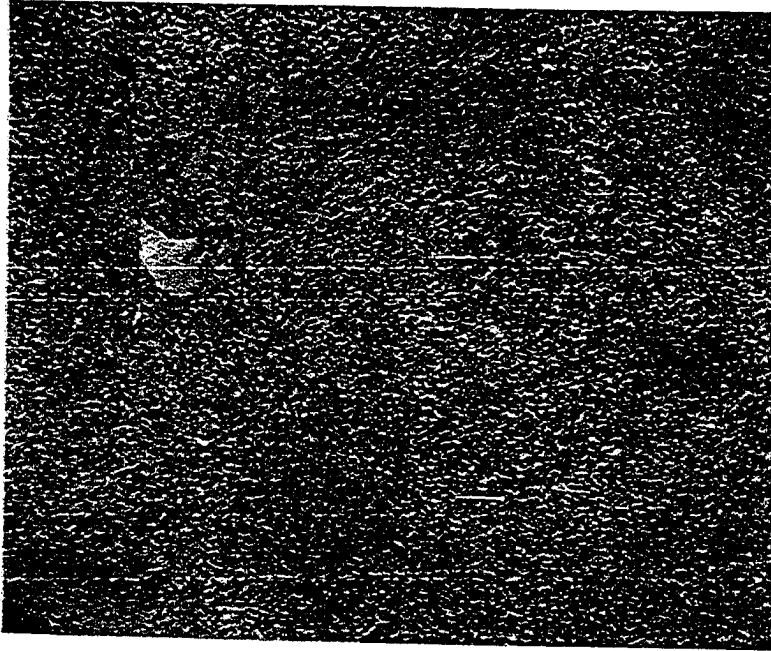


Figure 31. Malpighian corpuscle of the spleen from a mucosal disease affected animal. X 95. Note neutrophils at the periphery of lymphatic nodule. Hematoxylin and eosin stain.

(M.D. No. 90A10)

Figure 32. Higher magnification of the periphery of the lymphatic nodule of Figure 31 showing neutrophils. X 495. Hematoxylin and eosin stain.

(M.D. No. 90A10)



The presence of a yellowish-brown pigment was also observed to be especially prominent in areas immediately adjacent to the Malpighian corpuscle (Figures 33 and 35). This pigment was also found diffusely scattered throughout the red pulp of the spleen in affected animals. Sections from twenty affected animals and ten normal animals that were stained with Gomori's iron reaction revealed that the pigment was probably hemosiderin. These sections also made it apparent that very little if any hemosiderin was present within the Malpighian corpuscles (Figures 34 and 36). In some of the cases the iron positive material was not concentrated at the periphery of the nodule but was scattered diffusely throughout the red pulp (Figure 37).

Generally speaking the amount of hemosiderin in the spleens of mucosal disease affected animals was greater than that in the normal animals (Figure 38). In contrast, the amount of hemosiderin in the spleens of normal animals was graded as mild to moderate in three cases and mild in six cases, and negative in one case. In mucosal disease affected animals the amount was classified as mild in five, moderate in six, moderate to marked in five, and marked in four cases.

Hemal nodes Histological study of the hemal nodes of mucosal disease affected animals revealed that the changes were very similar to those which occurred in the lymph nodes and spleen. The changes consisted primarily of a marked decrease in the number of small lymphocytes. In some

Figure 33. Spleen from a mucosal disease affected animal.
X 95. Note brown pigment at periphery of the
lymphatic nodule. Hematoxylin and eosin stain.
(M.D. No. 72B3)

Figure 34. Section from same area as Figure 33 showing
hemosiderin. X 95. Note the blue staining
of the hemosiderin. Gomori's iron stain
counterstained with Kernechtrot.
(M.D. No. 72B3)

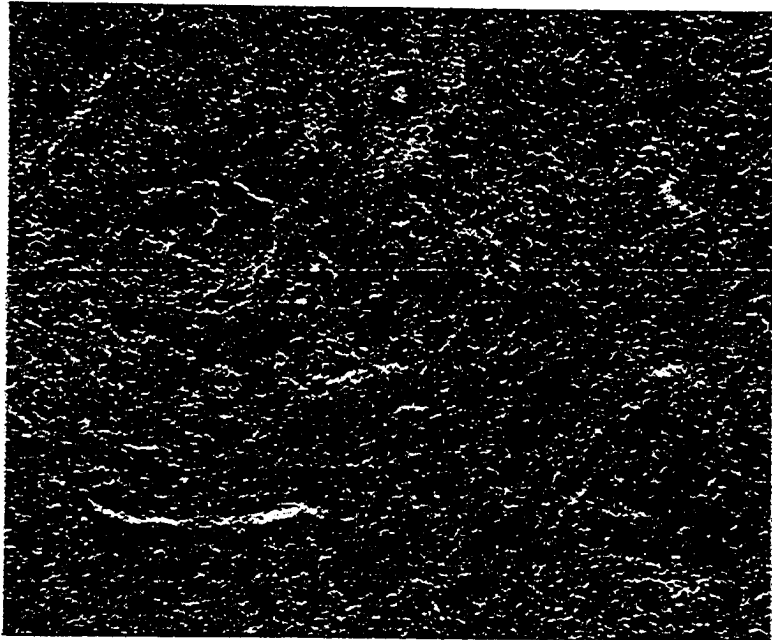


Figure 35. Enlargement of a portion of the field in Figure 33. X 495. Compare with Figure 36. Hematoxylin and eosin stain.

(M.D. No. 72B3)

Figure 36. Higher magnification of a portion of the field in Figure 34. X 495. Gomori's iron stain counterstained with Kernechtrot.

(M.D. No. 72B3)

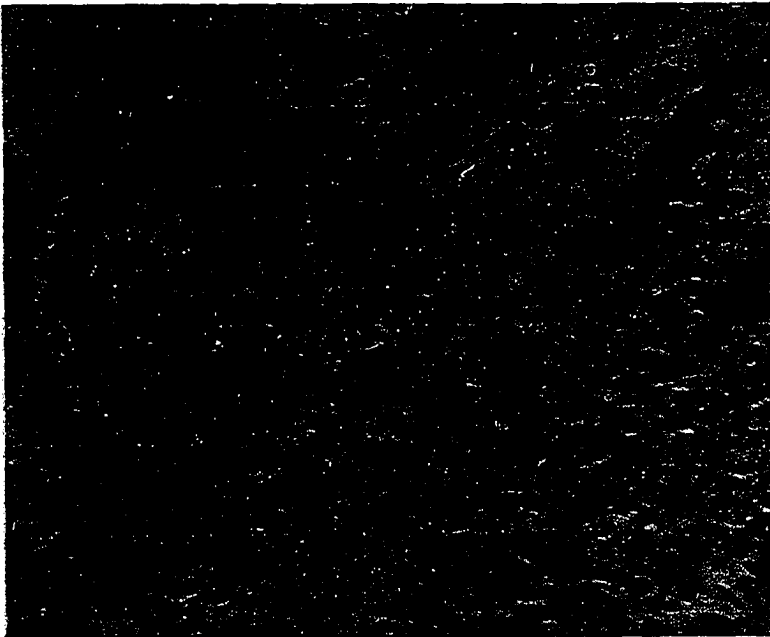
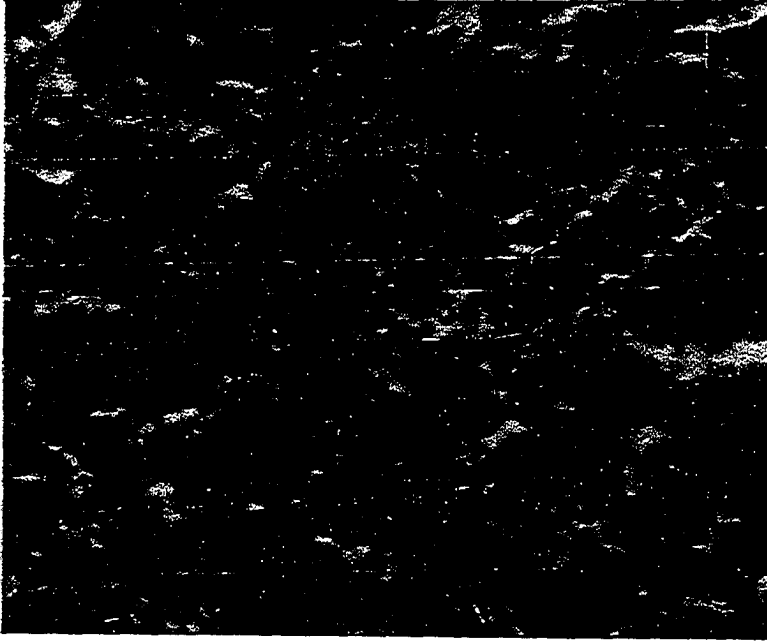
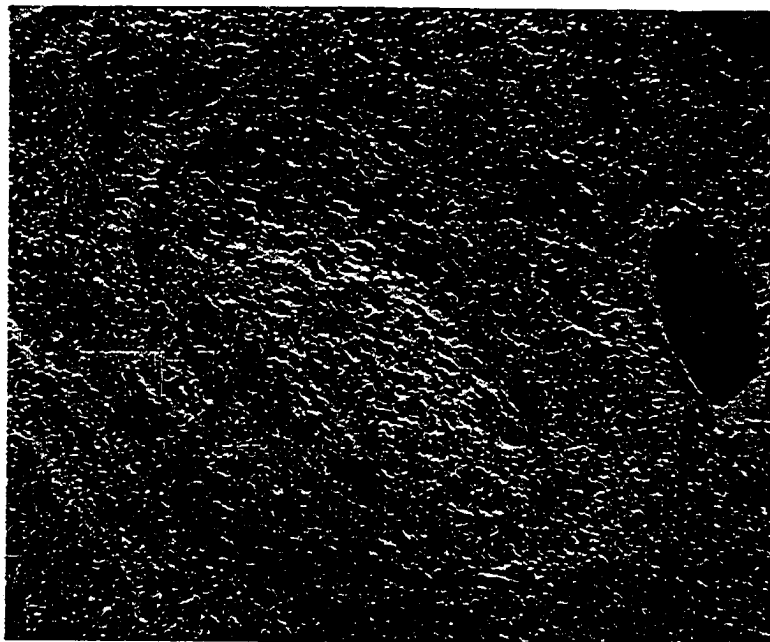
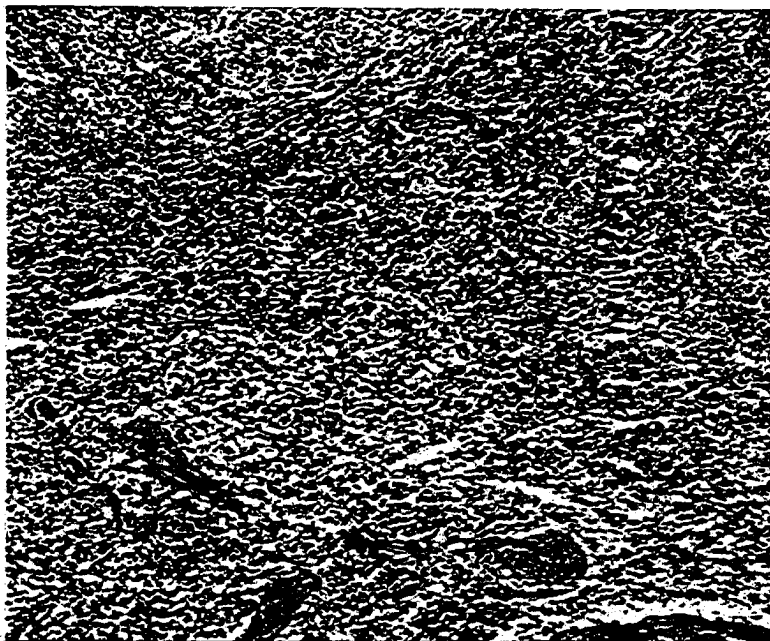


Figure 37. Diffuse appearance of hemosiderin in the spleen of a mucosal disease affected animal. X 95. Note absence of hemosiderin in lymphatic nodule. Gomori's iron stain counterstained with Kernechtrot.

(M.D. No. 76A20)

Figure 38. Spleen from normal animal. X 95. Note the lack of hemosiderin. Gomori's iron stain counterstained with Kernechtrot.

(M.D. No. 108A11)



instances focal eccentric accumulation of eosinophilic material in the nodules of lymphatic tissue was observed. In a majority of the hemal nodes variable numbers of erythrocytes were seen in the lymphatic tissue and an apparent increase in the amount of blood in the entire node was observed. Mitotic figures were absent or few in number.

Thymus Some difficulty was encountered in the gross identification of the thymus in most of the affected animals. There was an apparent decrease in its size and at times it had a mottled appearance. The normal buff color was interrupted by small grayish white areas that were found on microscopic examination to be lipid or fat.

Histological examination revealed that a marked change in the normal architecture of the thymus had occurred in affected animals. The differentiation of the thymus into medulla and cortex noted in normal animals (Figures 39 and 40) was not found in mucosal disease animals. Small foci containing numerous thymocytes were observed in only one affected animal (Figures 40, 41 and 42).

The consistent finding in all affected animals was a marked diffuse disappearance of thymocytes accompanied by an apparent increase in amount of eosinophilic material (compare Figures 43, 44, 45 and 46). One component of the eosinophilic material was thought to be coagulated serum protein and was found both in the lumen of blood vessels and in the medullary parenchyma (Figure 46). In other instances a

Figure 39. Thymus from a normal animal. X 95. Note differentiation of cortex and medulla.

(M.D. No. 108B4)

Figure 40. Thymus from mucosal disease affected animal. X 95. Note the focus of densely packed thymocytes at lower center.

(M.D. No. 119E1)

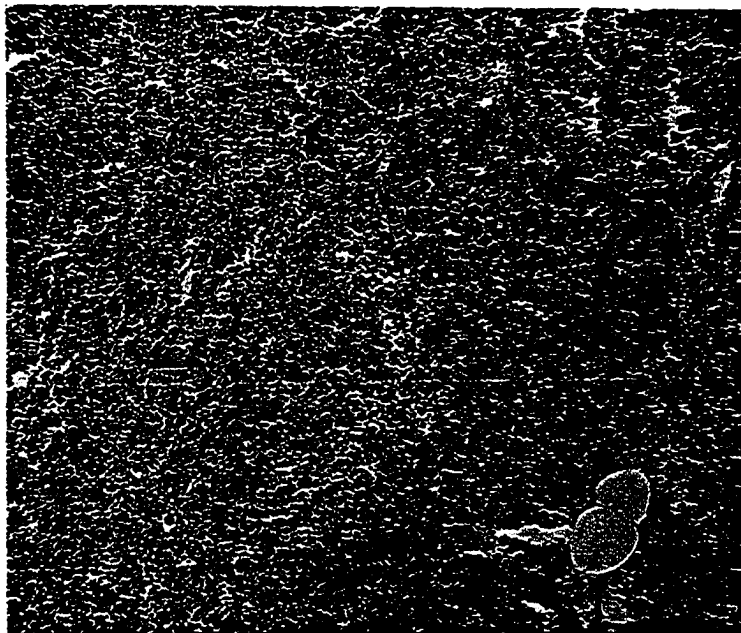


Figure 41. Higher magnification of the area of densely packed thymocytes of Figure 40. X 495.

(M.D. No. 119E)

Figure 42. Higher magnification of a portion of the field in Figure 40. X 495. Compare the number of small thymocytes with Figure 41.

(M.D. No. 119E1)

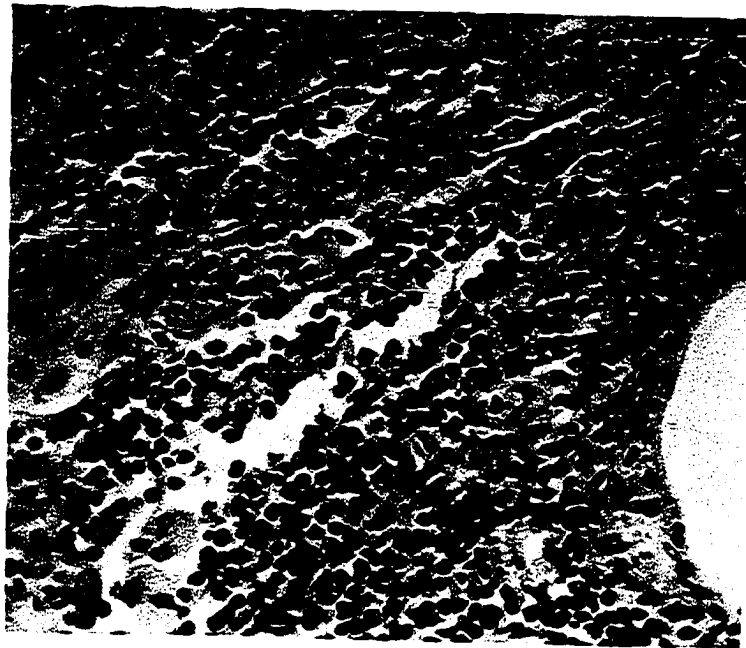
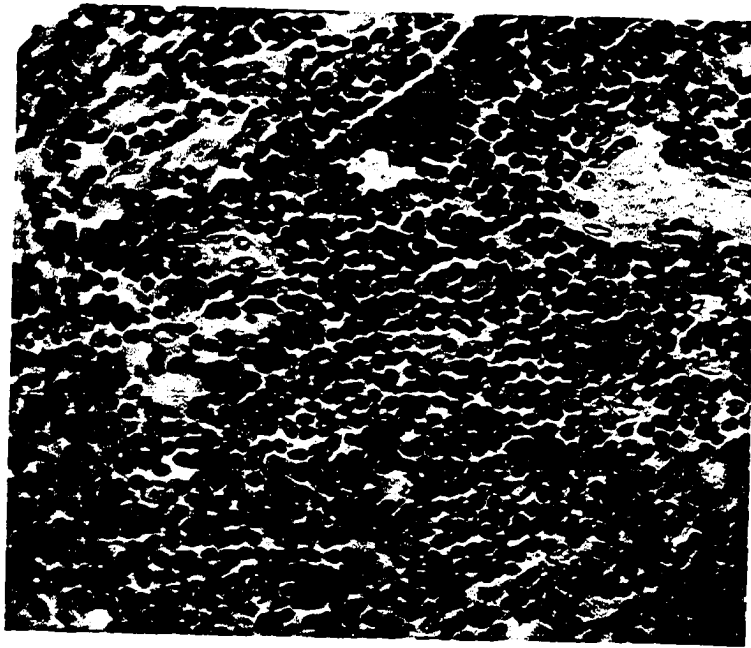


Figure 43. Thymus from a normal animal. X 95. Compare with Figure 44. Giemsa stain.

(M.D. No. 108B4)

Figure 44. Thymus from mucosal disease affected animal. X 95. Note that few thymocytes and much eosinophilic material are present. Giemsa stain.

(M.D. No. 90A5)

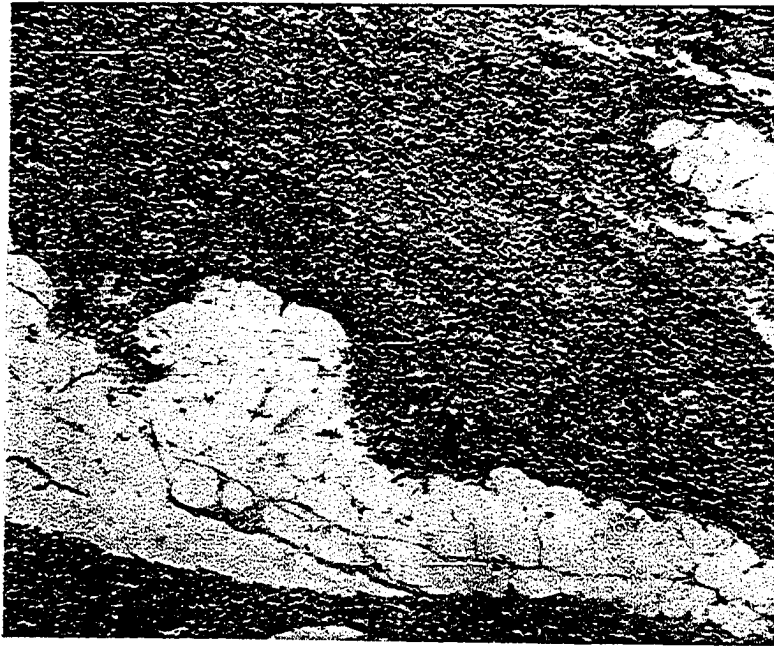
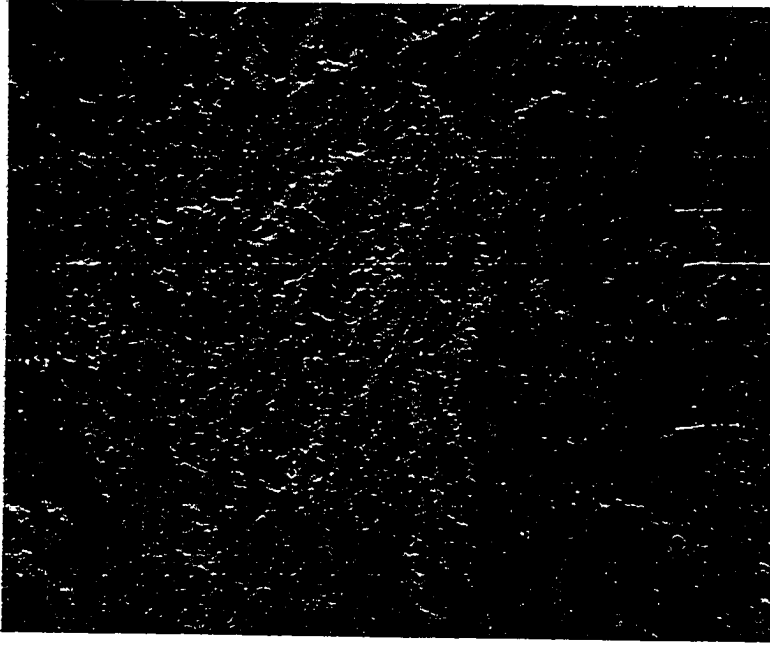
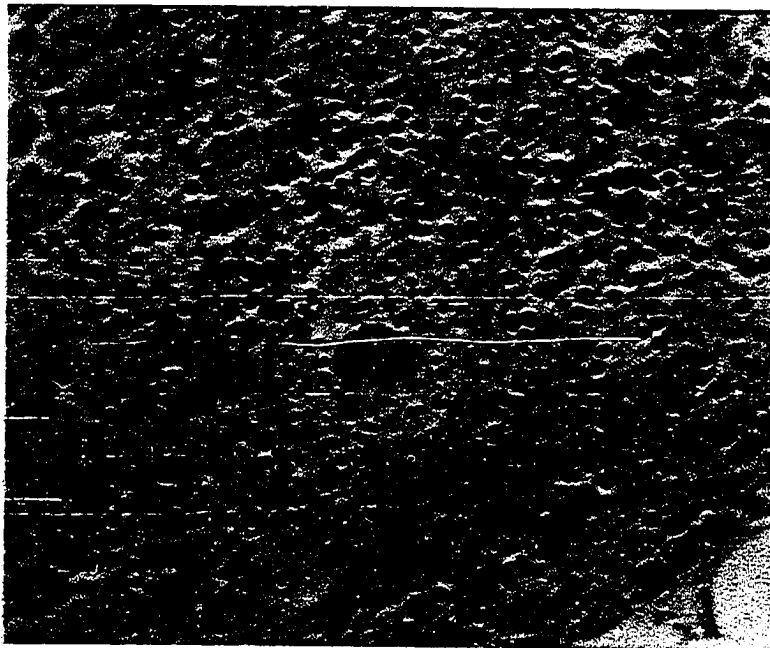
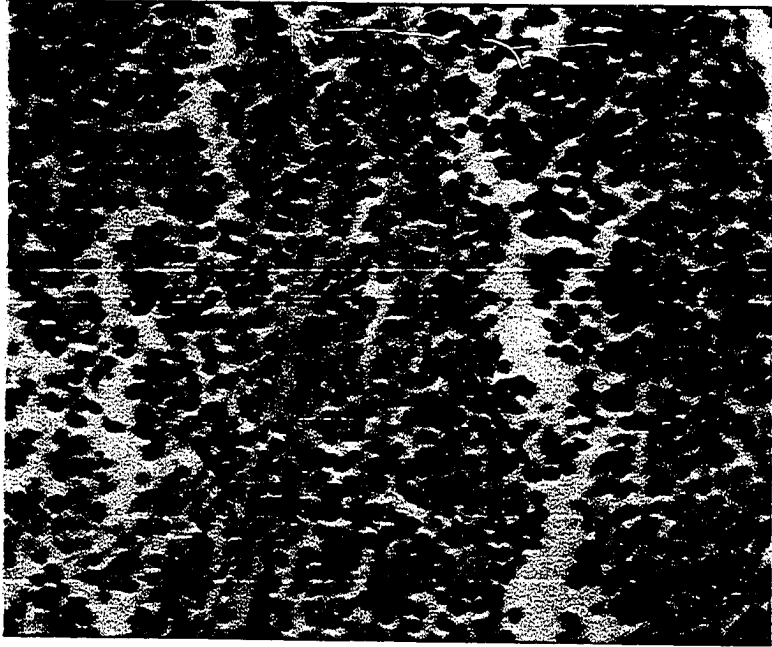


Figure 45. Higher magnification of a portion of the field in Figure 43. X 495. Giemsa stain.

(M.D. No. 108B4)

Figure 46. Hyaline-like mass surrounded by neutrophils in the thymus from an animal with mucosal disease. X 495. From same animal as Figure 44. Giemsa stain.

(M.D. No. 90A5)



greater portion of the increase in eosinophilic material was apparently due to an increase in the number of Hassall's corpuscles present in the medulla (Figure 47). Infrequently neutrophilic leukocytes were found in great numbers in the thymic parenchyma.

Eosinophils were found in the thymus of affected animals more frequently than neutrophils, but eosinophilic leukocytes were also frequently observed in the normal animals.

Tonsils Gross observation of the tonsils failed to reveal any marked difference between the mucosal disease affected animals and the normal animals.

On histological study, the tonsils of the mucosal disease animals exhibited a diffuse loss of lymphocytes, with a rather constant replacement by large mononuclear cells. Neutrophilic and eosinophilic infiltrations of the lymphatic tissue of the tonsil were occasionally observed but were not generally marked. In three animals some of the germinal centers exhibited eosinophilic staining material that was thought to be coagulated protein (Figures 48 and 49). Neutrophil packing of the arterioles occurred infrequently.

In most of the diseased animals, the tonsillar crypts were filled with a mixture of neutrophils, eosinophils and desquamated epithelial cells. This type of change was also a prominent finding in the tonsils obtained from normal animals.



Figure 47. Thymus from mucosal disease animal. X 920. Note hyaline-like material, eosinophils and absence of thymocytes. Giemsa stain.

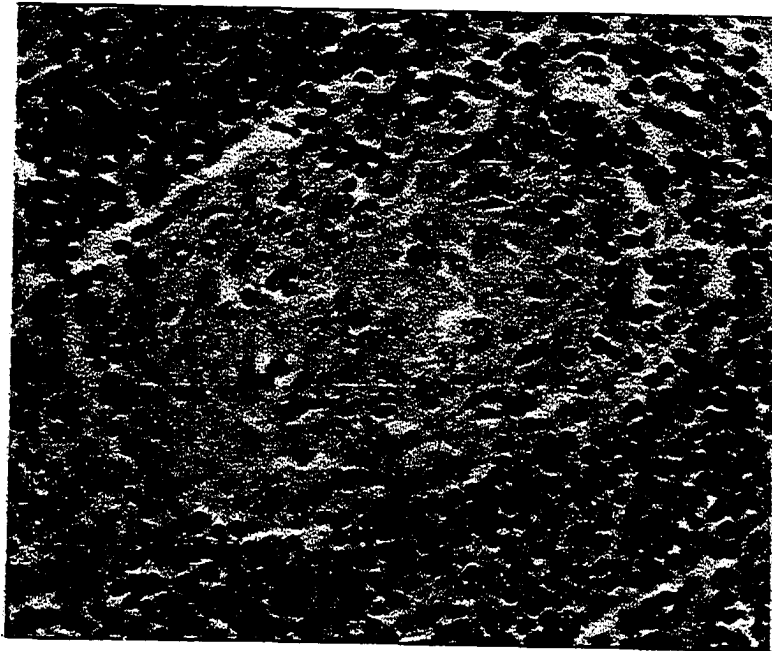
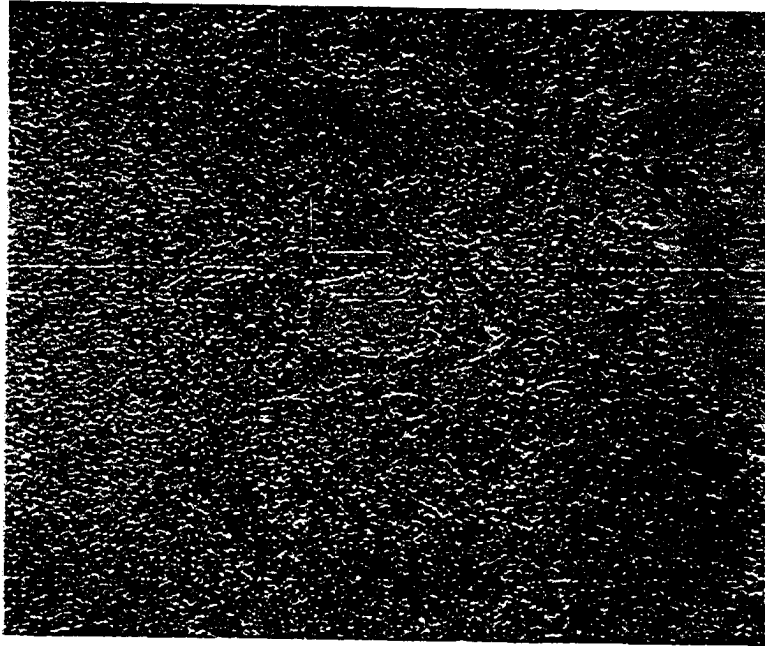
(M.D. No. 90A5)

Figure 48. Tonsil from a mucosal disease affected animal.
X 95. Note eosinophilic material in germinal
center. Hematoxylin and eosin stain.

(M.D. No. 107A8)

Figure 49. Enlargement of the germinal center in Figure 48.
X 495. Hematoxylin and eosin stain.

(M.D. No. 107A8)



Peyer's patches The gross lesions in the mucosa of the ileum over Peyer's patches varied from initial necrosis and hemorrhage to complete necrosis and sloughing of the entire mucosa leaving a hemorrhagic crater.

In numerous cases an accumulation of excessive mucus was present in the region of Peyer's patches. The changes closely correspond to those given by Ramsey (1956).

Histological examination of the Peyer's patches always revealed a marked decrease in the number of lymphocytes present (Figures 50 and 51).

In many cases a coagulative necrosis involving an entire lymphatic nodule was observed. Nuclear debris in an eosinophilic granular matrix was seen in cases in which coagulative necrosis had occurred. The predominant cell remaining in these areas was the mononuclear phagocyte, whose cytoplasm often contained nuclear debris and sometimes hemosiderin. Occasionally neutrophils but more often eosinophils were present in a lymphocyte depleted area.

Infrequently a focal coagulative necrosis that involved only a portion of the lymphoid tissue in Peyer's patches was noted. These focal lesions occurred only in those animals that had been sacrificed and only in the animals which did not show marked changes of the mucosa over the lymphoid tissue.

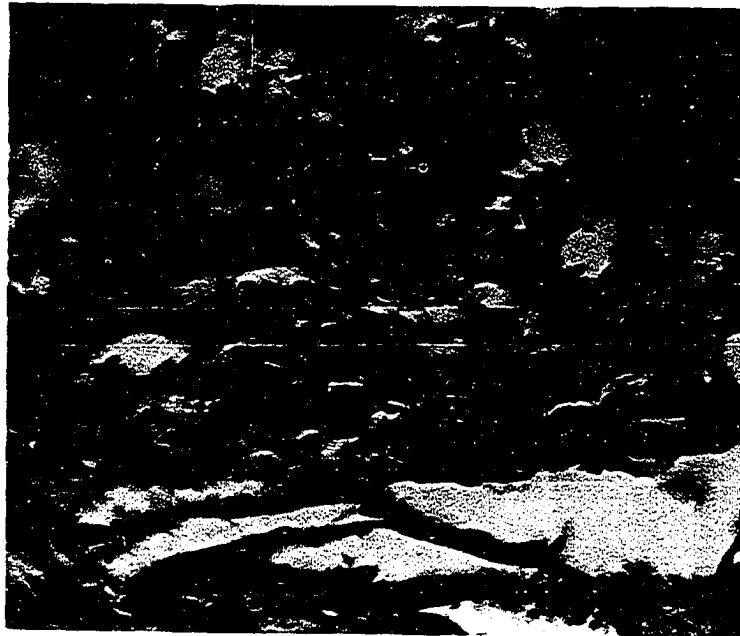
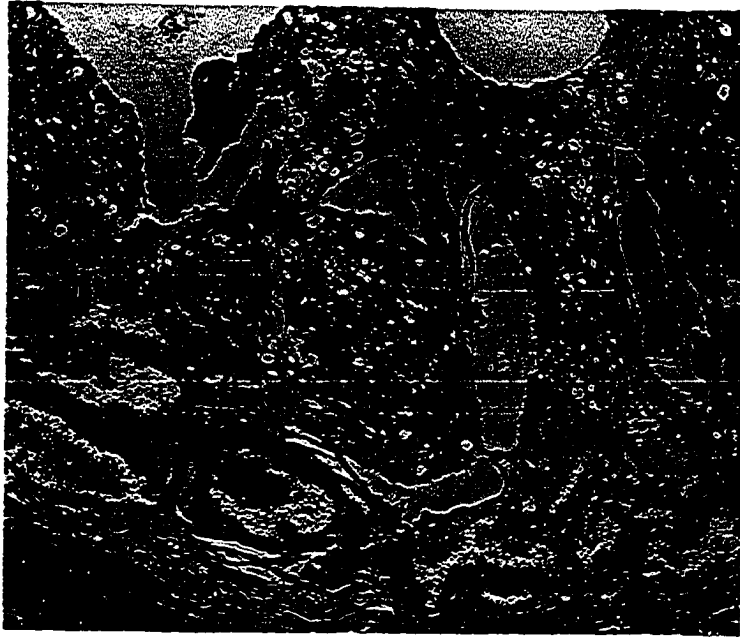
Hyperemia and hemorrhage in the lymphoid tissue was

Figure 50. Peyer's patch from an animal with mucosal disease. X 95. Note that few small lymphocytes are present.

(M.D. No. 12102)

Figure 51. Higher magnification of a portion of the field in Figure 50. X 495.

(M.D. No. 12102)



often observed in conjunction with the focal type of lesion.

The changes observed in the mucosa were the same as those described by Ramsey (1956). They consisted of congestion, hemorrhages and necrosis of the epithelium. Ulceration was a frequent finding.

In some cases a marked depletion of lymphocytes in submucosal solitary nodules of the jejunum was noted. In these cases the stroma appeared to be more easily seen and was shown to be intact by special reticulum staining (Figures 52 and 53). In the cases which exhibited a coagulative necrosis the reticulum was not intact and apparently had disappeared (Figures 54 and 55).

Changes in the submucosa varied with the extent of damage to the mucosa. The most constant changes observed were edema, congestion and hemorrhages. The degree of neutrophilic and eosinophilic reaction was quite variable but generally was not marked in most cases.

Bone marrow

The reaction of the bone marrow was variable. In general a greater number of granulocytes were observed in the sternal marrow of mucosal disease affected cattle than in the normal cattle (compare Figures 56 and 58 with Figures 57 and 59). In a few cases the increase in granulocytes was focal in nature but generally the reaction was diffuse and a majority of the cells were of the neutrophilic type.

Figure 52. Submucosal lymphatic nodule in jejunum of animal affected with mucosal disease. X 95. Note that reticulum is present and lymphocytes have disappeared. Gomori's reticulum stain.

(M.D. No. 51A8)

Figure 53. Higher magnification of lymphatic nodule in Figure 52. X 495. Gomori's reticulum stain.

(M.D. No. 51A8)

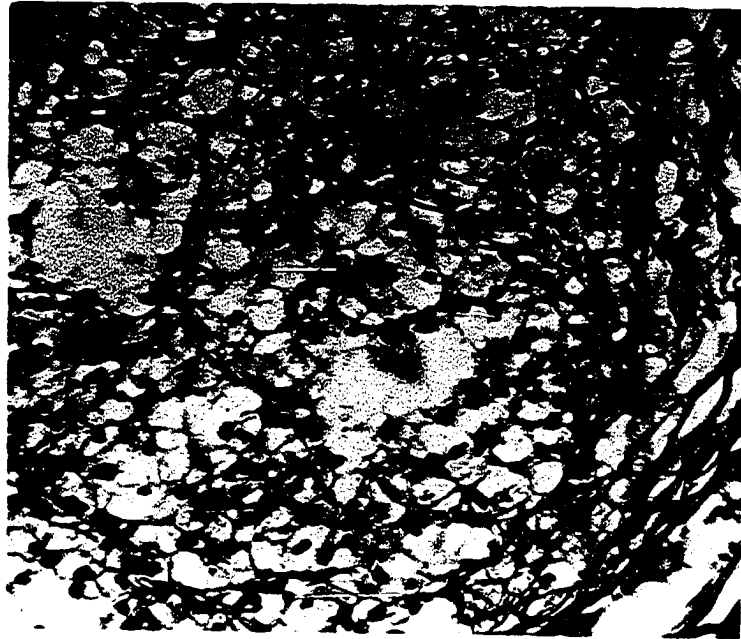


Figure 54. Necrosis of lymphatic nodule in the ileum of animal affected with mucosal disease. X 95. Note that the reticulum has apparently disappeared. Gomori's reticulum stain.

(M.D. No. 84C22)

Figure 55. Higher magnification of a portion of the field in Figure 54. X 495. Gomori's reticulum stain.

(M.D. No. 84C22)

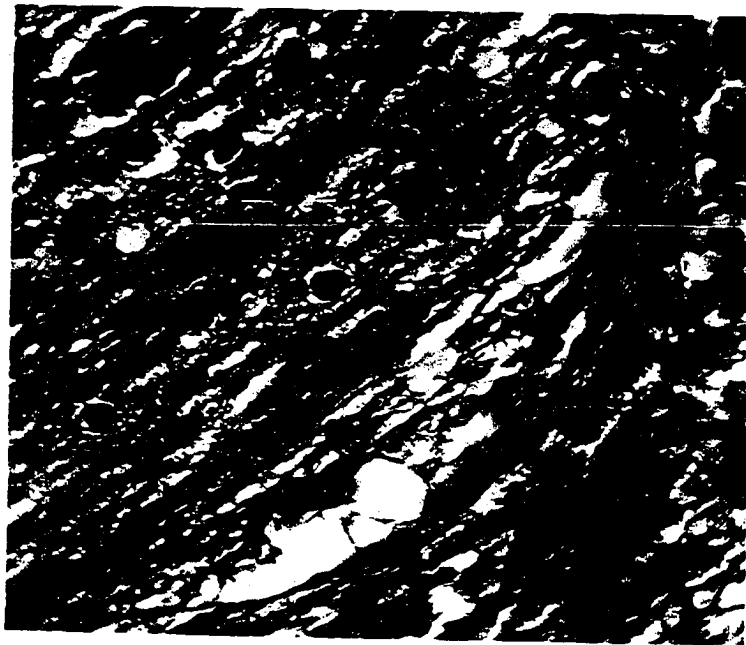


Figure 56. Bone marrow from an animal affected with mucosal disease. X 95. Note the cellularity and compare with Figure 57. Hematoxylin and eosin stain.

(M.D. No. 79E2)

Figure 57. Bone marrow from a normal animal. X 95. This animal was the same age as the one in Figure 56. Hematoxylin and eosin stain.

(M.D. No. 115C11)

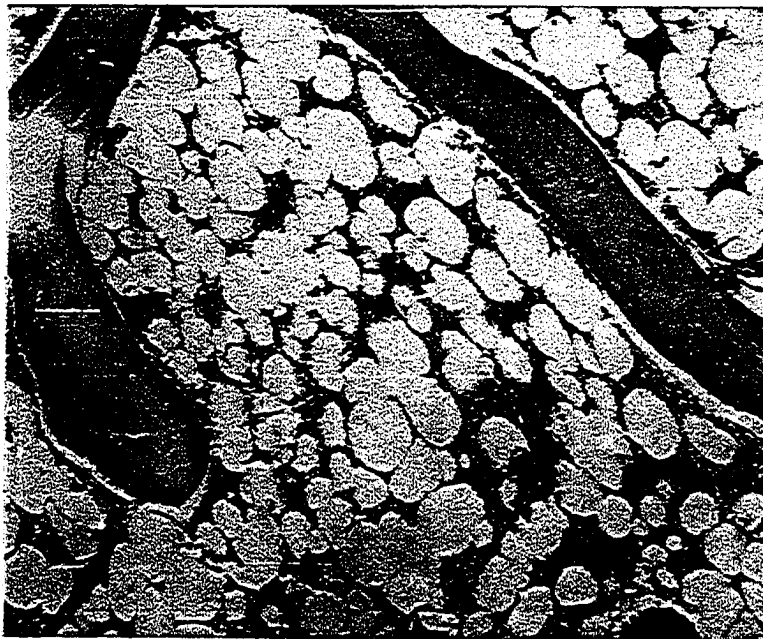
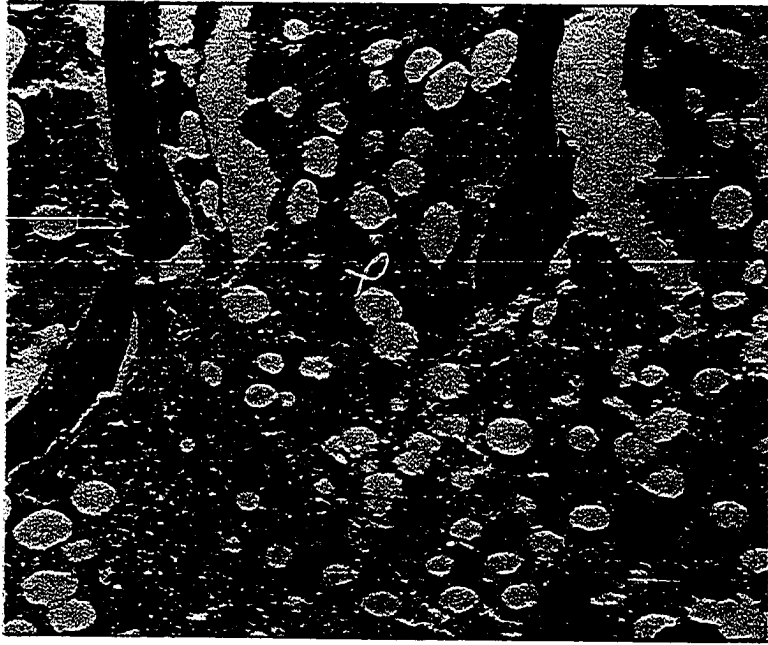
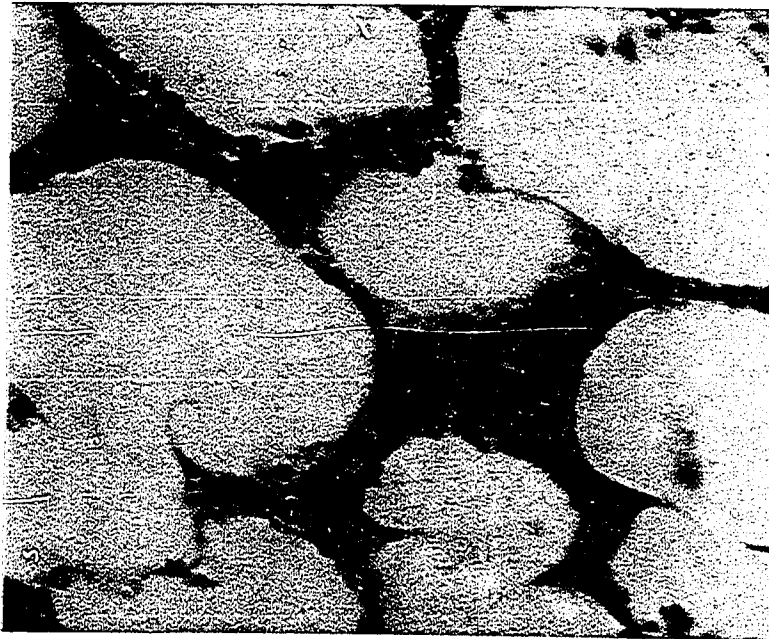
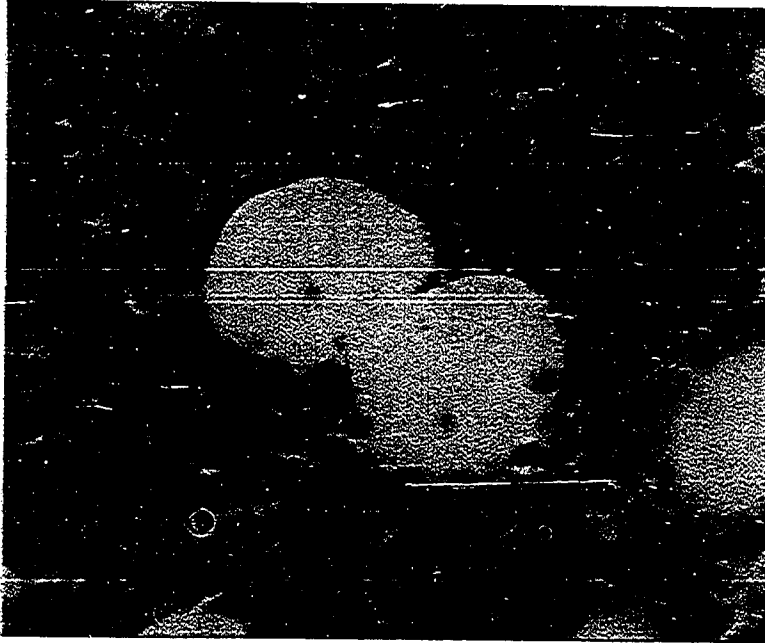


Figure 58. Bone marrow from mucosal disease affected animal exhibiting myeloid hyperplasia. X 495. From same animal as Figure 56. Hematoxylin and eosin stain.

(M.D. No. 79E2)

Figure 59. Higher magnification of a portion of the field in Figure 57. X 495. Compare with Figure 58. Hematoxylin and eosin stain.

(M.D. No. 115C11)



An apparent increase in the number of megakaryocytes was observed in about one-half of the cases.

Blood Vascular System

Heart

Gross lesions consisting of subepicardial and subendocardial hemorrhages were frequently noted in those animals that died during the natural course of mucosal disease. However, careful gross examination of the hearts of animals that were sacrificed failed to show any apparent gross lesions.

Histopathological study of sections of cardiac muscle from affected animals failed to reveal significant changes. Occasionally a small focal area of muscle would be more eosinophilic than the surrounding muscle but this was not observed consistently. Sections stained with Gomori's one step trichrome stain did not indicate that necrosis of muscle fibers had taken place.

Aorta

Gross lesions were not detected in the aorta in any of the affected animals.

Microscopic study of sections of aortas revealed an abnormality only in one case. In this instance a focal calcification of the media of the aorta had occurred.

Peripheral arteries and veins

Significant changes in the arteries and veins were absent in the affected animals. In three cases a small amount of eosinophilic material between the internal elastic membrane and the endothelium was found.

Arterioles, venules and lymphatic vessels

Changes were observed in five of the affected animals, consisting of thrombosis of the venules, lymphatic vessels and arterioles. In these cases degeneration of the media accompanied by an accumulation of neutrophils in and around the adventitia of arterioles was observed. The arterioles were located in the submucosa of the abomasum, small intestine or the colon in all instances where ulceration of the mucosa, coagulative necrosis and severe edema of the submucosa were present.

Hematological Studies

Blood

Several interesting observations were noted on gross examination of blood from mucosal disease animals. The blood was dark red in color, very viscid and dripped slowly from the bleeding needle (15 gauge). The clotting time was apparently very short as the blood frequently clotted in the needle during bleeding from the external jugular vein. It was also noted that clot retraction was slow and incomplete.

Serum yield was poor and serum separation was difficult in most cases. In advanced cases only 5 to 10 cubic centimeters of serum were obtained from 40 cubic centimeters of blood.

Erythrocyte counts The erythrocyte counts in mucosal disease affected animals are tabulated in Table 1. The number of erythrocytes per cubic millimeter of blood varied from 6,000,000 to 12,350,000. In general the number of erythrocytes per cubic millimeter of blood was within the normal range or increased.

Leukocyte counts Total leukocyte counts are given in Table 1. Five animals (numbers 31, 32, 60, 72, and 77, Table 1) revealed leukocyte counts below the normal range at the time the animals were first examined. In the remaining forty-five animals the total leukocyte counts were either within the normal range or elevated at the time of the first examination. Twenty-eight animals had two or more total leukocyte counts taken from them. In the remaining twenty-two animals only one count was made prior to the death of the animal.

It should be observed that the total leukocyte counts of five animals (numbers 32, 60, 72, 78 and 134, Table 1) were below normal in the last counts that were made prior to the death of the animal.

Of the remaining forty-five animals the total leukocyte counts were either normal or above normal just prior to death. It should be noted that in the case of three animals

Table 1. Erythrocyte and total leukocyte counts and hemoglobin, blood urea and hematocrit values in animals affected with mucosal disease^a

Case no.	Date	Erythrocytes per mm. ³	Leukocytes per mm. ³	Hemoglobin (gm. per 100 cc.)	Blood urea nitrogen (mg.%)	Hematocrit (%)
1	4-27-56	10,760,000	5,560	8.3	-	-
11	9-28-56	10,960,000	9,800	9.85	84	-
16A	1-11-57	7,850,000	14,250	13.5	12.3	-
	1-12-57	7,140,000	7,050	11.9	13.6	-
	1-13-57	7,820,000	8,300	11.7	16.1	-
	1-14-57	8,970,000	7,200	12.4	15.3	-
	1-15-57	7,740,000	7,450	14.2	-	-
	1-16-57	8,640,000	6,850	15.2	23.8	-
	1-17-57	9,230,000	7,750	16.8	43.4	-
	1-18-57	9,740,000	14,350	18	67.2	-
	1-19-57	9,670,000	15,300	16.4	119	-
	1-21-57	9,060,000	16,950	16.4	125	-
16B	1-11-57	9,390,000	30,250	14.2	52.7	-
22	2-27-57	12,530,000	22,300	9.54	-	-
	2-28-57	11,060,000	29,150	10.05	200	-
23	2-26-57	8,330,000	6,300	12.5	188.7	-
24	2-26-57	9,230,000	8,000	16.0	91	-
	2-28-57	10,100,000	12,500	17.0	200	-
28	3- 4-57	6,000,000	7,900	7.9	19.6	-
	3- 5-57	6,030,000	6,550	8.0	23.1	-
	3- 6-57	8,530,000	9,800	8.2	23.8	-
	3- 7-57	8,030,000	7,100	8.1	25.5	-
	3- 8-57	8,160,000	7,350	8.5	-	-
	3-13-57	8,270,000	5,900	9.0	49.3	-
	3-16-57	9,060,000	5,000	11.5	65.5	-
28A	3- 4-57	8,250,000	10,000	12.8	28.1	-
	3- 5-57	9,330,000	13,100	16.0	70.6	-
31	3-13-57	6,060,000	4,100	6.6	24.7	-
	3-14-57	7,080,000	4,950	8.6	19.6	-
	3-15-57	8,170,000	5,800	14.3	57.8	-

^aData obtained from cattle submitted to Iowa State University Veterinary Clinic.

Table 1 (Continued).

Case no.	Date	Erythrocytes per mm. ³	Leukocytes per mm. ³	Hemoglobin (gm. per 100 cc.)	Blood urea nitrogen (mg.%)	Hematocrit (%)
32	3-26-57	9,380,000	4,000	15	155.6	-
34	3-29-57	9,820,000	25,400	10.7	119	-
35	3-30-57	9,860,000	5,100	16.2	34	-
	4- 1-57	9,910,000	5,700	17.8	161.5	-
37	4- 9-57	9,310,000	19,200	14.3	81.6	-
40	4-17-57	9,020,000	6,200	11.8	21.3	-
	4-21-57	8,870,000	6,900	13.2	58.7	-
43	4-27-57	10,610,000	24,900	13.2	59.5	-
49	5-15-57	9,260,000	17,600	10.2	89.3	-
	5-18-57	6,580,000	14,200	10.4	142.8	-
51	5-29-57	9,990,000	12,100	14.0	300	-
53	6- 8-57	10,010,000	13,350	11.8	42.3	-
56	7-29-57	9,270,000	26,000	14.0	-	-
	7-30-57	9,060,000	25,200	14.3	-	-
60	10- 5-57	8,480,000	4,950	15.3	68	-
62A	1-10-58	8,890,000	13,150	7.11	-	33
66	1-24-58	9,130,000	22,900	-	-	-
	1-25-58	9,270,000	19,000	11.2	62	37
	1-26-58	9,020,000	16,500	8.95	-	30
	1-27-58	8,850,000	16,950	-	74	32
	1-28-58	8,970,000	22,350	-	-	35
68	2- 3-58	10,820,000	12,850	-	45	45
	2- 4-58	9,920,000	20,550	16.4	62	48
69	2-11-58	9,730,000	10,050	14.6	78	43
71	2-12-58	10,260,000	13,500	-	30.3	39
	2-13-58	9,890,000	42,300	13.4	54.2	43
72	2-13-58	8,010,000	4,850	11.95	36	36

Table 1 (Continued).

Case no.	Date	Erythro- cytes per mm. ³	Leuko- cytes per mm. ³	Hemo- globin (gm. per 100 cc.)	Blood urea nitrogen (mg.%)	Hema- tocrit (%)
73	2-13-58	9,700,000	12,350	15.5	45	43
	2-17-58	10,520,000	27,700	17.5	-	52
76	3- 8-58	8,580,000	9,700	12.6	148	36
	3- 9-58	6,720,000	16,700	14.6	108.4	38
77	3- 8-58	9,360,000	4,700	13.4	40	42
	3- 9-58	9,820,000	12,550	15.0	40.4	44
	3-10-58	8,630,000	14,500	16.4	95.6	49
	3-11-58	8,710,000	14,600	16.0	124	45
78	3-11-58	9,160,000	6,300	10.5	129	27
	3-13-58	6,470,000	4,150	10.2	98	33
79	3-22-58	8,490,000	7,950	-	124	38
84	3-29-58	9,870,000	16,550	16.0	116	41
85	3-29-58	9,110,000	7,500	13.8	60.6	33
	3-31-58	9,390,000	11,150	16.0	95.6	44
89	5- 4-58	9,460,000	17,450	15.5	-	44
90	5-29-58	8,360,000	18,050	-	108.4	42
91	7- 1-58	8,790,000	5,250	12.6	42	39
96	9- 4-58	10,280,000	21,400	14.6	47.8	52
101	10- 2-58	9,340,000	14,100	10.0	47.8	43
	10- 3-58	-	19,100	9.8	62	43
102	10- 7-58	-	10,750	-	-	-
	10- 8-58	8,840,000	9,500	10.0	36	43
	10- 9-58	-	11,150	10.2	-	44
	10-10-58	-	7,400	10.1	-	44
106	1-10-59	10,580,000	12,300	15.6	-	43
	1-11-59	9,850,000	6,200	15.6	-	41
107	1-10-59	9,990,000	16,500	15.2	-	41
	1-11-59	9,940,000	8,150	15.2	-	40
	1-13-59	9,870,000	7,800	16.5	-	44

Table 1 (Continued)

Case no.	Date	Erythro- cytes per mm. ³	Leuko- cytes per mm. ³	Hemo- globin (gm. per 100 cc.)	Blood urea nitrogen (mg.%)	Hema- tocrit (%)
118	2- 1-59	9,340,000	25,100	16.1	115	40
119	2-17-59	8,730,000	14,200	17.0	50	42
	2-19-59	-	21,850	18.0	50	52
121	2-25-59	9,740,000	38,200	20	57.5	51
	2-26-59	-	33,200	20	-	55
122	3-23-59	9,480,000	14,850	13.7	78.5	37
130	4- 2-59	9,230,000	12,300	18.5	26.0	39
	4- 4-59	-	17,600	20	62.5	49
132	4-26-59	9,790,000	20,400	16.1	46.5	41
134	5- 1-59	9,430,000	5,900	15.6	73.0	38
	5- 2-59	-	3,300	14.4	75.5	39
146	12-23-59	9,320,000	8,600	15.6	-	43

(Numbers 32, 60 and 72) only one count was performed and it was below normal in each case.

Differential leukocyte counts are tabulated in Table 2. The percentages of the different types of leukocytes are given on one line and the absolute numbers of each type are given immediately below. In almost every animal a relative lymphopenia and a relative neutrophilia was noted. Some animals showed a shift to the left. Eosinopenia was a constant finding.

Hemoglobin Hemoglobin concentrations (Table 1) were generally within the normal range or increased in cattle with mucosal disease. There was a tendency for the values to become very high as the disease progressed.

Blood urea nitrogen The blood urea nitrogen values (Table 1) were almost invariably higher than normal and in some cases the values were very high in the terminal stages of the disease.

Hematocrit values The hematocrit readings (Table 1) varied from twenty-seven to fifty-five percent in animals affected with mucosal disease. Many of the values are considered to be above the normal range and most of the values are above the average normal value.

Blood sugar determinations Blood sugar concentrations in affected animals are tabulated in Table 2. The concentrations ranged from 52 to 1,018 milligrams per 100 cubic centimeters. In twenty-one of the twenty-six animals concentrations

Table 2. Differential leukocyte and blood platelet counts and blood sugar levels in cattle affected with mucosal disease

Case no.	Date	Leuko-cytes per mm. ³	Differential leukocyte counts ^a					Plate-lets per mm. ³ (x10 ³)	Blood sugar (mg.%)
			Lymph.	Neut. ^b	Neut. ^c	Mono.	Eos.		
1	4-27-56	5560	38 2113	15 834	44 2446	3 167	0 0	-	-
11	9-28-56	9800	38 3724	34 3332	23 2254	0 0	5 490	-	-
16A	1-14-57	7200	47 3384	46 3312	4 288	2 144	1 72	-	-
	1-15-57	7450	25 1862	71 5290	3 223	0 0	1 75	-	-
	1-16-57	6850	44 3014	51 3494	3 206	1 68	1 68	-	-
	1-17-57	7750	24 1860	74 5735	2 155	0 0	0 0	-	-
	1-18-57	14350	21 3013	79 11337	0 0	0 0	0 0	-	-
	1-19-57	15300	15 2295	81 12393	4 612	0 0	0 0	-	-
	1-21-57	16950	23 3899	68 11526	7 1186	2 339	0 0	-	-
22	2-27-57	22300	17 3900	35 7700	47 10400	1 300	0 0	-	-
	2-28-57	29150	13 3789	74 21571	11 3207	2 583	0 0	-	-
23	2-26-57	6300	45 2835	46 2898	8 504	1 63	0	-	-
24	2-26-57	8000	39 3120	54 4320	6 480	1 80	0	-	-

^aNumbers on first line for each date are the percentages while numbers on the second line represent absolute numbers of each type of leukocyte.

^bMature neutrophils.

^cImmature neutrophils.

Table 2 (Continued)

Case no.	Date	Leuko- cytes per mm. ³	Differential leukocyte counts ^a					Plate- lets per mm. ³ (x10 ³)	Blood sugar (mg.%)
			Lymph.	Neut. ^b	Neut. ^c	Mono.	Eos.		
28	3- 4-57	7500	43	53	1	2	1	-	-
			3225	3975	75	150	75	-	-
	3- 5-57	6550	39	47	4	3	7	-	-
			2555	3078	262	197	458	-	-
	3- 6-57	9800	44	52	0	1	3	-	-
			4312	5096	0	98	294	-	-
28A	3- 4-57	10000	42	53	2	1	2	-	-
			2982	3763	142	71	142	-	-
	3- 5-57	13100	56	40	2	1	1	-	-
			4116	2940	147	73	74	-	-
	3- 6-57	9800	44	52	0	1	3	-	-
			4312	5096	0	98	294	-	-
31	3-13-57	4100	67	30	1	1	1	-	-
			2747	1230	41	41	41	-	-
	3-14-57	4950	72	24	0	1	3	-	-
			3564	1188	0	50	148	-	-
	3-19-57	5800	46	53	1	0	0	-	-
			2668	3074	58	0	0	-	-
32	3-26-57	4000	18	59	20	1	2	-	-
			720	2360	800	40	80	-	-
34	3-29-57	25400	19	68	13	0	0	-	-
			4826	17272	3302	0	0	-	-
35	3-30-57	5100	35	59	6	0	0	-	-
			1785	3009	306	0	0	-	-
	4- 1-57	5700	34	60	5	1	0	-	-
			1938	3420	285	57	0	-	-
37	4- 9-57	19200	34	53	11	1	1	-	-
			6528	10176	2112	192	192	-	-
40	4-17-57	6200	43	46	11	0	0	-	-
			2666	2852	682	0	0	-	-
	4-19-57	5900	65	21	14	0	0	-	-
			3835	1239	826	1	0	-	-
	4-21-57	6900	48	16	35	1	0	-	-
			3312	1104	2415	69	0	-	-

Table 2 (Continued)

Case no.	Date	Leuko- cytes per mm. ³	Differential leukocyte counts ^a					Plate- lets per mm. ³ (x10 ³)	Blood sugar (mg.%)
			Lymph.	Neut. ^b	Neut. ^c	Mono.	Eos.		
43	4-27-57	24900	15 3735	80 19920	3 747	2 498	0 0	-	-
49	5-15-57	17600	11 1936	81 14256	4 704	2 352	2 352	-	-
51	5-29-57	12100	30 3630	52 6292	13 1573	3 363	2 242	-	-
53	6- 8-57	13350	30 4005	67 8945	2 267	1 133	0 0	-	-
56	7-29-57	26000	26 6760	70 18200	4 1040	0 0	0 0	-	-
	7-30-57	25200	30 7560	60 15120	7 1764	2 504	1 252	-	-
60	10- 5-57	4950	43 2128	56 2772	1 50	0 0	0 0	-	-
62A	1-10-58	13150	29 3814	68 8942	2 263	1 131	0 0	-	-
66	1-24-58	22900	25 5725	71 16259	2 458	0 0	2 458	132	92
	1-25-58	19000	20 3800	72 13680	5 950	0 0	3 570	-	-
	1-26-58	16500	26 4290	71 11715	3 495	0 0	0 0	-	-
	1-27-58	16950	16 2712	77 13052	7 1186	0 0	0 0	-	86
	1-28-58	22350	16 3576	82 18327	2 447	0 0	0 0	-	-
68	2- 3-58	12850	22 2827	75 9638	3 385	0 0	0 0	-	290
	2- 4-58	20550	17 3494	77 15823	6 1233	0 0	0 0	-	328
69	2-11-58	10050	36 3618	60 6030	3 301	0	1 101	480	308
71	2-12-58	13500	18 2430	80 10800	2 270	0 0	0 0	540	122
	2-13-58	42300	14 5922	75 31725	10 4230	0	1 423	-	217

Table 2 (Continued)

Case no.	Date	Leuko- cytes per mm. ³	Differential leukocyte counts ^a					Plate- lets per mm. ³ (x10 ³)	Blood sugar (mg.%)
			Lymph.	Neut. ^b	Neut. ^c	Mono.	Eos.		
72	2-13-58	4850	39	58	2	0	1	220	102
			1892	2813	97	0	48		
73	2-13-58	12350	38	60	2	0	0	400	125
			4693	7410	247	0	0		
	2-17-58	27700	37	50	9	0	4	-	-
			10249	13850	2493	0	1108		
76	3- 8-58	9700	39	58	2	0	1	952	222
			3783	5626	194	0	97		
	3- 9-58	16700	42	53	5	0	0	-	-
			7014	8851	835	0	0		
77	3- 8-58	4700	38	59	1	0	2	1312	168
			1786	2773	47	0	94		
	3- 9-58	12550	25	73	1	0	1	-	-
			3138	9162	125	0	125		
	3-10-58	14500	23	75	2	0	0	620	152
			3335	10875	290	0	0		
	3-11-58	14600	21	71	7	1	0	-	240
			3066	10366	1022	146	0		
78	3-11-58	6300	39	59	2	0	0	-	129
			2457	3717	126	0	0		
	3-13-58	4150	42	50	7	0	1	624	98
			1743	2075	290	0	42		
79	3-22-58	7950	40	57	0	0	3	838	400
			3180	4532	0	0	238		
84	3-29-58	16550	22	70	8	0	0	868	182
			3641	11585	1324	0	0		
85	3-29-58	7500	39	57	4	0	0	-	156
			2925	4275	300	0	0		
	3-31-58	11150	34	63	3	0	0	764	144
			3791	7025	334	0	0		
89	5- 4-58	17450	22	78	0	0	0	880	-
			3839	13611	0	0	0		
90	5-29-58	18050	20	72	7	0	1	594	1018
			3610	12996	1264	0	180		
91	7- 1-58	5250	41	22	33	2	2	280	95
			2153	1155	1732	105	105		

Table 2 (Continued)

Case no.	Date	Leuko- cytes per mm. ³	Differential leukocyte counts ^a					Plate- lets per mm. ³ (x10 ³)	Blood sugar (mg. %)
			Lymph.	Neut. ^b	Neut. ^c	Mono.	Eos.		
96	9- 4-58	21400	29 6206	64 13696	3 642	3 642	1 214	973	509
101	10- 2-58	14100	13 1833	82 11562	5 705	0	0	390	419
	10- 3-58	19100	13 2483	83 15853	4 764	0 0	0 0	-	509
102	10- 7-58	10750	18 1935	50 5375	30 3225	2 215	0 0	-	52
	10- 8-58	9500	22 2090	60 5700	14 1330	4 380	0 0	586	62
	10- 9-58	11150	23 2565	64 7136	9 1004	3 334	1 111	-	62
	10-10-58	7400	24 1776	62 4588	10 740	2 148	2 148	-	74
106	1-10-59	12300	36 4428	25 3075	38 4674	1 123	0 0	500	66
	1-11-59	6200	62 3844	20 1240	18 1116	0 0	0 0	-	59
107	1-10-59	16500	42 6930	35 5775	21 3465	2 330	0 0	592	52
	1-11-59	8150	41 3342	23 1874	35 2852	1 82	0 0	-	86
	1-13-59	7800	22 1716	39 3042	38 2964	1 78	0 0	-	62
118	2- 1-59	25100	14 3514	55 13805	30 7530	1 251	0 0	824	300
119	2-17-59	14200	31 4402	40 5680	29 4118	0 0	0 0	668	138
	2-19-59	21850	18 3933	35 7648	47 10269	0 0	0 0	-	100
121	2-25-59	38200	19 7258	30 11460	48 18336	3 1146	0 0	526	100
	2-26-59	33200	14 4648	51 16932	30 9960	5 1660	0 0	-	82
122	3-23-59	14850	33 4900	31 4604	35 5197	1 149	0 0	488	300

Table 2 (Continued)

Case no.	Date	Leuko-cytes per mm. ³	Differential leukocyte counts ^a					Plate-lets per mm. ³ (x10 ³)	Blood sugar (mg. %)
			Lymph.	Neut. ^b	Neut. ^c	Mono.	Eos.		
130	4- 2-59	12300	43	31	25	1	0	542	45
			5289	3813	3075	123	0	-	-
	4- 4-59	17600	32	16	50	1	1	-	54
			5632	2816	8800	176	176		
132	4-26-59	20400	21	31	46	1	1	-	181
			4284	6324	9384	204	204		
134	5- 1-59	5900	45	24	30	1	0	208	286
			2655	1416	1770	59	0	-	-
	5- 2-59	3300	45	11	42	1	1	-	400
			1485	363	1386	33	33		
146	12-23-59	8600	31	34	31	3	1	-	-
			2666	2924	2666	258	86		

of 100 milligrams per 100 milliliters or higher were found and are considered higher than normal.

Blood platelet counts Blood platelet counts are recorded in Table 2. In most animals the counts were within the normal range.

Sedimentation rates The sedimentation rates were determined on thirteen animals. The greatest fall in erythrocytes was five millimeters in twenty-four hours. In all other cases the fall was 0 to 4 millimeters in twenty-four hours. This indicates that the sedimentation rate is not appreciably altered in cattle affected with mucosal disease.

Blood volume determinations Blood volume determinations were performed on five animals and the results are summarized in Table 3.

Table 3. Blood volume determinations on five animals with mucosal disease

Case no.	Date performed	Date died or destroyed	Body weight (kg.)	Total blood volume (cc.)	Plasma volume (cc.)	Blood volume (cc./kg.)
106	1-10-59	1-10-59 ^a	182	7,279	4,149	39.9
107	1-11-59		205	14,998	8,849	73.1
107	1-13-59	1-13-59 ^b	205	13,325	7,462	65.0
118	2- 1-59	2- 1-59 ^c	261	12,919	7,752	49.5
119	2-17-59		250	13,262	7,692	53.0
119	2-19-59	2-19-59 ^c	250	11,881	5,972	47.9
121	2-25-59	2-26-59 ^c	261	13,750	6,493	52.6

^aDied.

^bDestroyed; early case.

^cDestroyed when moribund.

In comparing these values with the average blood volume value of 57 cubic centimeters per kilogram of body weight (Reynolds, 1953) it is noted that four of the five animals have a decreased blood volume. The animal that had the highest value was an early case and euthanasia was performed before the disease had run its course. It is also worthy of mention that the animal that had the lowest blood volume, case 106, died the same day that the determination was made.

Cerebrospinal fluid

Cerebrospinal fluid studies were performed on twelve animals. The results are listed in Table 4.

Table 4. Cerebrospinal fluid studies

Case no.	Date	Cells/mm. ³	Sugar mg./100cc.	Protein mg./100cc.
69	2-11-58	2	111	-
70	2-13-58	5	228	77
72	2-17-58	3	33	15
73	2-17-58	2	62	33
76	2-17-58	4	-	-
77	3- 9-58	2	149	14
78	3-13-58	2	39	10
84	3-29-58	3	97	9
85	3-31-58	2	60	7
90	5-29-58	1	200	27
91	7- 2-58	3	52	17
96	9- 5-58	6	164	15

Cell counts The cell counts of 1 to 6 cells per cubic millimeter of fluid were within the normal range in all instances.

Sugar determinations The cerebrospinal fluid sugar levels (Table 3) were quite variable but there was some correlation of the levels of cerebrospinal fluid sugar and blood sugar. The sugar levels were high in six cases, low in two animals and normal in the other three. The values ranged from a high of 228 to a low of 33 milligrams percent.

Total protein determinations The values for total protein of cerebrospinal fluid ranged from a high of 77 to a low of 7 milligrams percent. They were low in 7 cases, normal in one case and high in two cases.

DISCUSSION

Possible Explanations of the Tissue Changes

Lymphatic tissue

Since the microscopic lesions observed in nearly all of the lymphatic tissue were similar in nature, the lesions will be discussed for the lymphatic tissue as a single entity except in certain cases.

Hyperemia, edema and hemorrhage It is felt that the hyperemia, edema and hemorrhage of the lymphatic tissue noted in histopathological studies probably result from a combination of factors. Apparently the etiological agent(s) of mucosal disease has (have) a marked affinity for the lymphatic tissue because microscopic lesions of this tissue were always very evident. Hence the hyperemia, edema, and hemorrhage are probably vascular changes that are accompanying an acute inflammatory reaction. Furthermore the severe diarrhea and decreased water intake always led to dehydration, marked hemoconcentration and disturbed balance of electrolytes and blood constituents. The blood was usually cyanotic indicating lowered oxygen tension. The absorption of bacterial toxins and toxic products from the alimentary tract could secondarily accentuate the already developing vascular lesions. All of these factors affect permeability and integrity of capillaries, resulting in hyperemia, edema and hemorrhage.

Neutrophilic and eosinophilic infiltrations The

neutrophilic and eosinophilic leukocyte infiltrations are indicative of an inflammatory reaction. The foci of necrosis in the lymphatic tissue can serve as an irritant and cause an infiltration of neutrophils. The presence of numerous eosinophils in some of the lymph nodes is more difficult to explain. The function of the eosinophil has not been satisfactorily established. Smith and Jones (1957, p. 141) noted that eosinophils are commonly found in inflammatory reactions associated with antigen-antibody reactions and parasitic invasion. Evidence of parasitic invasion of lymph nodes was not observed in animals affected with mucosal disease. Since the cause of mucosal disease has not been definitely established the possibility of an antigen-antibody reaction causing the infiltration of eosinophils cannot be critically evaluated. It is of interest that Winqvist (1954) sometimes observed eosinophils in the cortex of lymph nodes in normal calves up to six months of age.

Decrease in the number of mitotic figures The

decrease in the number of mitotic figures in the lymphatic tissues is considered to be the result of either one or a combination of two factors. Jackson (1925), in studying the effects of inanition on growth patterns, noted that there was a decrease in the number of mitotic figures in all the lymphatic tissue. It is not known whether the short period

of inanition that generally accompanies mucosal disease results in a decrease of mitotic activity or not.

Another possibility was suggested by the observations of Maurer et al. (1958) that the lymph nodes of swine affected with African swine fever and hog cholera appeared to be inactive. Maurer et al. (1958) concluded that the viruses of these two disease had a specific affinity for the lymphocyte but did not give any explanation for the lack of activity in the lymph nodes. Evidence indicates that mucosal disease is caused by an infectious agent and that this agent may also have an affinity for lymphoid tissue. If this is true, it would be expected that a decrease in mitotic activity could result from effects of this agent on the cell.

Decrease in number of lymphocytes The decrease in the number of small lymphocytes in the various organs may have been due to a number of influences. The influence of stress and adrenal cortical hormones must be mentioned in view of the hypertrophy of the adrenal cortex observed by Whiteman (1960). Selye (1946) observed an involution of all the lymphoid tissue of laboratory animals that had been subjected to a variety of stress conditions.

The influence of a great variety of factors and agents on lymphoid tissue has been reviewed by Drinker and Yoffee (1941). Most of the experiments have been confined to laboratory animals and very little work has been done with

cattle. Winqvist (1954) reported that the stress of an operation to cannulate the thoracic duct in calves caused only slight changes in the lymph nodes and spleen. He noted a spotty lymphocytolysis in the thymus of some animals, but in other animals sections of the thymus were normal. Similar results were obtained after treatment with adrenal corticotropic hormone. This work suggests that the bovine may not be as susceptible to stressing agents as are the laboratory animals and that possibly the decrease in number of lymphocytes may not be entirely associated with stress.

Another possibility that was considered as an explanation for the decrease in number of lymphocytes was that it could be due to direct action of a viral agent. A decrease in the number of lymphocytes in the lymph nodes and spleen has been observed in such viral diseases as rinderpest (Maurer et al., 1955) African swine fever and hog cholera (Maurer et al., 1958).

The isolation of virus-like agents from field cases of mucosal disease in the United States has been accomplished by Pritchard (1955), Underdahl et al. (1957), Noice and Schipper (1959), Tyler (1960) and by the author as one member of a research group* at Iowa State University. The preceding suggested that the possibility of direct action of a viral

*Other members of the group included, Ramsey, Dr. F.K., Richter, Dr. W.R. and Whiteman, Dr. C.E., Department of Veterinary Pathology, Iowa State University of Science and Technology, Ames, Iowa.

agent should be considered as a cause in the decrease in numbers of lymphocytes. The observation of focal areas of lymphocyte depletion would be more compatible with the activity of a viral agent than with hormonal influence.

Focal accumulation of eosinophilic hyaline-like material and coagulative necrosis The focal accumulation of relatively acellular eosinophilic material in the lymphatic tissue was thought to be the result of necrobiotic changes. The staining reaction suggested that the material might have been protein in nature. Since similar lesions were noted in the lymphatic tissue of cattle with rinderpest (Maurer et al. 1955) and swine affected with African swine fever (Maurer et al. 1958) it is more evident that the cause is probably a viral agent.

The coagulative necrosis of the mesenteric and colic lymph nodes of affected animals suggests that a marked irritation has occurred. In these cases the effects of the infectious agent could be enhanced by the absorption of bacterial toxins and toxic products from the damaged epithelium of the intestinal tract.

Pigment deposition The accumulation of hemosiderin at the periphery of the lymphatic nodules in the spleen may have been due to exaggeration of the normal accumulation of hemosiderin as noted by Winqvist (1954). This may be due to the viscosity of the blood, to the damage noted in the lymphoid tissue or to an abnormally rapid breakdown of

hemoglobin pigments. It is not known which one of these factors has the most influence in the accumulations of hemosiderin in the spleen.

The distribution and the variation in the amount of lipofuscin in lymph nodes of different animals were in agreement with the observations of Wyler (1952). These were considered as normal variations.

Concretion-like bodies in the mesenteric lymph nodes

Since calcium carbonate depositions were found in apparently normal animals and in animals with other diseases, it is felt that these bodies are not specific reactions of mucosal disease. It is believed that these objects represent a mineralization of proteinaceous material and that the further characterization of these objects does not lie within the scope of this paper.

Bone marrow

The hyperplasia of the granulocytic series of cells of the bone marrow was thought to be due to a polypeptide originating from widespread destruction of cells in the gut and other tissue.

Cardiovascular system

Some of the lesions of the cardiovascular system were thought to be secondary and not specifically related to mucosal disease. The epicardial and endocardial hemorrhages were thought to be due to terminal anoxemia or hypoxemia as

the hemorrhages were found only in animals that died. The lack of thrombosis, arteritis, and medial degeneration being consistent lesions in the vessels indicated that the lesions were not specific for mucosal disease. These pathological changes probably resulted from secondary bacterial invasion or absorption of toxic products through breaks in the epithelium or alteration of the mucosa of the intestine.

Hematology

The elevation of the erythrocyte counts, hemoglobin levels, hematocrit readings and blood urea levels in conjunction with the decreased values obtained in a limited number of blood volume determinations was indicative of hemoconcentration and dehydration. The profuse diarrhea that was observed in animals affected with mucosal disease was considered as the primary cause of the severe dehydration. A decreased water intake observed in some animals also contributed to the dehydration. The possibility exists that the hypertrophy of the adrenal cortex observed by Whiteman (1960) may also play a role in the dehydration and hemoconcentration. The hypertrophied adrenal cortex may secrete an excess of mineral corticoids and may assist in bringing about a disturbance in electrolyte balance. It can also be reasoned that the hypertrophy of the adrenal cortex may have been a result of the electrolyte imbalance rather than a cause of it.

The elevation of the total leukocyte counts may have been partially due to the liberation of leukocyte promoting factor from the damaged cells of the intestinal tract. The marked hemoconcentration in some animals may also have played a part in the elevation of total leukocyte counts. The leucocytosis was caused primarily by an increase in numbers of neutrophils. The increased levels of neutrophils also may have been influenced by the increased production of the hormones of the adrenal cortex. Winqvist (1954) observed that a neutrophilia and an eosinopenia occurred in calves treated with either ACTH or cortisone. He also noted that the numbers of lymphocytes were decreased but not to a marked degree. The eosinopenia observed in mucosal disease might also be due to the influence of the adrenal cortical hormones.

It was felt that the leukopenia observed early in the course of the disease in some animals may have been indicative of a virus infection. The decrease in the total white blood cell counts in the later stages of the disease was attributed to two possibilities. The first possibility was that the blood forming tissues may have been depressed by toxic products absorbed from the gastrointestinal tract. The second possibility was that exhaustion of the hemato-poietic tissues had occurred due to marked hyperactivity. The observation of myeloid hyperplasia of the bone marrow would tend to discredit the latter possibility.

The relative lymphopenia that was consistently observed may have been partially due to the increase in neutrophils. However, in the cases in which a leukopenia was observed, the lymphopenia was absolute as well as relative. The marked degenerative changes of the lymphoid tissue caused by a viral or infectious agent certainly could be responsible for the decrease in circulating lymphocytes.

The possibility that the elevation of blood sugar levels could be associated with the hemoconcentration that occurred during the later stages of the disease was considered. The glucocorticoids of the adrenal cortex were also considered as a factor in the elevation of blood sugar levels. Blood sugar levels as high as 200 milligrams per 100 milliliters were encountered in numerous cases. It was reasoned that in order for an elevation of this magnitude to occur from hemoconcentration alone, the blood volume would have to be decreased to one fifth of the normal blood volume. This great decrease of blood volume was considered unlikely to occur. Thus it was considered that probably the glucocorticoids of the adrenal cortex played a definite role in the elevation of blood sugar levels.

Blood platelet counts were in the normal range in most cases. It was felt that the low values recorded for the blood platelet counts may have been due to faulty collection of the sample. The blood was viscid and dripped slowly from the needle. The possibility that an agglutination of the

platelets with an adherence to the inner surface of the needle may have occurred.

The cell counts on the cerebrospinal fluid were considered to be in the normal range and will not be discussed. The sugar levels of cerebrospinal fluid were more difficult to evaluate. As was expected, in most cases the cerebrospinal fluid sugar levels were elevated and appeared to be correlated with blood sugar levels. It was suspected that in the cases in which low sugar values were recorded, too much time had elapsed between the collection of the sample and the determination procedure. It is possible that enzymes in the cerebrospinal fluid may have broken down a part of the glucose present. The reason for the low protein values in the cerebrospinal fluid was not known.

Comparison of Histopathological Findings and Hematological Studies with Other Reports on Mucosal Disease

Histopathology

Peyer's patches The microscopic lesions observed in Peyer's patches in this study were in agreement with those described by Ramsey (1954 and 1956), Seibold (1956), Blood et al. (1957), Carlson et al. (1957) and Schulz (1959).

The findings, however, did not agree with those of Rooney (1957). The presence of lesions in the liver, lungs, and kidneys suggested that the disease described by Rooney probably is an entirely different disease. Swope and

Luedke (1956) did not describe lesions in Peyer's patches. However, many of the lesions described were suggestive that they may have been working with hyperkeratosis or chronic chlorinated naphthalene poisoning.

Specific lesions in Peyer's patches were not mentioned by McCormack et al., (1959). However they concluded that the condition did not closely resemble mucosal disease as described by Ramsey (1956).

Lymph nodes The lesions observed in the mesenteric lymph nodes in this study were in agreement with those described by Ramsey (1956) and Carlson et al., (1957). Detailed descriptions of the lymph nodes were not made by Jarrett (1958), McCormack et al., (1959), or Schulz (1959). However, all three reports mentioned a marked involution of the lymph nodes which would be in agreement with the depletion in number of lymphocytes observed in this study. McCormack et al. also reported the occurrence of a "sinus catarrh" that probably would be in agreement with the neutrophilic packing of the subcapsular and medullary sinuses noted in this study.

Rooney (1957) did not mention any changes in the mesenteric lymph nodes. He described an edema, neutrophil packing of capsular and medullary sinuses and increased numbers of reaction centers in the suprathyroid, bronchial and mediastinal lymph nodes. He points out that these lesions were observed only in lymph nodes draining necrotic

suppurative areas. This finding is not in agreement with the results of the present study as lesions were noted in the prescapular, prefemoral and bronchial lymph nodes and suppuration or necrosis in the areas drained by these nodes were not found. This finding adds validity to the theory that the disease described by Rooney is a different entity than described by Ramsey (1956) and by the author in the present study.

Microscopic lesions of the other lymph nodes have not been reported in the literature.

Spleen The depletion in number of lymphocytes in the lymphatic nodules in the spleen observed in this study compare favorably with those described by Ramsey (1956), Carlson et al. (1957) and Schulz (1959). The only report of hemosiderin deposition and accumulation of neutrophils and eosinophils around the lymphatic nodules in the spleen is that of Rooney (1957). The variability of the lymphocyte depletion and lack of damage to other lymphoid tissue as described by Rooney suggest that the hemosiderin deposition and accumulation of neutrophils and eosinophils around the lymphatic nodules of the spleen may be secondary in nature and not related to damage of the lymphoid tissue.

Hemal nodes This study revealed that microscopic changes occurred in the hemal nodes of many animals. This finding does not agree with the findings of Ramsey (1956) that marked lesions did not occur in the hemal nodes.

However, in Ramsey's publication it was not stated whether the conclusions about the hemal nodes were made from gross or microscopic observations.

Thymus Histological examination of the thymus appears to have been made on only one animal (Rooney, 1957) affected with a mucosal type disease. The findings of the present study were essentially the same as those noted by Rooney.

Tonsil Descriptions of lesions in the tonsils of animals with mucosal disease were not found in the literature so no comparisons can be made.

Bone marrow Descriptions of histological study of the bone marrow from animals with mucosal disease were not found in the literature.

Cardiovascular system Ramsey (1956) was the only one reporting lesions in the cardiovascular system other than non-specific subepicardial and subendocardial hemorrhages. The changes observed by Ramsey (1956) in the arteries and arterioles are similar to the changes which were noted infrequently in this study. Ramsey now believes that the changes in the arterioles are probably not associated with mucosal disease but are only incidental lesions.*

* Ramsey, Dr. F.K., Department of Veterinary Pathology, Iowa State University of Technology and Science, Ames, Iowa. Arterial lesions in mucosal disease. Personal communication, 1959.

Hematological studies

Hematological studies were reported by Nielson et al. (1955), Pritchard (1955), Ramsey (1956), Dow et al. (1956), and Stöber (1959) in field cases of mucosal disease. Hollister et al. (1956) also reported the hematological findings in muzzle disease, but this disease probably is more similar to mycotic stomatitis than to mucosal disease.

The hemoconcentration observed in the present study was in agreement with the reports of Pritchard (1955), Ramsey (1956), and Stöber (1959). Nielson et al. (1955) and Dow et al. (1956) did not mention that hemoconcentration occurred but did report the occurrence of severe dehydration.

The occurrence of a severe leukopenia in the early stages of mucosal disease appears to be a well accepted fact, but a careful study of the various reports on mucosal disease lacks convincing evidence that such a leukopenia occurs. It should be emphasized that the leukopenia could escape detection because it occurs in the early stage of the disease before clinical signs are apparent and, as pointed out by Ramsey (1956), it may be of a very short duration. A leukopenia was noted in some animals by Ramsey (1956) and Pritchard (1955). Dow et al. (1956) observed a persistent leukopenia in some cases but this finding was not constant. This suggests the possibility that the disease described by Dow et al. may have been more closely related to virus diarrhea than to mucosal disease. Nielson et al. (1955) and

Stöber (1959) did not report the finding of a severe leukopenia even in animals considered to be in the early stage of the disease. They reported that a leukocytosis was the most common finding. This apparent contradiction is believed to be due to the interpretation of what is considered as an early case.

The results of differential leukocyte counts were reported by only three workers, Ramsey (1956), Pritchard et al. (1955) and Stöber (1959). Pritchard and co-workers reported that no striking change was observed in the differential leukocyte counts. Ramsey (1956) reported that a decided neutropenia occurred but on close examination of the results of the differential leukocyte counts, it was apparent that a relative lymphopenia and a relative neutrophilia were commonly recorded. The values recorded by Ramsey (1956) are in close agreement with the results of the present study. In contrast Stöber (1959) reported that a lymphocytosis occurred in the early cases while a neutrophilia with a shift to the left was observed in the later stages of the disease. The conclusion of Stöber (1959) that the neutrophilia was brought about by secondary bacteria was also considered a probability by the author.

No other reports were found in the literature that any other hematological procedures had been carried out on animals affected with mucosal disease.

Comparison of Findings in Mucosal Disease with
Similar Diseases of Cattle

Virus diarrhea-New York

Histopathological studies of virus diarrhea-New York have not been published so the comparison will be based mainly on gross lesions, clinical symptomatology and history as reported by Olafson et al. (1946) and Olafson and Rickard (1947). Apparently cattle of all ages were affected with virus diarrhea-New York, while in mucosal disease the greatest incidence is in animals from six to fourteen months of age. Virus diarrhea-New York seems to occur as an explosive disease condition which affects most of the animals in the herd. Mucosal disease affects a small number of animals in a herd at one time. Abortion was a common finding reported by Olafson et al. (1946) but abortions are not common in mucosal disease. This may be a reflection of the age of the animals affected. The gross lesions which were described in the oral and esophageal mucosa in cases of virus diarrhea-New York do not differ greatly from those observed in mucosal disease.

A great difference exists between the diffuse reddening of the small intestine described for virus diarrhea-New York and the severe necrosis and ulceration which is often observed in animals with mucosal disease.

The severe leukopenia described in some animals in virus diarrhea-New York was not encountered in animals affected

with mucosal disease.

This comparison of virus diarrhea-New York to mucosal disease is not entirely satisfactory because of inadequate description of gross lesions and the complete lack of histopathological study of cases of virus diarrhea-New York. A thorough histopathological and hematological study of virus diarrhea-New York might help clarify its relationship to mucosal disease.

Virus diarrhea-Indiana

The results of histopathological study of field cases of virus diarrhea-Indiana have been reported by Pritchard et al. (1955 and 1956) and Carlson et al. (1957).

The microscopic lesions in the oral cavity and esophagus do not differ significantly in type from those observed by Ramsey (1956) in mucosal disease, but the higher incidence of the lesions in mucosal disease does differ considerably from virus diarrhea-Indiana.

The microscopic lesions in the small intestine reported in virus diarrhea-Indiana were primarily hyperemia, edema and necrosis of the surface epithelium.

The most common histopathological changes reported to occur in Peyer's patches in virus diarrhea-Indiana was a severe edema. This change is certainly much milder than the necrosis and almost complete disappearance of lymphocytes noted in the Peyer's patches in animals affected with mucosal

disease.

The most constant histological feature of the lymph nodes reported in virus diarrhea-Indiana was edema. In some instances lymphoid exhaustion occurred in the lymph nodes and spleen. Necrotic foci in the lymph nodes and spleen were observed occasionally and did not appear to involve an entire germinal center. The conclusion of Carlson et al. (1957), that the lesions in the lymphatic tissue in animals affected with mucosal disease were much more severe than those observed in virus diarrhea-Indiana, is in complete agreement with the findings of the present study.

The fact that pathologic alterations were not noted in the hematopoietic system by Carlson et al. (1957) is different than the findings of the present study on mucosal disease. This difference serves to strengthen the theory that the destruction of cells is not as great in virus diarrhea-Indiana as in mucosal disease by virtue of the absence of myeloid hyperplasia in virus diarrhea-Indiana.

Some of the hematological findings of Pritchard et al. (1955 and 1956) in field cases of virus diarrhea-Indiana are different than those observed in the present study on animals affected with mucosal disease. Pritchard and co-workers reported that a relative lymphocytosis and a relative neutropenia occurred in the later stages of the leukopenia. They also reported that the leukopenia frequently recurred after diarrhea had been present for several days and, that

leukocyte counts of 1,000 to 3,000 per cubic millimeter were often found. The differential leukocyte counts on animals affected with mucosal disease generally were the exact opposite as those described above, namely, a relative lymphopenia and a relative neutrophilia. The lowest total white blood cell count recorded in mucosal disease was 3,300 cells per cubic millimeter and most white blood cell counts were within the normal range or elevated in affected animals.

The finding that the erythrocyte sedimentation rate was not altered in virus diarrhea-Indiana agreed with the findings in mucosal disease.

Rinderpest

Maurer et al. (1955) described the pathology of rinderpest. The microscopic lesions of the lymph nodes, Peyer's patches and spleen are very similar to those observed in this study. The microscopic lesions of the lymphatic tissue which are similar to mucosal disease are a disappearance of most of the small lymphocytes, the presence of edema spaces, a congestion of the capillaries, an increase in macrophages and neutrophils and the finding of a fibrillar eosinophilic acellular matrix in place of the highly cellular lymphoid follicle. Maurer and co-workers observed that in some cases lymphoid tissue necrosis causes sloughing of Peyer's patches even though the adjacent mucous membranes are normal.

The hematological studies of Roby and Hale (1946) and

Maurer et al. (1955) indicate that a persisting severe leukopenia occurs in cattle affected with rinderpest. The differential leukocyte counts show that the decrease in the total leukocyte count is due primarily to a decrease in the number of lymphocytes. The immature neutrophil was the predominant leukocyte in the differential counts. It was readily apparent that the microscopic lesions of the lymphatic tissue in rinderpest are very similar to those observed in mucosal disease and that they would be of little value in differential diagnosis. The persisting leukopenia occurring in rinderpest would be of some value in differential diagnosis, but since a leukopenia is also observed in some cases of mucosal disease, the usefulness of this feature is limited.

Bovine malignant catarrhal fever

Malignant catarrhal fever is a virus disease of cattle which is sometimes confused with mucosal disease because of the presence of erosions in the oral mucosa and esophagus and at times a severe diarrhea. Plowright (1953) described the pathology of malignant catarrhal fever. He reported that there was a rapid depletion of small lymphocytes from the spleen, lymph nodes and hemal nodes. He believed that the small lymphocytes were destroyed in situ with phagocytosis of the resulting nuclear debris taking place by the increased numbers of macrophages noted in the lymphatic tissue. A proliferation of all potentially lymphocytogenous elements

followed, and an abundance of mitotic figures were noted in the lymph nodes. The latter finding is strikingly different from the almost complete absence of mitotic figures in mucosal disease. Edema and hyperplasia of the lymphoid tissue were also observed in the lymph nodes and spleen of animals affected with malignant catarrhal fever.

The microscopic lesions of the vascular system consisted of dense mononuclear cell infiltrations in the adventitia of arteries and more frequently in the wall of the veins. The proliferative changes were often accompanied by degenerative changes of the media and intima of the veins. Plowright suggested that these proliferative changes in the vascular system were responsible for the erosions noted in the epithelial tissues by interfering with blood supply. Perivascular infiltrations also occurred in many of the parenchymatous organs with the liver, kidney, adrenal and brain being affected most frequently. It should be emphasized that the vascular lesions noted in a few cases of mucosal disease were of a different type and were probably secondary or non-specific changes.

The microscopic changes in malignant catarrhal fever tends to be proliferation of the lymphoid tissue whereas in mucosal disease primarily a degeneration of the lymphoid tissue is observed.

The hematological studies made by Plowright (1953) indicate that a leukopenia with a relative lymphocytosis

occurs in malignant catarrhal fever. In most cases a pre-mortem leukocytosis is observed and 80 to 90 percent of the cells are atypical large lymphocytes. An eosinopenia was also observed.

The hematological findings in malignant catarrhal fever could be used to tentatively differentiate it from mucosal disease on the basis of the differential leukocyte count.

Histopathological study of the lymphatic tissue might not definitely differentiate malignant catarrhal fever from mucosal disease but histological examination of the parenchymatous organs, particularly the brain and liver should definitely establish the diagnosis.

SUMMARY

1. Tissues for histopathological study were collected from 64 animals that were affected with mucosal disease-Iowa.

2. The material from the blood forming organs included sections of the prescapular, supratharyngeal, bronchial, prefemoral, parotid and mesenteric lymph nodes, spleen, hemal nodes, thymus, tonsils, Peyer's patches and sternal bone marrow.

3. The sections of the cardiovascular system included portions from the heart, aorta, the umbilical, internal iliac, internal pudic, external iliac, middle uterine, brachial, external maxillary, common carotid and femoral arteries and corresponding veins.

4. Similar materials from 20 apparently normal cattle were also obtained and compared with those from mucosal disease affected animals.

5. Hematological studies were made on 50 animals affected with mucosal disease. Erythrocyte enumeration, total and differential leukocyte counts, hemoglobin, hematocrit and blood urea nitrogen determinations were done. In addition, sedimentation rates, total blood volume values, blood platelet numbers, blood sugar concentrations and the cell counts, sugar levels and total protein content of cerebrospinal fluid were recorded in some of the animals.

6. Microscopic study of the lymph nodes revealed a

consistent marked depletion in the number of small lymphocytes. Other lesions noted were hyperemia, edema, hemorrhage, neutrophilic and eosinophilic leukocyte accumulations in the subcapsular and medullary sinuses and in the cortical parenchyma. Less frequently a focal accumulation of eosinophilic fibrinoid-like substance in the germinal centers and occasionally a marked coagulative necrosis of the cortical portions of the lymph nodes were observed. A rather definite order of the degree of involvement of the lymph nodes in an individual animal was observed. The following lymph nodes are listed in order from the most to the least severely involved: mesenteric, colic, supratharyngeal, bronchial, prescapular, parotid and prefemoral.

7. In the mesenteric lymph nodes of 19 of the 64 cases of mucosal disease calcium carbonate depositions occurred in a concentric-ringed matrix of material believed to be proteinaceous in nature. The observation of this same type of corpora amylacea-like bodies in apparently normal animals and in animals suffering from other diseases led to the conclusion that these bodies were not specifically concerned with the pathogenesis of mucosal disease.

8. Microscopic observation of the spleen and hemal nodes of affected cattle revealed a definite decrease in the number of small lymphocytes and at times a focal accumulation of the same type of eosinophilic substance noted in the lymph

nodes. In some affected animals increased accumulations of hemosiderin, neutrophils and eosinophils were noted at the periphery of the lymphatic nodules.

9. The microscopic lesions in the thymus were a marked depletion of thymocytes and an apparent increase in the numbers of Hassall's corpuscles.

10. The most consistent lesion in the tonsils was a marked decrease in number of lymphocytes. However, engorgement of blood vessels with neutrophils and erythrocytes was also encountered.

11. Peyer's patches from all affected cattle exhibited marked damage of the lymphatic tissue. Microscopic lesions ranged from severe depletion of small lymphocytes with an abundance of macrophages engulfing the nuclear debris to a complete coagulative and liquefactive necrosis of the lymphatic tissue.

12. An apparent hyperplasia of the myeloid elements of the bone marrow with a concomitant decrease in the normal amount of fatty marrow was observed in affected animals.

13. Epicardial and endocardial hemorrhages were found in 32 animals that died during the natural course of mucosal disease. Microscopic changes of the aorta and arteries were observed in only a few cases of mucosal disease and were considered to be non-specific or secondary changes.

14. Hematological study revealed increased erythrocyte counts, hemoglobin concentrations, hematocrit readings and

blood urea nitrogen levels, especially in the later stages of mucosal disease.

15. In most affected animals total leukocyte counts were normal or elevated, but low white blood cell counts were noted in a few animals. A relative lymphopenia and relative neutrophilia was observed in the differential leukocyte counts on most animals. In the cases in which a leukopenia was observed the lymphopenia was absolute as well as relative.

16. Blood sugar levels were normal in a few animals but were mildly to markedly elevated in a majority of affected animals.

17. Blood volume determinations were low in four out of five cases of mucosal disease.

18. Cerebrospinal fluid studies revealed a normal cell count, an increased sugar level in some cases that was correlated with elevated blood sugar levels and a decreased total protein concentration in most cases of mucosal disease.

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