BOVINE MUCOSAL DISEASE IN MICHIGAN

Thesis for the Degree of Ph. D.
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Gurwant Singh Bajwa
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This is to certify that the

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Gurwant Singh Bajwa

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Ph. D. degree in Veterinary Pathology

R. D. Barner
Major professor

Date 8-4-1961

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BOVINE MUCOSAL DISEASE IN MICHIGAN

By

Gurwant Singh Bajwa

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Veterinary Pathology

1961

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ABSTRACT

BOVINE MUCOSAL DISEASE IN MICHIGAN

by Gurwant Singh Bajwa

A total of 30 cases of mucosal disease, occurring on 26 farms in southern Michigan, has been studied. The greatest incidence was during fall and most of the cases were between 4 and 13 months of age.

The course of the disease varied from 4 to 22 days in animals terminating in death and from 3 to 71 days in those receiving euthanasia. The morbidity rate was 0.4 to 60 per cent and mortality was 100 per cent.

Clinically, the disease was marked by sudden onset, initial high fever, variable peripheral blood picture, frequent laminitis, serous to mucopurulent nasal discharge, profuse persistent watery to mucoid or bloody diarrhea, erosions and ulcerations of the muzzle and mouth, marked dehydration, rapid cachexia, progressive weakness, and acute, subacute or chronic form.

Pathological studies have shown that the disease possesses special affinity for the squamous epithelium, columnar epithelium of the gastrointestinal tract, and hemopoietic system (lymph tissue). Areas of extensive erosions and ulcerations, seen as punched-out defects, of the skin (especially of muzzle, coronary bands, interdigital space, scrotum, prepuce or vulvar labiae) and of the alimentary canal were the most outstanding findings. The lesions of the squamous epithelium emerged through hydropic degeneration of the germinal

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layer cells of the stratum spinosum and subsequent abundant ballooning degeneration (reticular colliquation) of all the layers. Catarrh, congestion, hemorrhage, edema and abscessation of crypts of the gastro-intestinal mucosa were also prominent. Caseation necrosis of gastro-intestinal mucosa was responsible for erosive and ulcerative defects which were particularly conspicuous over the necrotic and hemorrhagic Peyer's patches and intestinal solitary lymph follicles. Necrosis of the glandular epithelium and abscessation of the crypts have been considered as a specific response to the lethal action of the disease.

The lymph nodes, especially those draining the digestive tract, commonly revealed edema, congestion, hemorrhage, coagulation to caseation necrosis of the lymph tissue, and lymphocytic depletion. Similar changes were also noted in the Peyer's patches, intestinal solitary lymph follicles and germinal centers (lymph tissue) of spleen. Lymphocytic depletion and necrosis are believed to be a specific action of the disease.

Lymphocytic foci found in the adrenals and liver, seemingly developed to cope with the constant demand for lymphocytes in the body.

Tissue culture and transmission studies gave negative results. Therapy was of no value. The bacteriological and parasitological findings were insignificant. Differential diagnosis of the disease has been difficult but not impossible.

To

my loving father, S. Iqbal Singh Bajwa

and

my adorable mother, Pritam Kaur

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ACKNOWLEDGEMENTS

"The cause of all causes is God alone and none else. I am all for Him who is present in sea and land, and fills all space between heaven and earth."

Guru Arjun
The Psalm of Peace, Canto XI

The author is earnestly thankful to his major professor, Dr. R. D. Barner, for his unceasing enthusiasm, encouragement and suggestions during the course of this investigation and preparation of the thesis. It has been a pleasure and privilege to know him as a friend.

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This study was made possible by practicing veterinarians of Michigan, who deserve much credit for supplying the cases.

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The author is grateful to the staff of the ambulatory clinic, bacteriology diagnostic laboratory and virology laboratory for their

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excellent cooperation and to all others who made this study possible. The funds for this investigation were provided in part through the regional project NC-34, "The Mucosal Diseases of Cattle."

The author is, indeed, profoundly indebted to Mr. and Mrs. Clare Brown and family of Ada, Michigan, for their hospitality and spiritual encouragement.

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TABLE OF CONTENTS

Chapter

4

5

6

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Chapter

Table

LIST OF TABLES

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CHAPTER I

INTRODUCTION

Bovine mucosal disease has constituted a serious menace to the cattle industry in Michigan. Spontaneous cases of the disease have occurred sporadically in many parts of the state during the past few years. The disease has been studied for the first time in this state.

The so-called mucosal disease was initially encountered in Iowa in 1951 and first described by Ramsey and Chivers in 1953. Earlier reports indicate that the disease has probably existed from antiquity but remained obscure prior to its clear recognition in 1951. Several syndromes closely resembling mucosal disease have been described in the past and have been called by different names in many parts of the world. Some of the closely resembling syndromes are commonly and collectively referred to as "mucosal disease complex." The chief members of the complex are

virus diarrhea - New York (Olafson et al., 1946),

x-disease - Saskatchewan (Childs, 1946),

enzootic enteritis - Sweden (Hedstrom and Isaksson, 1951),

mucosal disease - Iowa (Ramsey and Chivers, 1953),

muzzle disease (Hollister et al., 1956)

virus diarrhea - Indiana (Pritchard et al., 1956),

mycotic stomatitis (Udall, 1956),

parotido-stomatitis (Pande and Krishnamurty, 1958),

infectious ulcerative stomatitis (Pritchard et al., 1958).

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Among the complex, complete identity of each disease and their relationship to each other have not been definitely established. Some maintain that mucosal disease represents an acute and fatal form of virus diarrhea of cattle. However, preliminary cross-protection studies indicate that the said diseases are immunologically distinct entities (Pritchard et al., 1956). Likewise, natural enzootics of mucosal disease have been encountered in buffaloes immune to rinderpest (Murty, 1958). Preliminary studies of several investigators indicate that the etiologic agent is infectious, probably a virus, but this remains to be conclusively proven. Further immunological, serological and experimental transmission studies are needed to determine whether mucosal disease and certain epitheliotropic diseases are caused by specific viruses.

The disease has been definitely identified in Australia (Blood et al., 1957; McCormack, 1959), Canada (Nielson et al., 1955), Great Britain (Dow et al., 1956; Huck, 1957; Jarrett, 1958), Holland (Reinders, 1959), India (Murty, 1958), New Zealand (Animal Research Division, 1959), and U. S. A. (Ramsey and Chivers, 1953 and 1957; others). Occurrence of the disease in widely separated geographical areas suggests its world-wide prevalence.

Mucosal disease occurs primarily in cattle, but enzootics have been observed in buffaloes in India (Murty, 1958), and a similar syndrome was encountered in deer in North Dakota (Richards et al., 1956).

Although the disease has been recognized for a decade, its pathogenesis and treatment are still unknown. Inadequate or difficult

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knowledge of its etiology, epizootiology, immunology and serodiagnostics constitutes the chief obstacle in controlling the disease. Several such problems connected with mucosal disease need solution before any concrete attempts can be instituted to combat the disease.

Close resemblance of the disease to several serious bovine epitheliotropic diseases has posed a crucial diagnostic problem. Consequently, its differential diagnosis is most difficult but not impossible. Rinderpest is known to exhibit several clinical and pathologic features closely resembling those of mucosal disease. Hence, in the early stages of an outbreak of rinderpest, it is highly possible to diagnose it as mucosal disease leading to alarming consequences.

It is readily evident from the foregoing that our knowledge of the disease is still inadequate and that further studies are needed to complete the picture of mucosal disease. The purpose of the present study is to add to the understanding of the disease. The disease, occurring in Michigan, has been studied in view to its

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CHAPTER II

REVIEW OF LITERATURE

A new syndrome of cattle appeared in Iowa in 1951 and was first described by Ramsey and Chivers in 1953. They designated the syndrome as "mucosal disease" and reported 42 cases of the disease in cattle aged six to 14 months from various parts of Iowa and adjoining states. The disease was characterized by fever, diarrhea (sometimes blood stained), profuse salivation, emaciation and dehydration, and mucopurulent nasal discharge. Necropsy of the affected animals revealed erosions, ulcerations and even cystic changes in the mucosa of the digestive tract. The disease lasted three to 10 days, and the mortality was high. The incidence was chiefly in winter and early spring. The disease had unknown cause, and response to treatment was unsatisfactory.

Harshfield (1955) studied mucosal disease in cattle in South Dakota and reported the findings which were like those referred to by Ramsey and Chivers (1953).

Nielson et al. (1955) observed mucosal disease in Ontario herds. Symptoms included anorexia, depression, shallow ulceration of the buccal or glossal mucosa, diarrhea and dehydration. It occurred as acute with short course and high fever or chronic with a prolonged course up to eight weeks. Erosions and ulcerations were seen in the oral cavity and any part of the gastrointestinal tract. Transmission

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trials were unsuccessful, and bacteriological examination of the feces and rectal scrapings did not reveal significant organisms.

Mucosal disease, occurring in Indiana, was described by Pritchard (1955) as marked in early stage by fever, anorexia, depression and nasal discharge and in two to three days by mucosal erosions of the entire oral cavity and dorsum of the tongue. During the first week there was diarrhea which became increasingly severe with dehydration and possible pityriasis. The course varied from four to 30 days. Morbidity varied from a single case to 50 per cent of a herd, whereas mortality was only slightly less than the morbidity. The disease was sporadic and affected mainly animals eight to 14 months of age. Leukopenia occurred early followed by hemoconcentration. Erosions appeared throughout the digestive tract. Edema and hemorrhage of the lymph nodes and subepicardial hemorrhages were frequent. In one herd of 55, 11 died over a 13 week period; nine others had temperatures over 103°F; of these three had leucocytic counts below 5, 000, three had mouth lesions and three were visibly ill but survived. Seven of the seven animals inoculated intravenously with defibrinated blood from field cases developed leukopenia and signs of the disease, but only one test animal died in 37 days. Pritchard (1955) also reported that the disease has become widespread since its recognition in 1951, appearing chiefly in the midwestern corn belt during the winter months.

Paulette (1955) described the disease in a 10-month old Hereford steer which was admitted to the veterinary clinic of the University of

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Georgia. The steer was one of 25 animals in a herd. The disease was characterized by fever (104°F), salivation, laminitis, diarrhea, nasal discharge, encrustation of the muzzle and interdigital skin, small superficial macules of the tongue, mucopurulent nasal discharge and rapid wasting. Post-mortem examination revealed mucosal erosions of the buccal cavity, esophagus, abomasum, and small intestine; emphysema of the lungs; great enlargement of the gall bladder with viscid bile and petechiation of the bile ducts.

Schipper and Eveleth (1955) described mucosal disease in North Dakota and reported that the disease is widespread in the midwest and is increasing in incidence. Schipper et al. (1955) reported that little is known of etiology and mode of transmission of mucosal disease, and it has been frequently misdiagnosed as coccidiosis, avitaminosis, infectious keratitis, hemorrhagic septicemia and rabies.

Seibold (1955) reported nine cases of mucosal disease observed at the Alabama Polytechnic Institute. Erosions and ulcerations were seen along the mucosa of the digestive tract. Lesions of the anterior digestive tract consisted of the necrosis of the stratified squamous epithelial cells giving the appearance of a raised focus or eventual ulceration. Hemorrhages and dilatation of crypts of the gastrointestinal mucosa were frequent. The lesions were particularly severe in the posterior ileum, especially over the Peyer's patches, and in the cecum and colon.

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Epizootics of mucosal disease on 35 farms in Britain have been described by Dow et al. (1956). The disease had no seasonal incidence; ages varied from three weeks to seven years, the majority of the animals affected were Ayrshire, and morbidity was as high as seventy per cent. The disease was recognized in mild acute, severe acute and chronic forms. It was characterized by fever (104-106°F), diarrhea, laminitis, leukopenia, and by erosions and ulcerations of the digestive tract, muzzle, interdigital space and coronary bands. Abortion occurred in two cases. Course varied from 24 hours to six months. Experimental transmissions were successful in 31 calves by intraperitoneal inoculations of spleen suspensions.

A mucosal-type disease in weanling calves in two beef herds in Virginia was described by Hoag et al. (1956). The disease had a short incubation period (two-eight days), a transient leukopenia, and marked lameness. Erosions of the dorsum of the tongue, necrosis of Peyer's patches and inflammatory hemorrhages of the digestive tract were not seen. Focal necrosis and fatty degeneration of the liver were prominent grossly. The disease was transmissible by contact, by parenteral injection of spleen suspension and by inoculation of the yolk sac of the embryonating eggs.

Olson and Hoerlein (1956) observed epizootics of mucosal disease in two herds in central Nebraska. Fifty-three calves were affected and 43 died of the disease in a group of 180. In a second herd, 34 of 233 calves were affected with only three recoveries, but only one nonfatal case

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The chief clinical and pathological aspects of virus diarrhea and mucosal disease in Indiana have been discussed and compared by Pritchard et al. (1956). They reported that cross-protection studies indicate immunological differences between virus diarrhea - New York, mucosal disease and virus diarrhea - Indiana.

The mucosal disease has been extensively studied in Iowa, and Ramsey (1956) reported the findings of 116 animals from 87 herds observed since 1951. It occurred predominantly in Hereford and Aberdeen Angus but less commonly in Shorthorn, Holstein-Friesian and Gurnsey breeds. The animals varied from six to 14 months of age, and course was between five and 30 days. Morbidity ranged from two to 50 per cent in different herds, and mortality was over 90 per cent. Clinical and gross pathologic findings were essentially those reported in the earlier reports (Ramsey and Chivers, 1953; Ramsey, 1954). Lesions were primarily erosive, ulcerative and cystic, confined principally to lamina epithelia and mucosa

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of the alimentary canal. Lymphoid tissue of the intestine, lymph nodes and spleen commonly revealed depletion and necrosis. Hyperemia, hemorrhages, thromboses, arteritis and periarteritis were the frequent lesions of the circulatory system. Necrosis and fatty degeneration of the liver and cloudy swelling of the kidneys were observed. Bacteriological examination of the liver, spleen, kidneys and heart blood were negative for pathogens. Experimental transmission studies yielded inconclusive results.

Swope and Leudke (1956) encountered mucosal disease in a herd of 20 beef cattle in Pennsylvania, six months after the introduction of new animals. At least four animals died and 12 others were affected. Experimental transmission was unsuccessful by contact or inoculation of affected tissues, tissue culture material, or inoculated embryonating eggs. In addition to the erosive and ulcerative lesions of the alimentary canal, mucosal cysts in the maxillary sinus, wart-like proliferations in the rumen, and intracellular inclusion bodies in the esophageal squamous epithelium were observed.

A syndrome of white tailed deer and mule deer in North Dakota was described by Richards et al. (1956). Necropsy of both species of deer revealed catarrhal, ulcerative and hemorrhagic inflammation of the mucosa of the alimentary canal. Signs and lesions of the syndrome resembled those of the mucosal disease of cattle. The disease was transmissible from deer to deer, and deer to antelope, producing typical signs and lesions.

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Two cases of mucosal disease were reported in three and 18 month old cattle in the county of Cumberland in Australia by Blood et al. (1957). Diarrhea, fever, erosive lesions of the buccal mucosa, salivation, raw ulcers of the muzzle, medial canthus of the eyes, and interdigital skin were the most obvious clinical signs. Gross and histologic pathological findings were identical with those described for mucosal disease by Ramsey and Chivers (1953). Transmission studies of the disease in cattle and sheep were negative.

Huck (1957) described the investigations of outbreaks of mucosal disease in Great Britain. Enzootics of the disease were encountered in various breeds of cattle maintained under varying conditions of management at all times of the year. The outbreaks varied from mild transient illness characterized by pyrexia with mucoid nasal discharge and ulceration of the mouth followed by diarrhea of short duration and having high morbidity but low mortality, to a severe acute hemorrhagic enteritis with ulceration of all or part of the alimentary canal occurring in animals four to eight months of age and having a 60 per cent morbidity and very high mortality. Cross-protection tests in experimental calves showed that immunity was variable and sometimes weak. The experimental disease was very mild. Distinct differences between strains were not detected.

Clinical and pathologic findings of mucosal disease in calves in Britain have been described by Huck (1957). High fever, mucoid nasal discharge, diarrhea (sometimes blood stained) were observed. High mortality was common. Necropsy of the affected animals revealed

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lesions varying from mild enteritis to a hemorrhagic enteritis with free blood in the lumen of the bowel. Ulceration of the mouth, sometimes extending into the larynx and esophagus, and abomasal hemorrhages were frequent. Lymph nodes were sometimes enlarged and showed perinodal edema. On section, the lymph nodes often had a cherry-red appearance. The experimental disease, produced by inoculation of the citrated blood, plasma, and lymph node and brain suspensions prepared from the tissues of the calves from an outbreak, was very mild. It was characterized by an incubation period of six to 10 days with a high fever lasting for 24 hours and often accompanied by mucous nasal discharge. A diphasic temperature rise was observed in some cases. Diarrhea and coughing were constant in the experimental disease. Ulceration of the oral mucosa was infrequent.

Occurrence of the disease in 20 states of the U. S. A. and in Canada was reported by Ramsey and Chivers (1957). They reiterated their previous findings and proposed that their transmission studies indicate the cause of the disease to be an infectious agent.

Rooney (1957) reported the clinical, pathological and histopathological findings in 14 natural and six experimental cases of mucosal-type disease of young cattle in Virginia described earlier by Hoag et al. (1956). Primary lesions were located in the squamous epithelium and mucosa of the alimentary canal, interdigital skin and rarely in the turbinate mucosa. Lesions of the squamous epithelium resulted from ballooning degeneration of the cells, while coagulation necrosis and

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crypt abscesses characterized lesions in the columnar epithelium. Morbidity in two outbreaks was near 100 per cent and mortality about 50 per cent.

A mucosal-like disease in calves was studied by Schipper and Eveleth (1957), and they reported that the signs and lesions of the disease are similar to the early stage of mucosal disease in older animals. Numerous reports by farmers indicated its wide occurrence in North Dakota during the past calving season. Many cases of peracute enteric and respiratory conditions in calves proved to be mucosal-like. Experimental transmission of the syndrome by feeding milk or inoculation of blood or splenic emulsions to apparently susceptible calves were unsuccessful.

Isolation and cultivation in tissue culture of a cytopathogenic agent recovered from tissues of cattle with mucosal disease from two separate herds has been reported by Underdahl et al. (1957). A homologous tissue culture system was used with bovine embryonic kidney cells and newborn, antibody-free calf serum. The virus was activated by temperatures above $50^{\circ}C$ for 15 minutes, passed an 03 Selas filter and had an 11th passage titer of 10^{-5}. The virus stimulated the formation of neutralizing antibodies in sheep. A preliminary neutralization study indicated that antibodies are common in animals from herds having no previous history of mucosal disease.

Jarrett (1958) reported that in Britain a syndrome affecting cattle, which has come to be known as mucosal disease, is characterized

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at some stage by buccal ulceration, fever, leukopenia, diarrhea and high morbidity. Most cases are very mild, exhibiting only a few small buccal vesicles, ulcers or a winter scour type of syndrome, only a few severe, frequently fatal cases are recognized. The disease has an incubation period of seven to nine days and can be transmitted experimentally by most routes using bacteria-free suspensions of spleen, blood or feces of affected animals. Resistance to further challenge does not occur until 40 days after infection while repeated ulcer formation can continue for two months.

Mucosal disease in buffaloes in India has been observed by Krishnamurty (1958), and this was characterized by high fever, mucous nasal discharge, diarrhea, rapid wasting, erosive and ulcerative defects of all or any part of the alimentary canal, and high mortality. The disease was experimentally transmissible to young buffaloes immune to rinderpest.

Ramsey et al. (1958) have reported that factors such as difficulty of diagnosis, incomplete records and insufficient herd observations prevent compilation of accurate data in Iowa. However, mortality of five per cent in a herd is fairly common and in rare instances mortality has reached 20 to 30 per cent. In the last six years the total number of deaths definitely has averaged about 100. There are no indications that incidence of the disease has decreased since 1951.

A disease of mucosal disease-virus diarrhea complex in young cattle in South Australia was observed by McCormack et al. (1959), and

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the features resembled those previously described for the complex. The buccal erosions seen in the field cases were reproduced in experimental calves by intravenous inoculation of blood. None of the experimental calves became sick or showed any but transient diarrhea.

Noice and Schipper (1959) isolated a virus from cattle with mucosal disease in North Dakota, and it was grown in tissue cultures of trypsinized bovine kidney cells in Mixture 99. Two calves were inoculated with tissue culture virus, and neutralizing antibodies were demonstrated in their serum between 15 and 25 days later. Serological tests in rabbits indicated the similarity of viruses isolated from four herds of cattle in North Dakota.

A fatal syndrome of cattle resembling mucosal disease has been encountered in several herds in the Wairarapa district in New Zealand. The disease was characterized by rapid wasting, diarrhea, enteritis, nephritis and ulcers of the mouth, esophagus, and stomach. A virus was isolated from the affected animals (Animal Research Division of New Zealand, 1959).

Reinders (1959) described two cases of mucosal disease in three years and eight months old cattle. Signs included fever, diarrhea, rapid wasting, lacrimation, mucopurulent nasal discharge, encrustation of muzzle, and erosive and ulcerative defects of the oral mucosa. Necropsy of the eight-months-old calf revealed erosions and ulcerations of the alimentary canal, enlargement of liver and gall bladder, swelling and hemorrhages of the kidneys, and endocardial hemorrhages.

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Intra-herd transmission of mucosal disease has been investigated by Schipper and Noice (1959), and they have reported that the transmission of the mucosal disease agent to experimental animals is inconsistent when based on clinical observations, and that drinking water and possibly feed serve as means of intra-herd spread of the disease.

Jones (1960) described mucosal disease of cattle in South Dakota and reported that incidence of the disease has increased during 1959. The morbidity and mortality rate has been about 20 per cent in the state. It has been more prevalent in February and March. Cause is unknown and it does not respond to treatments. Stresses may play a significant role in the epizootiology of the disease.

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CHAPTER III

INCIDENCE

Materials and Methods

A total of 30 cases of mucosal disease (MD) was collected from 26 farms in Michigan during July, 1956 to December, 1958. The majority of cases were referred by the practicing veterinarians and a few were admitted to the veterinary clinic of the College of Veterinary Medicine. Records were kept on: geographical distribution, seasonal incidence, age, breed, sex, husbandry practices, morbidity, mortality and susceptibility of new additions or purchased animals.

Results

Geographical Distribution

The cases came from 16 counties in the southern part of the state. The disease appeared sporadically and enzootics were seldom seen on the adjoining farms. The distribution of the cases did not indicate any regions of particular concentration.

Season

The greatest incidence of the disease was in September, October and November but enzootics were noted in all months of the year (Diagram 1). Cases showed a marked decline during spring and summer.

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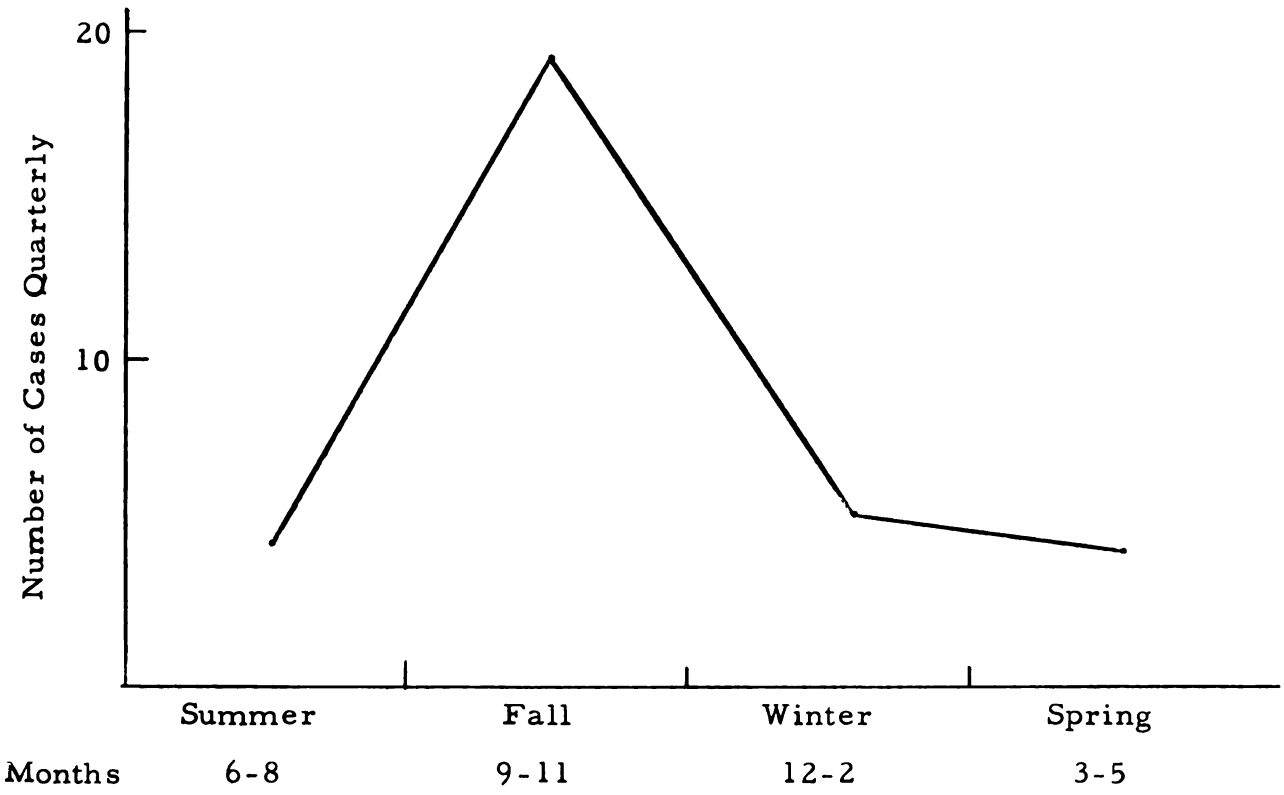
DIAGRAM 1



Seasonal Distribution of Mucosal Disease Cases
During July, 1956 to December, 1958

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Age, Breed and Sex

The disease appeared primarily in young animals and those between four and 13 months of age were most susceptible (Table I). The distribution of cases by age was as follows:

Age	Number of Cases
1 1/4 to 6 months	7
7 to 12 months	15
13-18 months	2
19 months and over	4
Total	30

The youngest animal affected was 1 1/4 month old whereas one case of disease occurred in an animal 24 months of age. Frequently the disease appeared in only younger animals even though they were housed or pastured along with the older animals which remained unaffected.

No particular breed susceptibility was noted but the greatest number of cases was seen in Holstein cattle (Table I). The distribution of cases by breed was as follows:

Breed	Number of Cases
Angus	6
Brown Swiss	2
Grade	2
Guernsey	2
Holstein	12
Hereford	6
Jersey	1
Total	30

TABLE I. His

Case number
A 60
A 116
A 234
A 262
A 263
A 286
A 390
A 421
A 430
A 580
A 581
A 948
A 1532
A 1587
A 1634
B 221
B 496
B 1305
B 1419
B 1457
B 1459
B 1615
B 1912
B 3098
B 3173
B 3697
B 3698
B 5133
C 1219
C 2227
C 2286

A = Angus; B
GR = Grade; H
Natural.

TABLE I. History of mucosal disease cases

Case number	Date of necropsy	Breed	Sex	Age (months)	Illness (days)	Nature of death
A 60	7-20-56	J	F	12	21	E
A 116	8-7-56	H	M	24	21	E
A 234	9-10-56	GR	F	8	10	N
A 262	9-13-56	H	F	20	71	E
A 263	9-13-56	H	F	20	63	E
A 286	9-16-56	HE	F	9	14	E
A 390	9-31-56	G	F	9	23	E
A 421	10-12-56	H	F	13	?	E
A 430	10-18-56	H	F	20	16	E
A 580	11-14-56	H	F	12	?	E
A 581	11-14-56	H	F	12	?	E
A 948	1-28-57	GR	M	8	7	N
A 1532	4-24-57	G	F	12	22	N
A 1587	4-29-57	A	F	10	5	N
A 1634	5-4-57	A	F	11	3	E
B 221	7-16-57	H	F	12	?	E
B 496	8-2-57	A	F	12	?	N
B 1305	10-11-57	H	F	3.5	21	E
B 1419	10-19-57	H	F	8	7	N
B 1457	10-24-57	A	F	4	11	N
B 1459	10-24-57	HE	M	?	21	N
B 1615	11-7-57	H	F	1.25	7	N
B 1912	11-29-57	BS	F	6	5	N
B 3098	1-20-58	A	F	4	9	N
B 3173	1-24-58	A	M	4	6	E
B 3697	2-14-58	HE	F	12	6	E
B 3698	2-14-58	HE	F	12	6	E
B 5133	4-12-58	HE	M	7	30	E
C 1219	9-12-58	BS	F	13	4	N
C 2227	11-11-58	HE	M	5	3	N
C 2286	11-15-58	H	F	4	30	E

A = Angus; BS = Brown Swiss; E = Euthanasia; F = Female; G = Guernsey; GR = Grade; H = Holstein; HE = Hereford; J = Jersey; M = Male; N = Natural.

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No particular sex susceptibility was apparent and the disease occurred equally severely in males and females.

Morbidity and Mortality

Usually only one or two animals were affected in a herd; rarely, several animals developed the disease simultaneously. Among the different herds, the morbidity rate varied from 0.4 to 60 per cent (Table II). In 12 of the 30 cases, the disease had completed its natural course and terminated in death. The remainder of the cases had gone down moribundly and were administered euthanasia. Had these cases been allowed to complete a natural course of the disease, they would have eventually succumbed in time. None of the cases with full-blown disease recovered and the mortality rate of the affected animals was 100 per cent. Recurrence of the disease during succeeding years was reported in only one herd.

Course

The course ranged from 4 to 22 days in animals which had terminated in death following completion of the natural disease. In the cases receiving euthanasia, the course varied from 3 to 71 days. Among the different herds, the disease lasted from 4 to 7 months, averaging about 7 weeks (Table II).

TABLE II. He

Case number	
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B 1912	
B 3098	
B 3173	
B 3697	
B 3698	
B 5133	
C 1219	
C 2227	
C 2286	

HR = Home-ra

PU = Purchas

TABLE II. Herd history of mucosal disease cases

Case number	Breed	Animals per herd	Deaths per herd	Course of the disease per herd (weeks)	Source of herd
A 60	Jersey	6	4	3	PU
A 116	Holstein	85	6	24	HR
A 234	Grade	?	3	20	HR
A 262	Holstein	15	2	8	HR
A 263	Holstein	"	"	"	"
A 286	Hereford	250	1	3	Oklahoma
A 390	Guernsey	63	5	8	HR
A 421	Holstein	20	2	8	HR
A 430	Holstein	25	1	2	HR
A 580	Holstein	?	2	4	HR
A 581	Holstein	"	"	"	"
A 948	Grade	15	1	1	PU
A 1532	Guernsey	?	1	3	HR
A 1587	Angus	74	3	1	PU
A 1634	Angus	"	"	"	"
B 221	Holstein	?	1	?	HR
B 496	Angus	160	8	?	North Dakota
B 1305	Holstein	?	5	3	HR
B 1419	Holstein	4	1	1	HR
B 1457	Angus	?	?	2	HR
B 1459	Hereford	?	1	3	HR
B 1615	Holstein	83	6	4	HR
B 1912	Brown Swiss	300	?	28	HR
B 3098	Angus	?	3	2	HR
B 3173	Angus	"	"	"	"
B 3697	Hereford	20	2	1	HR
B 3698	Hereford	"	"	"	HR
B 5133	Hereford	11	1	4	HR
C 1219	Brown Swiss	?	?	12	HR
C 2227	Hereford	?	?	1	Saskatchewan
C 2286	Holstein	15	4	1.5	HR

HR = Home-raised

PU = Purchased but source unknown

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Susceptibility of Purchased and Home-Raised Animals

The affected animals originated from 20 home-raised and six purchased herds (Table II). Of the six purchased herds, three herds were brought in from Oklahoma, North Dakota and Saskatchewan, respectively. The disease in the purchased herds appeared as early as three weeks and as late as 11 months following the arrival of different herds. The purchased herds were in no case added to the home-raised stock and had no contact with animals from other herds.

Husbandry Practices

The disease appeared in animals on various types of feed rations and the incidence was equally common in animals on pasture and in those housed indoors. Occasionally, the disease appeared and progressed undiscovered for days in animals on pasture. A cow developed the disease shortly after calving. In all cases, there was no history of contact with cattle from other infected or noninfected herds. In general, enzootics were encountered in cattle under varying conditions of management.

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CHAPTER IV

SYMPTOMATOLOGY

Signs and symptoms were observed in 28 of a total of 30 Michigan field cases of mucosal disease. The observation periods varied from one day to five weeks in different animals.

The disease onset was sudden without showing any preliminary signs of impending acuteness and was commonly marked by high fever varying from 104° to 107° F, dullness, occasional erythema of muzzle, slight serous nasal discharge and depressed appetite. In the majority of cases, body temperature receded to normal level in two to four days. A diphasic rise in temperature occurred in a few animals, but it rarely reached the initial peak. Subnormal temperature was noted in animals with severe diarrhea especially during the cold months or just before death.

Nasal discharge prominently occurred and changed from serous in the beginning to mucopurulent in the terminal stages, when it usually dangled from the muzzle and nostrils as tnacious and often blood-tinged stringy exudate (Fig. 1 B and C and Fig. 2). Encrustation of the muzzle usually followed nasal exudation and gradually developed into irregular shallow erosions and ulcerations. Nasal exudation was absent in four animals, but three of these revealed conspicuous reddening or erythema of the muzzle. The external nares often had discrete and shallow erosions adjacent to the nostrils and these were always contiguous with the muzzle lesions.

In the early phase of the disease serous ocular discharge occurred from the medial canthi in one-third of the cases. It coursed its way downwards along the lateral surface of the face resulting in swaths of matted hair. In some cases, the ocular discharge persisted during the terminal phase of the disease and became vicid in nature. The eyelids and medial canthi in these cases also revealed caked exudative deposition (Fig. 3). Bilateral and unilateral corneal opacity resembling "pink-eye" was noted in two animals respectively. Moraxella bovis was isolated from the former while bacteriological studies were not made on the latter case.

Soon after the decline in temperature to normal or just before the diphasic rise, the buccal mucosa revealed hyperemia especially of the gums and dental pad, and grayish minute foci 1 to 4 mm in size which later developed into irregular, yellow to brown and shallow erosions and ulcers. Occasionally, an odoriferous pseudomembrane was seen covering the oral cavity. Profuse salivation was apparent in five cases.

Among the sick animals, diarrhea, dehydration, anorexia and cachexia were the prominent clinical manifestations. Persistent diarrhea occurred conspicuously, and the stool usually varied from watery in the beginning to mucoid and bloody to blood-tinged in the terminal stages. The nature of stools in different cases was as follows:

Nature of Diarrhea	Number of Cases
Bloody and blood-tinged	7
Mucoid	5
Watery	18
Total	30

The fecal material was often fetid and sometimes melenic but rarely contained admixed gaseous bubbles. Evacuations were forceful in the early stages of the sickness; later, they became more frequent and progressively exiguous. Intense tenesmus invariably accompanied evacuations, and in terminal stages only scant mucus or blood was voided. The animals commonly stood with hunched back and raised tail (Fig. 1 A). Fecal accretion of the hindquarters and tail was common.

Panting and accelerated heart beat were noted in animals during high fever. In the terminal stages, respirations became shallow and barely noticeable, whereas weak and rapid pulse was a constant finding. Respiration rate of up to 56 per minute and heart beat up to 120 per minute were recorded. Pronounced dyspnea occurred in three animals with pneumonia. Dry cough was noted in some animals.

Decreased appetite was noted in the early phase, and anorexia was prominent in the terminal or advanced clinical phase of the disease. The majority of animals went off feed completely while others ate when given soft or liquid food. Complete cessation of ruminal contractions and rumination occurred in all cases. Grinding of teeth was evident in

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Acute laminitis was observed in eight animals causing stiffness of gait and painful movement. Cleft and coronary bands of feet revealed epidermal congestion, hyperthermia and erosions.

Excoriation, encrustation and dryness of the skin were particularly prominent in the prolonged cases. Severely affected animals usually had a fetid breath and repulsive body odor.

Severe dehydration and pronounced wasting were a constant and prominent finding. Sunken eyes and flanks with a tucked-up appearance of the abdomen was common due to severe emaciation. Ribs and certain visible skeletal protuberances of markedly emaciated animals became progressively prominent. Dullness and depression were common. The sick animals usually exhibited marked weakness before going down moribundly. One animal remained comatose for a week before death.

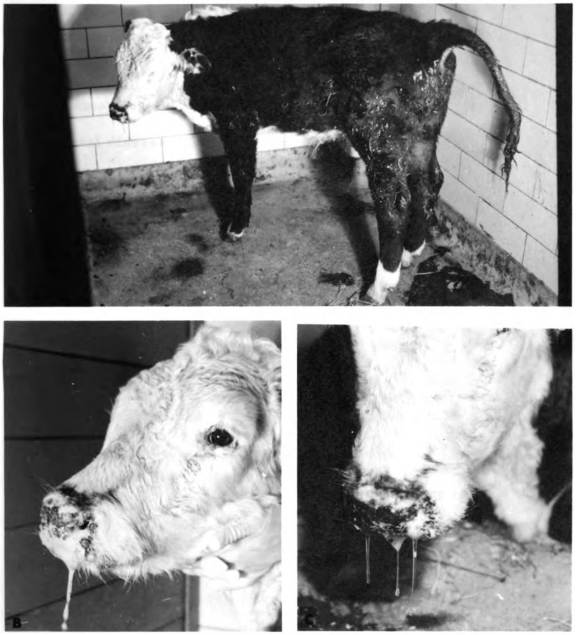

Fig. 1 A. A typical case of mucosal disease with wasting and fecal accretion of the hindquarters and tail. B. Close up of head showing typical muzzle erosions, ocular discharge and exudative caking of the eyelids. C. Close up of muzzle showing erosions and mucous nasal discharge.

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CHAPTER V

CLINICAL PATHOLOGY

Material and Methods

Hematological studies were conducted on 15 Michigan field cases of mucosal disease. In most of the cases, animals on arrival were moribund, hence only one blood sample could be obtained for analysis. The course or stage of the disease had varied at the time of collection of blood samples and, generally, the animals were either in the terminal stage or advanced clinical phase of mucosal disease. Urine was collected for analysis from two animals.

Results

Peripheral circulating blood picture was considerably variable among the animals (Table III). Various components of blood did not show any definite pattern of significant diagnostic value. Pronounced leucocytosis was noted in two-thirds of the cases. The leucocyte counts ranged from 4, 000 to 42, 000 per mm^3 of blood, averaging 12, 700. Only three cases had counts less than 5, 000. Neutrophilia occurred prominently in some cases with pronounced leucocytosis. In four cases, marked lymphocytosis was observed along with severe neutropenia. Hyperhemoglobinemia and erythrocytosis accompanied acute dehydration in the terminal stages. The hemoglobin concentration varied from 7. 0 to 15. 0 gm per cent and averaged 11. 5 gm.

TABLE III.

Case number	Date
A 60	7-2
A 116	8-7
A 262	9-1
A 262	9-2
A 263	9-1
A 263	9-2
A 390	10-
A 421	10-
A 430	10-
A 580	10-
A 580	11-
A 581	10-
A 581	11-
A 1532	4-2
B 221	7-1
B 1457	10-
B 3698	2-1
C 1219	9-1
C 2286	10-
C 2286	10-
C 2286	11-

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TABLE III. Body temperature and peripheral circulating blood picture of mucosal disease animals

Case number	Date	Body temperature (degrees F)	Hemoglobin*	Erythrocytes per mm^3 (millions)	Leucocytes per mm^3 (thousands)	Differential leucocyte count (%)				
						Nonsegmented neutrophils	Segmented neutrophils	Lymphocytes	Monocytes	Eosinophils
A 60	7-20-56	106.0	11.7	..	4.30	..	..	..	.	.
A 116	8-7-56	100.6	11.4	6.83	16.90	56	9	34	1	.
A 262	9-13-56	100.0	7.0	5.25	4.00	15	7	69	.	9
A 262	9-26-56	100.1	7.9	4.48	4.20	26	2	69	4	.
A 263	9-13-56	100.2	8.1	5.90	4.80	15	7	74	.	4
A 263	9-26-56	100.1	7.4	4.94	4.35	14	6	78	2	.
A 390	10-16-56	102.6	17.0	7.93	5.15	7	13	77	1	2
A 421	10-12-56	101.5	12.5	7.84	8.30	10	23	57	3	7
A 430	10-16-56	103.0	10.3	5.86	18.90	15	37	45	2	1
A 580	10-30-56	103.2	9.9	6.05	11.25	9	20	64	4	.
A 580	11-1-56	103.2	14.0	8.18	7.85	8	4	83	.	5
A 581	10-30-56	103.0	9.9	7.39	9.00	..	..	..	.	.
A 581	11-1-56	103.0	10.0	8.34	5.25	20	17	59	.	4
A 1532	4-24-57	100.0	12.5	8.24	7.70	12	3	83	.	1
B 221	7-16-57	99.6	12.2	9.94	42.70	..	..	..	.	.
B 1457	10-24-57	97.4	14.4	11.47	17.90	10	40	32	9	.
B 3698	2-14-58	99.8	..	..	5.80	44	4	50	2	.
C 1219	9-11-58	100.8	15.8	..	23.00	17	55	24	3	1
C 2286	10-15-58	104.0	15.0	11.35	8.55	..	..	..	.	.
C 2286	10-22-58	102.8	12.2	12.20	10.40	..	..	..	.	.
C 2286	11-12-58	98.8	10.7	7.80	2.40	..	..	..	.	.

*Grams per 100 milliliters of blood.

Likewise, the erythrocyte counts ranged from 4.48 to 11.7 millions per mm^3, averaging 7.62 millions. Blood urea studies in two animals did not show significant deviation from the normal range.

Urine from two animals was negative for sugar and albumin. Liver, kidney and intestines from two animals were negative for heavy metals.

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Table IV. Tre

Case number	
A 262	Peni
A 263	Peni
A 286	Peni
A 430	Anti tran
A 948	Anti
A 1587	Tetr
B 221	Bloo intra
B 1305	Anti
B 1419	Sulfo
B 1615	Vita
B 3098	Terr
B 3173	Terr
C 2227	Com sulfo

CHAPTER VI

THERAPY

A total of 13 Michigan field cases of mucosal disease were given treatments by the practicing veterinarians or by the ambulatory clinic staff of the College of Veterinary Medicine. Various medications were administered but none of the cases responded to the therapy (Table IV).

Table IV. Treatment observations

Case number	Medication	Results
A 262	Penicillin and sulfonamides	Negative
A 263	Penicillin and sulfonamides	Negative
A 286	Penicillin-streptomycin	Negative
A 430	Antibiotics, arsenicals and blood transfusions	Slight temporary improvement
A 948	Antibiotics	Negative
A 1587	Tetracycline	Negative
B 221	Blood transfusions and P. M. T. intravenously	Slight temporary improvement
B 1305	Antibiotics	Negative
B 1419	Sulfonamides, Longicil and tartar emetic	Negative
B 1615	Vitamin E	Negative
B 3098	Terramycin	Negative
B 3173	Terramycin	Negative
C 2227	Combiotic, Biosul, kaolin and sulfonamides	Negative

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CHAPTER VII

PATHOLOGIC ANATOMY

Material and Methods

Pathological studies were made on a total of 30 Michigan field cases of mucosal disease. Of 30 cases, 19 were received alive and were killed by electrocution, using 120-volt alternating current. In 11 of the 30 cases, the disease had completed its natural course and terminated in death.

Animals dead on arrival were immediately examined. Necropsy was completed within a minimum lapse of time following arrival or euthanasia. Tissues from the parenchymatous organs (adrenals, liver and kidneys) were collected and fixed as soon as possible to avoid postmortem decomposition while tissues from other organs were similarly processed in due course of necropsy. Each system and each organ were examined for alterations in color, size, shape, or consistency.

During the course of each necropsy at least one piece of tissue from almost every organ was taken for histopathologic examination. The tissue slices, approximately 0.5 cm thick, were fixed in 10 per cent formalin with sodium acetate (Armed Forces Institute of Pathology Manual, 1957). The tissue slices were stored in the fixative at room temperature for three to six days before trimming for subsequent preparation of histopathologic sections.

The trimmed tissue pieces were next dehydrated in 80 per cent, 90 per cent, 100 per cent ethyl alcohol, consecutively. The tissues were then passed through xylene to remove all traces of alcohol and to clear them. Subsequent infiltration with paraffin was achieved by placing the tissues in melted paraffin and this was followed by embedding in new paraffin. The tissues were then sectioned at a thickness of six microns and mounted on albuminized slides. Sections were stained routinely with the hematoxylin and eosin method described by Malewitz and Smith (1955). Special stains employed were Lendrum's, periodic acid-Schiff, Shorr's and phloxine-methylene blue. The procedures for these stains were those described in the Armed Forces Institute of Pathology Manual (1957). The phloxine-methylene blue stain was modified in that the sections were stained in phloxine for three hours at 56°C or overnight at room temperature. The decolorization of the sections was accomplished by employing one per cent acid (HCl) in 95 per cent alcohol for ten seconds.

Frozen sections were cut from formalin-fixed tissues at 15 microns thickness and stained with Sudan IV and hematoxylin.

Results

Among the subjects, the course of the disease had varied; hence these cases represented different stages of mucosal disease at the time of euthanasia or death. Marked dehydration and emaciation were common. Wasting was characterized by marked atrophy of skeletal musculature along with severe depletion and gelatinoid alteration of the subcutaneous

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1. Skin

Gross. The appearance of the skin had varied from glossy to dull and roughened. The latter alteration and dehydration were produced in animals with prolonged course of sickness. Occasionally, tufting of the hair was found. Fecal accretion with mucoid, fetid and occasionally blood-flecked feces was always present over the skin of the hindquarters and tail (Fig. 1 A). Often these animals emitted a fetid odor which attracted flies.

In many animals, the skin was less pliable due to dehydration but its thickness was unchanged. Looseness of the skin was quite apparent in animals with marked wasting. Alopecia was uncommon but hair pulled off easily in prolonged cases.

Lesions of the skin were common, ranging from encrustations to large and irregular erosions and ulcers. The encrustations appeared as discrete, irregular, grayish, dull elevations one to 15 mm in diameter and these were particularly prominent along the inner surface of the legs, udder or scrotum, inguinal and perineal regions, and the postero-ventral abdomen. The crusts gradually desquamated leaving irregular, shallow, and discrete epidermal excoriations two to 20 mm in diameter.

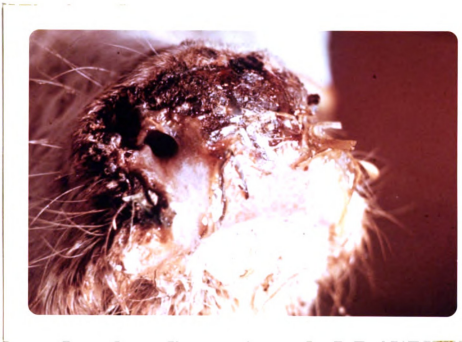

Fig. 2. Muzzle showing mucopurulent nasal discharge, encrustation and erosion.

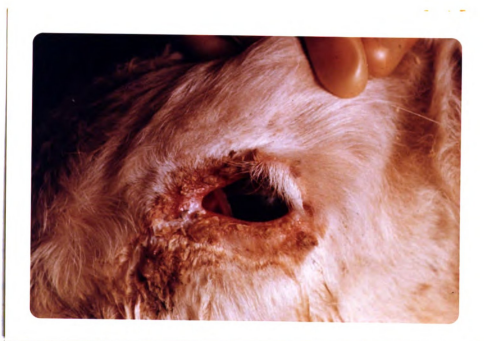

Fig. 3. Mucopurulent ocular discharge and exudative caking of the eyelids.

Desquamated crusts were often seen as gray flecks entangled in the hair at the base of the horns and inside of the external ears.

Erosive and ulcerative lesions of prepuce or vulvar labiae occurred in a few animals. These were discrete in the beginning, but tended to be confluent and conspicuous in the later stages. Occasionally, these areas were covered with a yellowish pseudomembrane which peeled off easily, exposing large, raw, irregular, shallow ulcers. The pseudomembrane was usually fetid due to putrefactive decomposition.

The lesions of the foot consisted in discrete and irregular erosions of the coronary bands and irregular, raw and bleeding ulcers of the interdigital space. The interdigital space usually revealed a dark pseudomembrane and was always fetid due to putrefactive changes.

The muzzle was most commonly involved, showing lesions ranging from pronounced erythema to diffuse encrustation and ulceration. In the early stages, it was either erythematous in a few cases or had a patchy appearance due to encrustation in most of the cases (Fig. 2). In some animals the muzzle was diffusely covered with a pseudomembrane which stripped off easily, exposing a raw surface studded with drops of exuding serum. The lesions gradually developed into ulcers of irregular outline, soft granular base, shallow floor, ragged edges and with serous to serohemorrhagic exudation. These were usually contiguous with those of the nostrils and upper lip. A tenacious, mucoid to mucopurulent nasal discharge commonly occurred (Fig. 1 A and B).

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Microscopic. The lesions were principally confined to the epidermis (squamous epithelium) and were basically identical throughout the skin. These were essentially degenerative in nature; viz., hydropic degeneration, reticular colliquation (ballooning degeneration), acantholysis and necrosis of the squamous epithelial cells.

In detail, an earliest recognizable change was seen as hydropic degeneration of individual or small groups of cells in the deep layer of stratum spinosum and occasionally, in the basal layer (Fig. 4 A). The affected cells acquired a signet-shape due to intracytoplasmic vacuolation and peripheral displacement of the nucleus. The nuclei had shrunken and become misshapen. Gradual swelling of the cells due to hydropic degeneration caused obliteration of the intercellular bridges. Russell's bodies were sometimes present in less severely affected cells (Fig. 4 A).

Occasional necrotic cells, recognized by their homogeneous, deeply eosinophilic cytoplasm, and pyknosis or karyorrhexis, were often scattered throughout the epithelium (Fig. 4 A and B). Mild spongiosis was not uncommon, producing mechanical separation of the prickle cells and intercellular vacuolation in the deeper layers adjacent to the dermal papillae (Fig. 4 A).

In advanced lesions, the affected cells revealed marked deterioration due to ballooning degeneration. This was noted as diffuse and abundant reticular colliquation especially in the stratum granulosum and stratum lucidum. Often the stratum corneum had completely

Fig. 4 A. Early epidermal lesions of the skin from medial surface of thigh showing hydropic degeneration of the cells of the deeper layer of stratum spinosum (1) and basal layer (2), spongiosis of the basal layer and stratum spinosum (3), necrosis of the epithelium (4) and intracytoplasmic Russell's bodies (5). H and E stain; x 360

B. Lesions similar to "A" widely scattered in the epidermis. H and E stain; x 120.

C. Diffuse ballooning degeneration and vesiculation (1) of epidermis of skin from the udder. H and E stain; x 180.

D. Partially detached necrotic membrane (1), reticular colliquation (2) and hemorrhagic exudation (3) of epidermis of the vulvar labium. H and E stain; x 180.

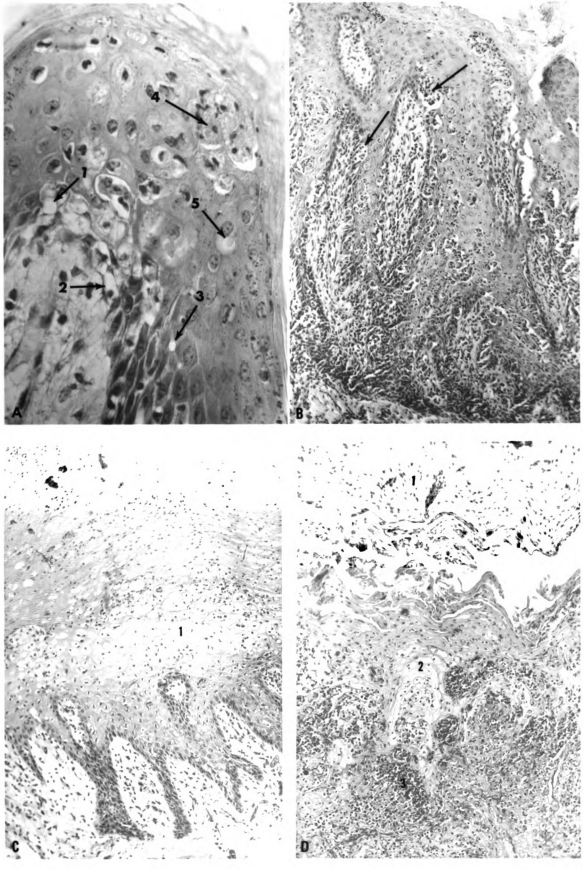
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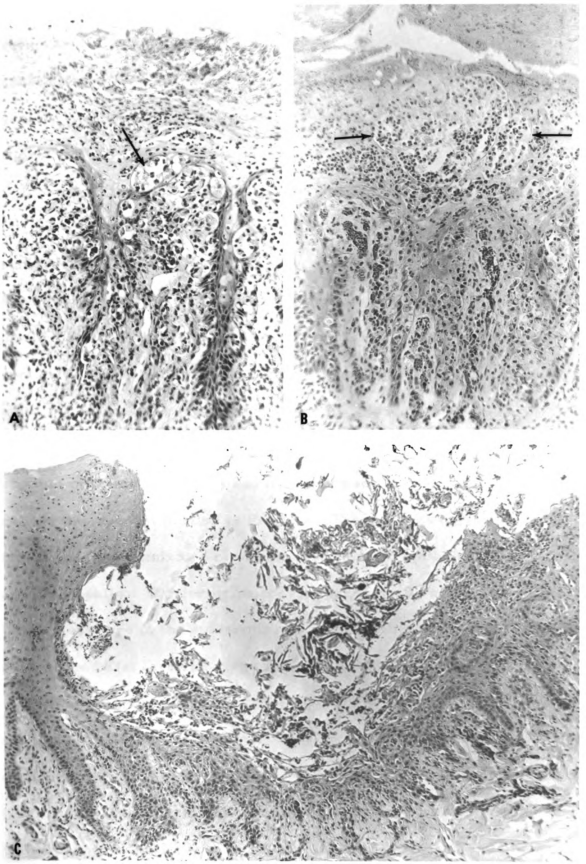
Fig. 5 A. Microscopic vesicles (arrow) in the deeper layer of stratum spinosum and basal layer resting over the dermal papillae of the muzzle. H and E stain; x 100.

B. Large microscopic vesicle (arrows) beneath a partially detached necrotic membrane covering the epidermis and congestion of dermal papillae of the muzzle. H and E stain; x 100.

C. Typical erosion of the muzzle. H and E stain; x 72.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disappeared and desquamation was apparent in some. Focal areas of reticular colliquation accompanied by desiccation, were responsible for crust seen grossly along the skin. In detail, the affected cells appeared greatly swollen through intracellular edema. Their cytoplasm stained poorly and the nucleus displayed pyknosis and increased basophilia. Ballooning of the cells resulted in complete obliteration of the intercellular bridges, while the resisting cell wall became conspicuous and homogeneously eosinophilic. Finally, these cells enlarged to such an extent as to rupture, thus causing them to merge; only the resisting and deeply eosinophilic cell walls and fragments of the nuclear chromatin remaining more or less as a network, thus forming intracellular or multilocular vesicles or pustules (Fig. 4 C and Fig. 5 A). The roof of the vesicle or pustule was usually formed by the stratum lucidum and stratum corneum (Fig. 5 B) and the floor was formed by the degenerated cells of the deepest portion of the rete. The vesicles or pustules contained variable admixture of serum, degenerated epithelial cells, fibrin and heterophils. Wandering leucocytes occasionally accompanied vesiculation elsewhere in the epidermis. Similar minute vesicles were also seen in the basal layer resting over the dermal papillae.

Necrosis and sloughing of the roof of the vesicle or pustule caused spilling of the contents leaving an erosion or ulcer. Acantholysis of the degenerated layers also resulted in erosion or ulceration of the epidermis (Fig. 5 C). The base of the ulcer was formed by denuded corium covered with fibrin or necrotic tissue. The walls of the erosions and ulcers were

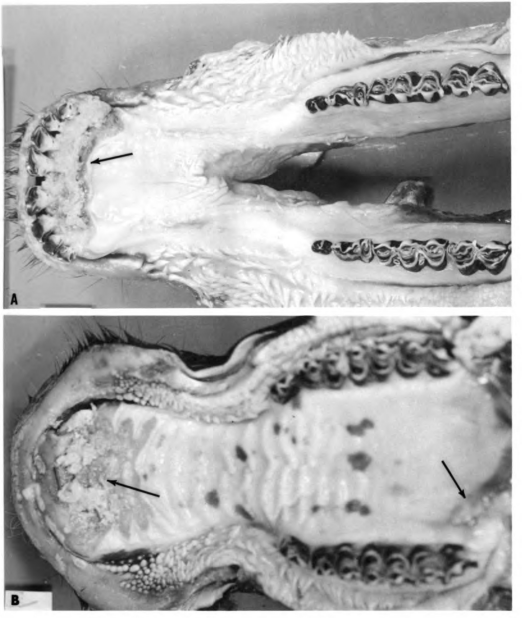

Fig. 6 A. Typical erosive and ulcerative lesions (arrows) of the buccal mucosa adjacent to the incisor teeth and of the lower lip. B. Erosions and ulcerations (arrows) of the buccal mucosa, the upper lip, dental pad and hard palate.

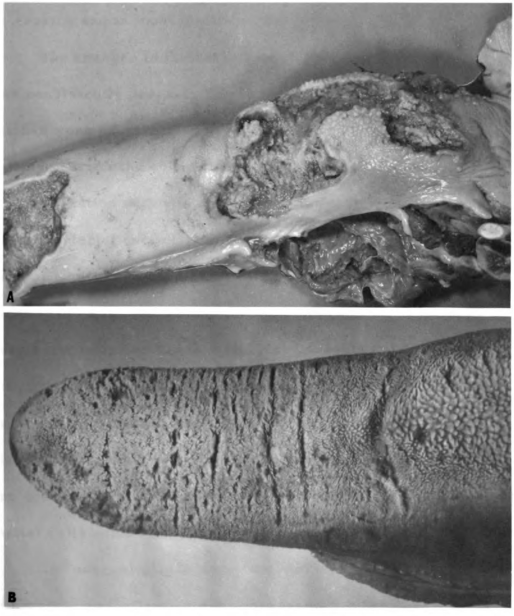

Fig. 7 A. Large ulceration of the tip and dorsum of the tongue. **B.** Typical erosions and ulcerations resulting in transverse fissures of the dorsal surface of the tongue.

always frayed and formed by acantholytic and ballooned cells. Reticular colliquation usually extended quite a distance from the wall of the ulcer or erosion and in most instances was present diffusely.

The changes in the corium were usually minimal. Variable edema was consistently present. The lymphatics adjacent to the epidermal lesions were usually dilated, while the accompanying edema caused pulling apart of the cellular elements (Fig. 4 A).

Caseation necrosis and acute inflammatory reactions also occurred, due to bacterial secondary invasion. Occasionally, congestion of the dermal papillae was the only finding at the base of the deep erosion or ulcer (Fig. 5 B). However, infected ulcers often had congested, hemorrhagic and inflamed bases. The blood vessels adjacent to these ulcers frequently showed hyaline plugs or thrombi. In case of inflammatory reaction, heterophils made up the major portion of the leucocytic infiltrate, along with sparsely interspersed eosinophils, plasma cells, lymphocytes and occasional macrophages. Proliferation of the fibroblasts and endothelial cells sometimes occurred beneath a highly irritated ulcer.

The adnexal glands were involved only secondarily by the extension of necrotic and inflammatory processes from the deep ulcers. The squamous epithelial portion of the hair follicles and glandular excretory ducts revealed changes similar to those of the epidermis (Fig. 10 A and B).

2. Eyes

Gross. The eyes of most animals appeared dull and lusterless. Animals with advanced wasting revealed strikingly sunken eyes. Exudation, consisting of slight lacrimation to exudative caking, was frequently found along the eyelids and medial canthi (Fig. 1 B and C and Fig. 3). Erosive and ulcerative changes were not observed. Bilateral and unilateral corneal opacities were present in two animals, respectively. Moraxella bovis was isolated from the former but bacteriological studies were not carried out on the latter case. Corneal opacity was considered as incidental rather than characteristic of the disease.

Microscopic. Microscopic examination did not show any discernible changes except in those with the so-called "pink-eye."

3. Alimentary Canal

a. Oral Cavity

Gross. The lesions of the oral cavity were consistently present but varied considerably in location, nature and extent. No portion of the oral lining was immune, although the tongue, gums and dental pad were most commonly involved (Fig. 6 A and B, Fig. 7 A and B, and Fig. 9). Occasionally, the entire oral mucosa was erosive or covered with yellowish-gray necrotic pseudomembrane (Fig. 8). The erosions were irregular, shallow, 10 to 35 mm in diameter and discrete, but they sometimes assumed large proportions due to coalescence.

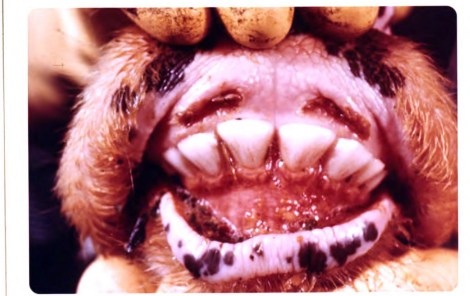

Fig. 8. Hemorrhage, necrotic pseudomembrane, erosion and ulceration of the dental pad and gums along the incisor teeth.

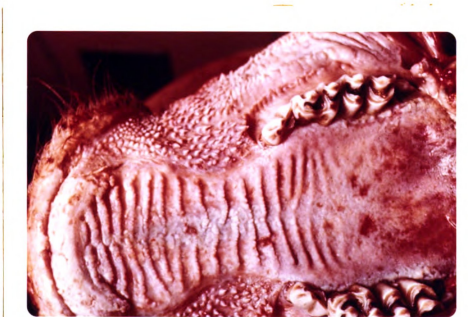

Fig. 9. Diffuse superficial necrosis, erosion and ulceration of the mucosa of upper lip, dental pad, cheeks and hard palate.

Fig. 10 A. Characteristic hydropic degeneration (1) and necrosis (2) of the squamous epithelium of a hair follicle of the muzzle. H and E stain; x 120.

B. Acantholysis (1), and necrosis (2) of the squamous epithelium accompanied by intraluminal collection of acantholytic cells (3) and cell debris (4) of an adnexal secretory duct of the muzzle. H and E stain; x 132.

C. Edge of a typical epidermal erosion (1), degeneration of the stratum spinosum (2) and diffuse reticular colliquation of the stratum granulosum and lucidum (3) of the tongue. H and E stain; x 120.

D. Diffuse reticular colliquation of the stratum lucidum (1) of the tongue. H and E stain; x 260.

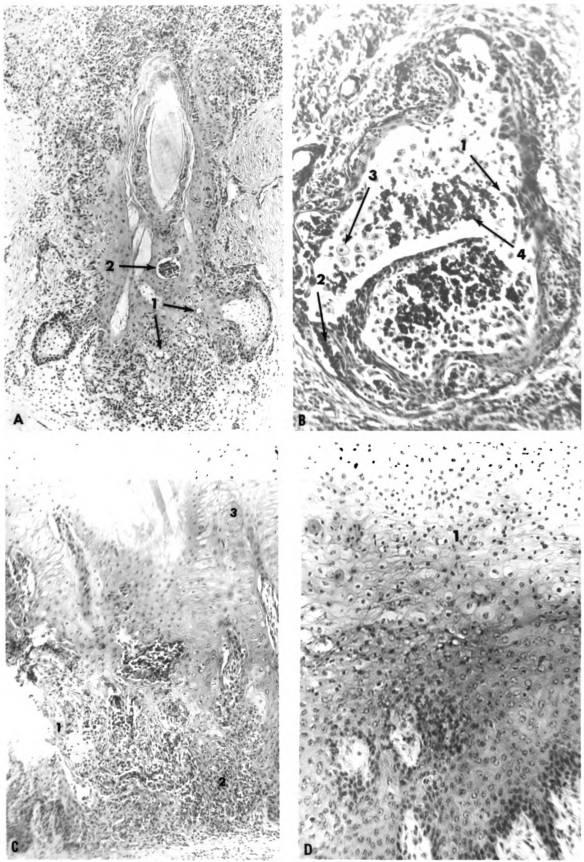
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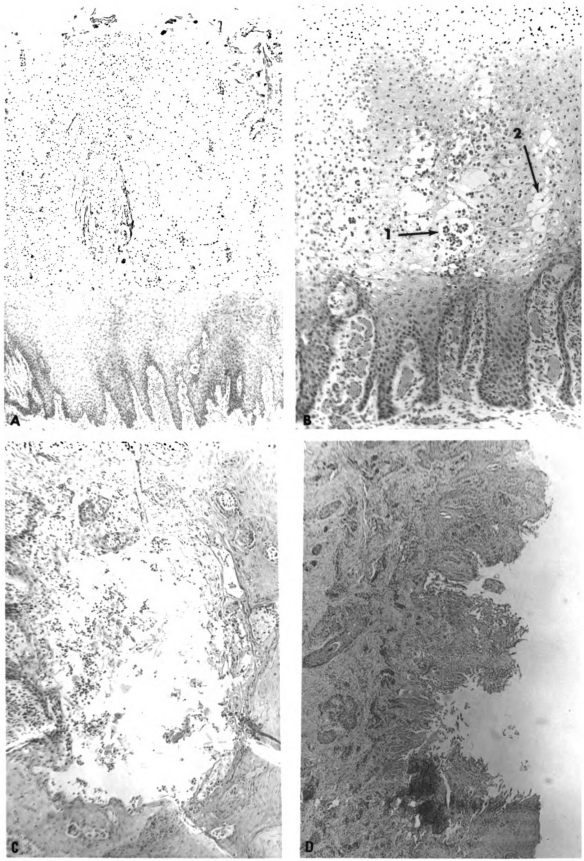
Fig. 11 A. Diffuse reticular colliquation of stratum granulosum and stratum lucidum of the tongue. H and E stain; x 72.

B. Spongiform vesicles (1) and diffuse reticular colliquation (2) of the upper layers of stratum spinosum and of stratum lucidum, and severe congestion of the lamina propria (3) of the tongue. H and E stain; x 120.

C. Large microscopic intralaminal vesiculation of squamous epithelium of the tongue. H and E stain; x 72.

D. Ulcer of the ventral surface of the tongue. H and E stain; x 60.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They imparted a brownish discoloration to the oral mucosa (Fig. 5A). Ulcerations of the oral mucosa were seen especially along the tongue, gums and dental pad; the ulcers were 0.5 to 5 cm in diameter and were characterized by irregular outline, punched-out appearance, soft granular base, shallow hyperemic floor, ragged edges and clear serous exudate (Fig. 6, Fig. 7, Fig. 8, and Fig. 9). They varied in color from yellowish-gray to reddish-brown. The epithelium between the ulcers usually appeared dull. The erosions and ulcerations of the tongue were located especially along the anterior two-thirds of the dorsal and lateral surfaces, and at the tip along the ventral surface. The ulcers were usually disposed at random but in a few cases they extended from side to side along the dorsal surface of the tongue producing transverse fissures (Fig. 7 B). Petechial to diffuse mucosal hemorrhages of the gums, cheeks, dental pad and ventral surface of the tip of the tongue were occasionally present.

Microscopic. The lesions were primarily confined to the squamous epithelium and were identical in nature to those described for skin (Fig. 10 C and D, Fig. 11, A, B, C and D and Fig. 12 A and B).

b. Salivary Glands

The glands did not show any clearly significant lesions.

Fig. 12 A. Acantholysis (1) leading to a deep erosion and diffuse reticular colliquation of stratum lucidum, stratum granulosum and upper layers of stratum spinosum (2) of the pharynx. H and E stain; x 100.

B. Early erosion and diffuse reticular colliquation of the pharynx. H and E stain; x 120.

C. Necrotic pseudomembrane covering a small ulcer of the pharynx. H and E stain; x 72.

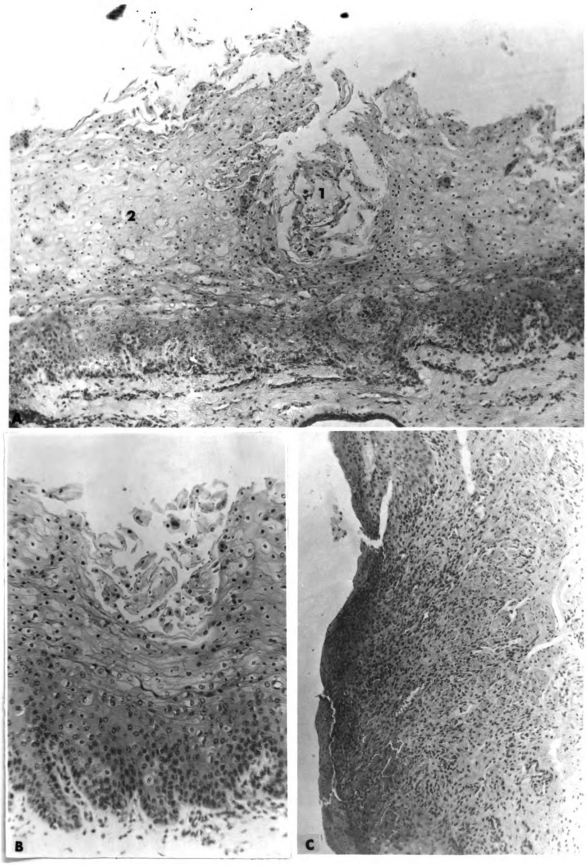
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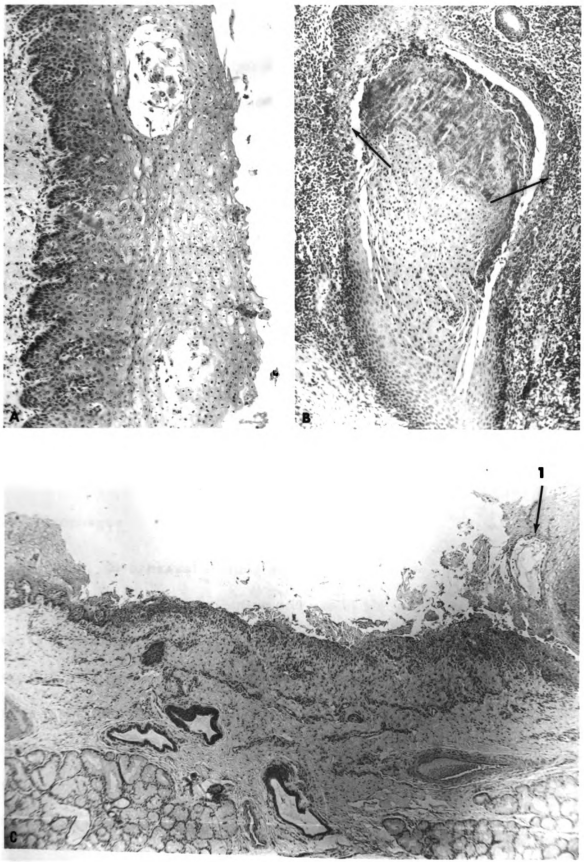
Fig. 13 A. Intralaminal cavitations and diffuse reticular colliquation of the stratum granulosum and stratum lucidum of the pharynx. H and E stain; x 72.

B. Necrosis and hydropic degeneration of the squamous epithelium (arrows) of the pharyngeal crypt. H and E stain; x 60.

C. Large deep erosion, intralaminal cavitation (1) and diffuse reticular colliquation of the squamous epithelium of the pharynx. H and E stain; x 20.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c. Pharynx

Gross. The lesions of the pharyngeal mucosa were not common. Discrete necrotic areas, present in some cases, appeared as minute white elevations which could be easily scraped off exposing shallow depressions. In a few instances, the entire mucosa was covered with a thin, dull and necrotic membrane. Rarely, shallow, narrow and linear erosions occurred longitudinally along the pharynx and these often extended a short distance into the esophagus. Sometimes a granular mucosal appearance was the only appreciable finding. Small, narrow and linear ulcers were also present occasionally.

Microscopic. The alterations were prominently limited to the squamous epithelium of the pharyngeal mucosa and crypts. These resembled closely those of the skin (Fig. 12 C and Fig. 13 A, B and C).

d. Esophagus

Gross. Esophageal lesions were found with few exceptions. They varied considerably in distribution and extent but tended to be more severe and pronounced along the posterior two-thirds of the esophagus. Occasionally, minute, necrotic lesions appeared as barely macroscopic linear elevations which escaped notice on casual examination. In some instances, the mucosa was covered throughout with an easily removable, dull, necrotic pseudomembrane. Longitudinally linear erosions and ulcerations with white necrotic edges commonly occurred (Fig. 14 A and B).

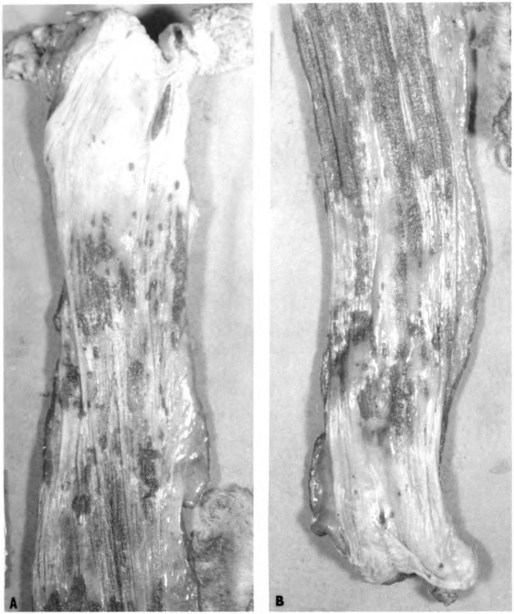


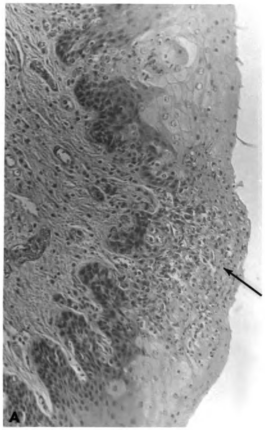
Fig. 14 **A.** Necrosis, erosions and ulcerations of the mucosa of the anterior portion of the esophagus. **B.** Similar lesions of the posterior portion of the esophagus.

Fig. 15 A. Epithelial necrosis (arrow) and diffuse reticular colliquation of the stratum granulosum and stratum lucidum of squamous epithelium of the esophagus. H and E stain; x 100.

B. Diffuse reticular colliquation of the upper strata of squamous epithelium of the esophagus. H and E stain; x 100.

C. Ulcer and reticular colliquation of squamous epithelium of the esophagus. H and E stain; x 20.

D. Ulcer of the esophagus. H and E stain; x 72.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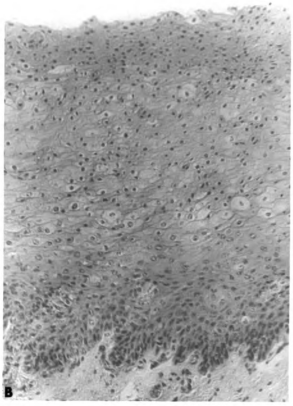
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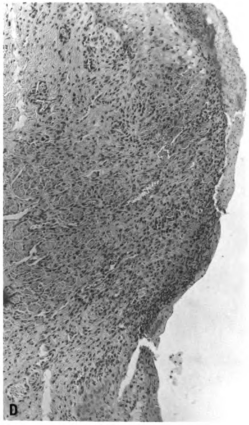
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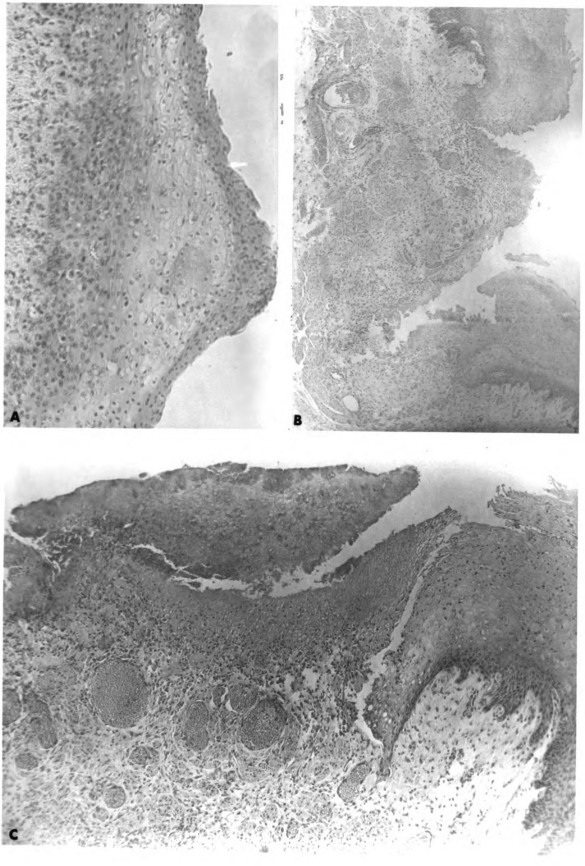
Fig. 16 A. Diffuse superficial necrosis and reticular colliquation of the squamous epithelium of the esophagus. H and E stain; x 100.

B. Small deep ulcer and diffuse reticular colliquation of squamous epithelium of the esophagus. H and E stain; x 20.

C. Ulcer and marked reticular colliquation of the squamous epithelium of the esophagus. H and E stain; x 60.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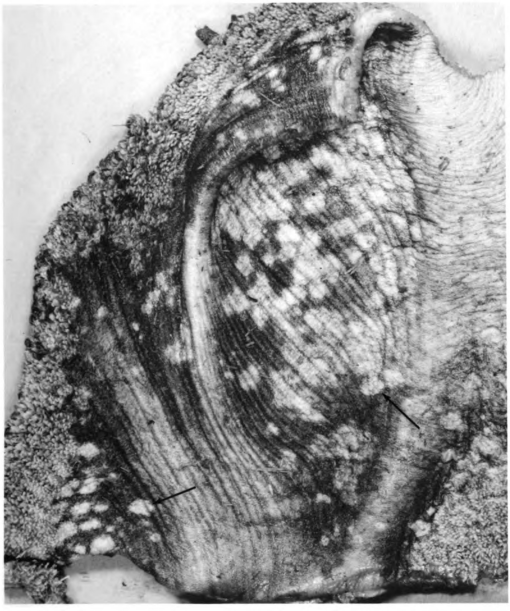


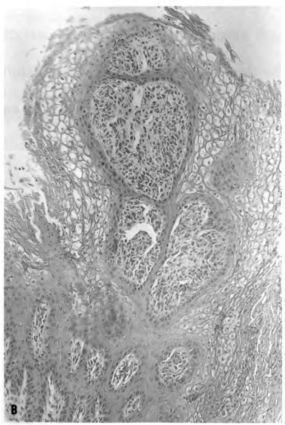
Fig. 17. Characteristic erosions and ulcerations (arrows, appearing as areas of depigmentation) of the mucosa of the ruminal pillars and adjacent areas.

Fig. 18 A. Diffuse ballooning degeneration of squamous epithelium of the rumen. H and E stain; x 20.

B. Diffuse ballooning degeneration of a papilla of the rumen. H and E stain; x 20.

C. Small ulcer of the rumen. H and E stain; x 60.

A



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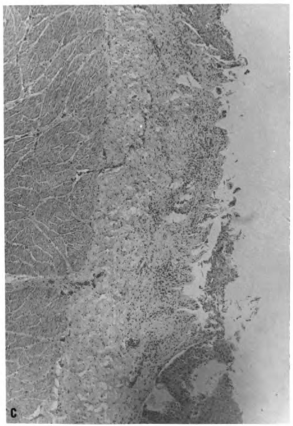


C

These were always irregular and, in severe cases, had coalesced especially in the thoracic portion of the esophagus producing large, denuded, hyperemic or brownish areas. Diffuse and extensive sloughing of the necrotic epithelium had frequently resulted in a denuded, reddish to brown appearance of the esophageal mucosa throughout. Petechial to diffuse mucosal hemorrhages also occurred but less commonly.

Microscopic. The changes were principally confined to the squamous epithelium and bore a close resemblance to those of the epidermis (Fig. 15 A, B, C and D and Fig. 16 A, B and C).

e. Forestomachs

Gross. The ruminal mucosa consistently revealed macroscopic lesions which were quite variable in distribution, nature and extent. Extensive superficial necrosis was a common finding and appeared as dull yellowish-gray, loosely attached epithelium which scraped off easily, exposing reddish lamina propria. Erosions, ulcerations and focal necrosis were found and commonly, were conspicuous as areas of depigmentation especially along the ruminal pillars and their vicinity (Fig. 17). Food material was often found adhering to the necrotic epithelium. Petechial to diffuse hemorrhages of the ruminal mucosa were a prominent feature in a few cases. The ruminal contents were always scanty and varied from a relatively dry mass to watery, fetid ingesta.

Lesions of the reticulum, though rare, closely resembled those of the rumen. Often these extended from the rumen.

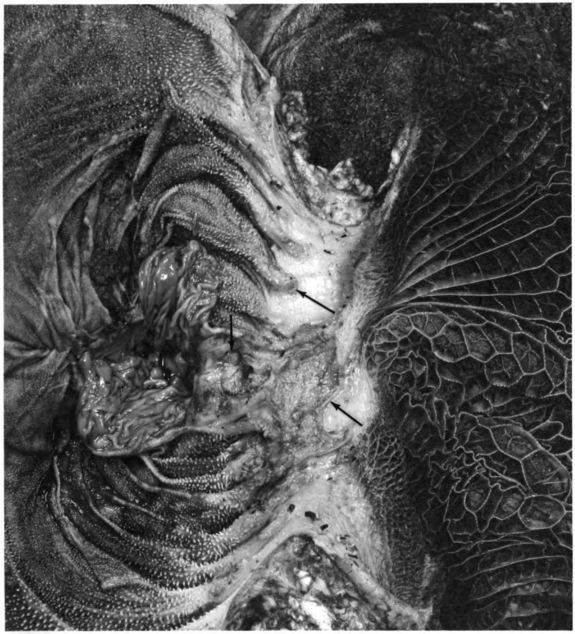
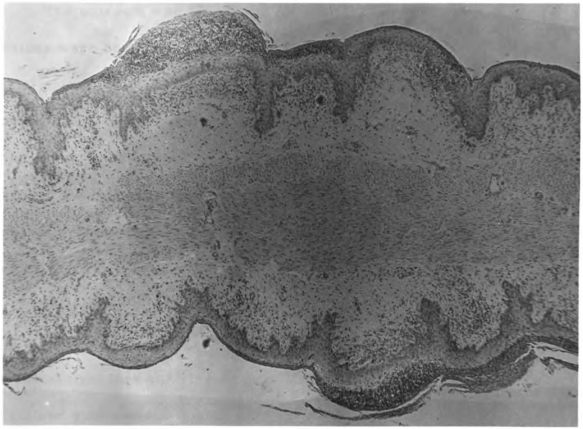


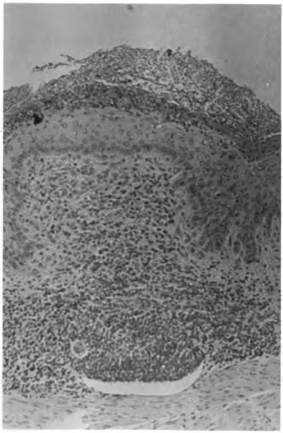
Fig. 19. Erosions and ulcerations of the esophageal groove and omasum (arrow).

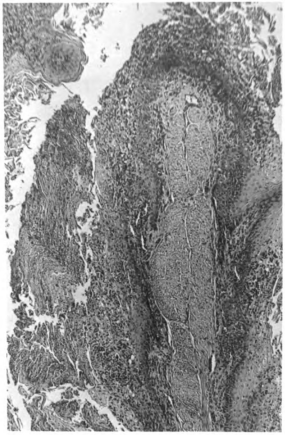
Fig. 20 A. Caseation necrosis of superficial layers of squamous epithelium of the omasum. H and E stain; x 30.

B. Lesion similar to "A" of squamous epithelium of the omasum. H and E stain; x 120.

C. Extensive and diffuse caseation necrosis of superficial layers of squamous epithelium of the omasum. H and E stain; x 30.







The omasum was frequently affected and, as in the rumen, the lesions were necrotic, erosive and ulcerative in nature. Diffuse superficial epithelial necrosis occurred conspicuously in a few cases. Irregular erosions and ulcerations were particularly numerous along the margins of the omasal leaves. Sometimes the ulcerations had penetrated through the leaves. Commonly, the omasum contained liquid and fetid ingesta. The esophageal groove had lesions resembling those observed in the esophagus (Fig. 19).

Microscopic. The lesions of the rumen (Fig. 18 A, B and C), reticulum, omasum (Fig. 20 A, B and C) and esophageal groove were identical in nature and closely resembled those of the upper digestive tract and epidermis.

f. Abomasum

Gross. The abomasum was commonly the site of a variety of alterations such as congestion, hemorrhages, edema, superficial necrosis, erosions and ulcerations of the mucosa, especially of the fundic spiral folds. Superficial mucosal necrosis appeared as focal to diffuse areas of dullness. Erosions and ulcerations were seen as irregular, shallow, and punched-out depressions covered with a thin, yellowish-gray and mucoid or necrotic pseudomembrane (Fig. 21 A and B). These usually varied from the barely visible to 2 cm in diameter and often had a corona composed of necrotic mucosa or, occasionally, a hemorrhagic ring formed with numerous petechiae (Fig. 21 B). The fundic folds and submucosa throughout were frequently swollen and gelatinoid due to edema.

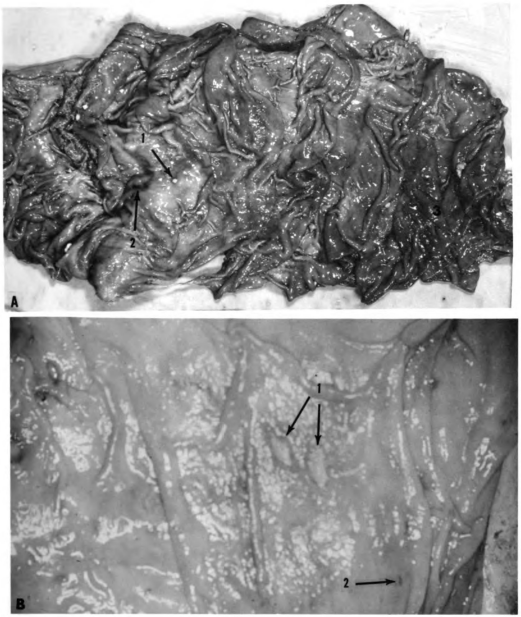


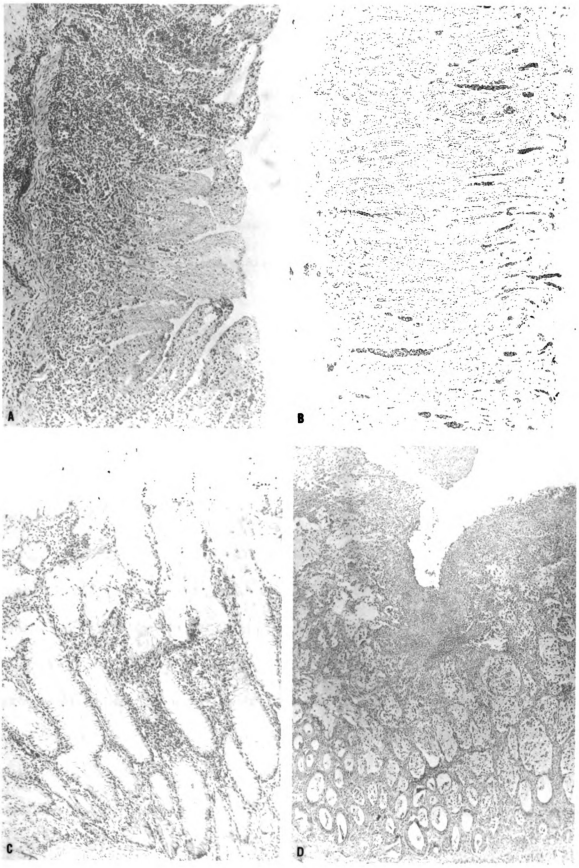
Fig. 21 A. Erosions (1), hemorrhages (2) and diffuse congestion (3) of the mucosal spiral folds of the pylorus of the abomasum. B. Similar lesions of the fundus of the abomasum.

Fig. 22 A. Desquamation of epithelium and coagulation necrosis of lamina propria of gastric mucosa preliminary to development of erosions and ulcerations of the abomasum. H and E stain; x 100.

B. Obliteration of crypts due to epithelial necrosis and marked congestion of lamina propria of the abomasal mucosa. H and E stain; x 60.

C. Severe catarrhal enteritis of the jejunum. H and E stain; x 72.

D. Small early erosion and accompanying abscessation and dilatation of crypts of the ileum. H and E stain; x 60.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Commonly the abomasal mucosa had a fiery red appearance due to marked congestion (Figure 21 A). Sometimes the hemorrhages were found as clusters of ecchymoses. The lesions of the pyloric and fundic portions of the abomasum were alike but the latter was usually more severely affected.

Microscopic. Coagulation necrosis of the glandular epithelium was a prominent feature. Extension of the process deeply often resulted in complete obliteration of the glandular epithelium and collapse of the lamina propria. The necrotic epithelial cells appeared shrunken with deeply eosinophilic cytoplasm and pyknotic, fragmented or lysed nuclei. Glandular architecture was markedly disrupted due to necrosis and detachment of the epithelial cells (Fig. 22 A). Superficial necrosis was usually accompanied by necrosis of individual epithelial cells in the deeper portion of the crypts. The crypts appeared to be affected selectively, since some persisted while others were completely obliterated. Abscessation and dilatation of the crypts often occurred and was manifested by accumulation of mucous, desquamated and often fragmented epithelial cells, and accompanying heterophilic infiltration. Crypt abscesses were scattered at random affecting individual and occasionally groups of two or three adjacent glands. Extensive mucosal necrosis appeared as erosions and frank ulcers. Among the various epithelial cells of the abomasal glands, the parietal cells were found to be more resistant to destruction; hence were the last to degenerate and disappear. In many instances, the lamina propria was denuded, atrophied or completely collapsed due to necrosis and loss of epithelial cells.

Fig. 23 A. Hemorrhage and necrosis of Peyer's patch accompanied by mucosal congestion and hemorrhage of the ileum. B. Severe mucosal congestion and hemorrhage of the jejunum.

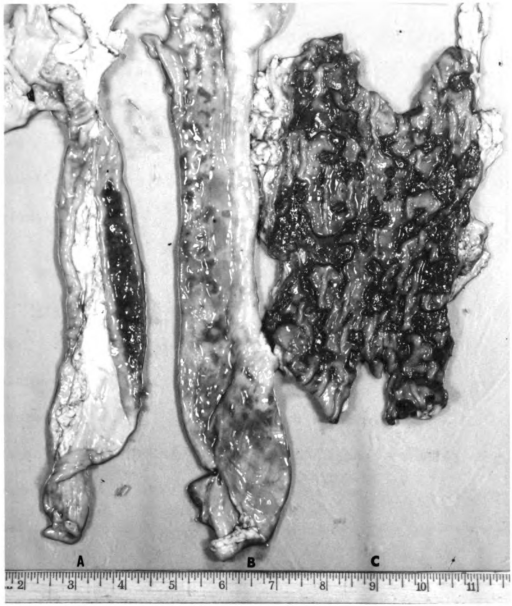


Fig. 24 A. Severe necrosis and hemorrhage of Peyer's patch. B. Mucosal congestion and hemorrhages of the ileum. C. Characteristic erosive and ulcerative lesions of the mucosa of the ileum.

The inflammatory reaction in the abomasum was usually minimal and was characterized by leucocytic infiltration, hemorrhages, capillary dilatation and hyperemia (Fig. 22 B) in the lamina propria and submucosa. Edema and lymphatic dilatation were also conspicuous in the lamina propria. Occasionally, the lamina propria was infiltrated with a few heterophils, eosinophils, lymphocytes and plasma cells. Lumina of blood vessels in the submucosa often contained increased numbers of various leucocytes.

g. Small Intestine

Gross. Appearance of the small intestine was considerably variable. The intestinal mucosa was covered with thick, glistening, and tenacious mucus throughout, and usually revealed petechial to diffuse hemorrhages (Fig. 25). The duodenum was commonly a site of catarrhal enteritis. The jejunum and the ileum were often severely involved, showing necrosis, hemorrhages, and areas of extensive erosions and ulcerations (Fig. 24). In many cases, necrosis and hemorrhage conspicuously occurred over the solitary lymph follicles and Peyer's patches (Fig. 23 and 24). Erosions and ulcerations here were covered with tenacious mucoid exudate and closely conformed to the configuration of the local lymph tissue. Elsewhere the erosions and ulcerations were irregularly disposed and were characterized by an irregular outline, punched-out appearance, shallow to deep base, supple hemorrhagic floor, ragged to clear cut edges, tenacious secretion and a tendency to coalesce (Fig. 24 C).

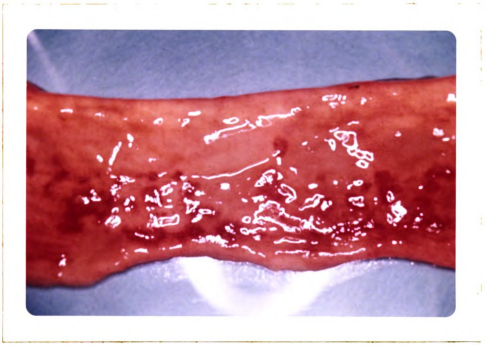


Fig. 25. Tenacious mucous exudate and petechial to diffuse hemorrhages of the jejunal mucosa.

Among the small intestines, the ileum was usually most severely affected especially along its terminal portion. In severe cases, it was either extensively eroded, ulcerated and congested or diffusely covered with dull pseudomembrane.

The lumina of the jejunum and ileum were often filled with glistening mucoid or dull whitish exudate. Marked congestion and petechial to diffuse hemorrhages were constantly noted (Fig. 23 and 24). Enterorrhagia occurred in some cases and was marked by blood-tinged contents, free blood, melena or frank blood clots in the intestinal lumen. The terminal portion of the small intestine often contained a single large, dark colored blood clot causing distention of the intestine. Small blood clots were also occasionally seen attached to the mucosa over the necrotic and hemorrhagic Peyer's patches. Enterorrhagia and necrotic Peyer's patches were readily discernible through the usually hyperemic serosa upon opening the abdomen. Sometimes erosions and ulcerations could likewise be seen without opening the intestines.

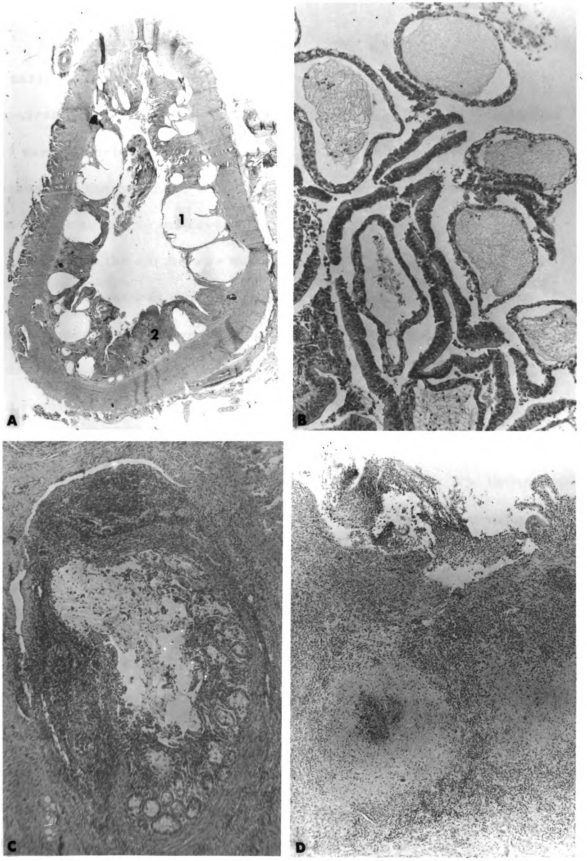
In three cases, the iliac mucosa was studded with cysts 10 to 25 mm in diameter interspersed between the erosions and ulcerations. Cross-section of the ileum usually revealed variable thickening due to edema. Mesentery in the vicinity of the severely affected intestine was commonly congested and edematous. In severe cases, the mesenteric and intestinal serosal veins were conspicuous due to dark discoloration and engorgement.

Fig. 26 A. Typical vesiculation (1) and necrosis (2) of mucosa of the jejunum. H and E stain; x 20.

B. Vesiculation of the cecal crypts. H and E stain; x 360.

C. Necrosis and mucous degeneration of a submucosal gland of the cecum. H and E stain; x 100.

D. Caseation and necrosis of a Peyer's patch of the ileum. H and E stain; x 100.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Microscopic. Mucous degeneration was the most common finding in early stages of the disease. In severe cases, the intestinal crypts appeared greatly distended with abundant mucus, epithelial cell debris and variable heterophilic infiltrate (Fig. 22 C and D). Coagulation necrosis of the columnar cells, and mucosal congestion, hemorrhage, and edema accompanied severe catarrh. In some instances, serous exudation into the crypts was noted, appearing as small cysts (Fig. 26 B).

The lesions were generally severe in advanced clinical or terminal stages of the disease. Caseation necrosis of the intestinal mucosa over the usually necrotic Peyer's patches and solitary lymph follicles had resulted in deep ulcerations. These ulcers rested over the muscular layers, and their base was often covered with a yellowish gray pseudomembrane composed of fibrin, dead cell debris, mucus, and inflammatory cells. Elsewhere, focal caseation necrosis was noted as erosions and ulcers confined to the mucosa. Marked depletion and coagulation to caseation necrosis of the intestinal lymph tissue was frequent.

Obliteration and abscessation of the mucosal and submucosal crypts occurred prominently. Congestion, hemorrhage, edema, and inflammatory cell infiltrate were regularly present, especially adjacent to the infected ulcers. In some cases, the disease was of such a fulminating nature as to cause diffuse caseation necrosis and profuse hemorrhage of the mucosa. Grayish and often hemorrhagic pseudomembrane was found covering the intestinal mucosa in most of these cases. In others the mucosa had completely disappeared. Cystic enteritis was occasionally observed (Fig. 26 A).

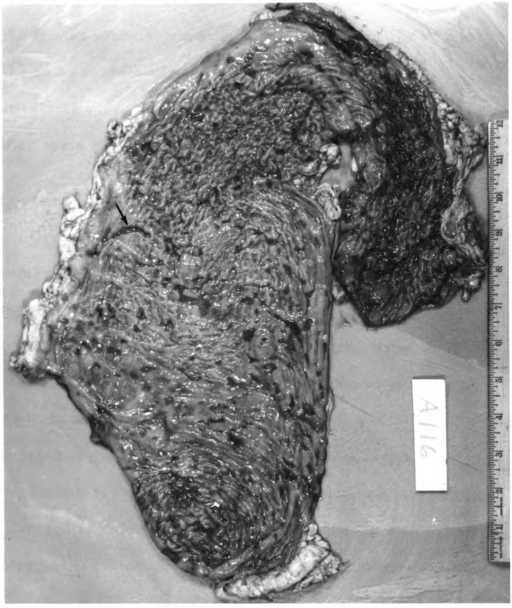

Fig. 27. Typical mucosal erosive and ulcerative lesions (arrow), and congestion of the cecum.

Variable hyperemia and edema of the lamina propria and submucosa of the small intestine was common, whereas hemorrhages occurred only in the lamina propria, especially of the jejunum and ileum. Thrombosis of the blood vessels adjacent to the ulcers was frequently noted. Tissues, particularly surrounding the infected ulcers, regularly revealed heterophilic, eosinophilic and plasma cell infiltration.

h. Large Intestine

Gross. This portion of the intestines was often most severely affected. Similar to the small intestine, the lesions here also varied considerably in extent, nature, distribution and severity. In some cases, severe involvement of the large intestine showing marked reddening, discoloration or ulceration, was readily apparent when the abdomen was opened. Congestion and edema of the serosa commonly occurred, and similar changes were also noted in the regional mesentery in severe cases.

Extensive areas of erosions and ulcerations, appearing as punched-out, irregular defects, occurred diffusely but were often particularly severe and conspicuous along the ileo-cecal valve, cecum, colon and anterior rectum (Fig. 27, 28 and 29). These defects varied considerably in size from a few millimeters to several centimeters, and were easily visible through the serosa of the unopened large intestine as irregular, discolored spots. The mucous membrane between these defects was often hyperemic, hemorrhagic, melenic and/or occasionally studded with variable sized cysts containing serous to serosanguineous exudate.

The intestinal mucosa was usually reddened throughout due to acute hyperemia and commonly revealed petechial to diffuse hemorrhages. In a few cases, diffuse hemorrhage and melena were so severe as to produce a sharp line of demarcation between the rectal mucosa and the anal epidermis (Fig. 30). In the case of fulminating disease, the colonic, cecal and rectal mucosa showed more or less superficial sloughing of diphtheritic exudate and surface epithelium. The pseudomembrane was often hemorrhagic, and straw fibers were occasionally noted embedded in it. The membrane scrapped off with ease exposing large hemorrhagic ulcerations and hyperemic mucosa.

The intestinal contents were often scanty, fetid and mucoid to watery or occasionally hemorrhagic to melenic due to enterorrhagia. Severe extravasation was characterized either by free blood or large, frank blood clots which filled the cecal and colonic lumina. These cruors were usually melenic due to decomposition of blood.

The lesions of the large intestine closely resembled those of the jejunum and ileum, and were marked by catarrhal, hemorrhagic, erosive, ulcerative, cystic and/or necrotic typhlitis, colitis and proctitis (Fig. 27, 28, 29 and 30).

Microscopic. The lesions were descriptively similar to those observed in the small intestine (Fig. 26 B and C, Fig. 31 A, B, C and D, and Fig. 32 A, B, C and D).

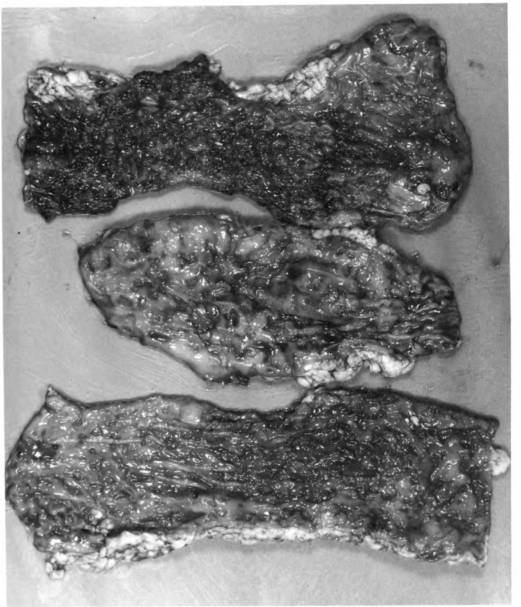

Fig. 28. Typical erosive, ulcerative, vesicular and hemorrhagic colitis.

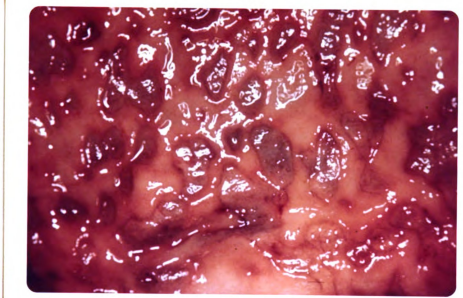

Fig. 29. Characteristic cecal erosions and ulcerations having a typical punched-out appearance.

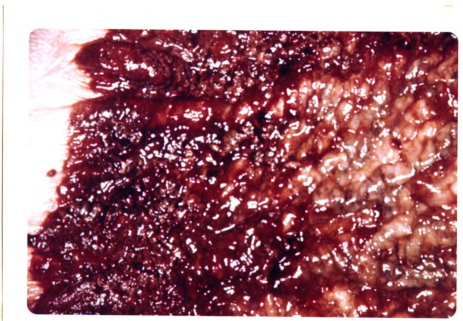

Fig. 30. Hemorrhage, melena and necrotic pseudomembrane of the terminal rectum.

Fig. 31 A. Extensive abscessation of crypts (arrows) of the cecum. H and E stain; x 100.

B. Bacterial colonization (arrow) of abscess of a crypt of the colon. H and E stain; x 100.

C. Abscessation of crypts of the cecum. H and E stain; x 240.

D. Abscessation of crypts and catarrhal enteritis of the colon. H and E stain; x 240.

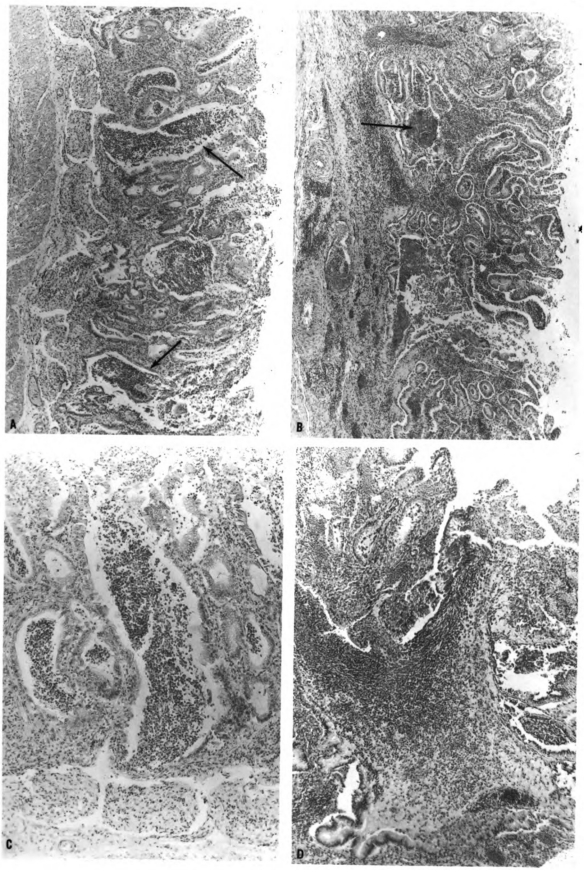
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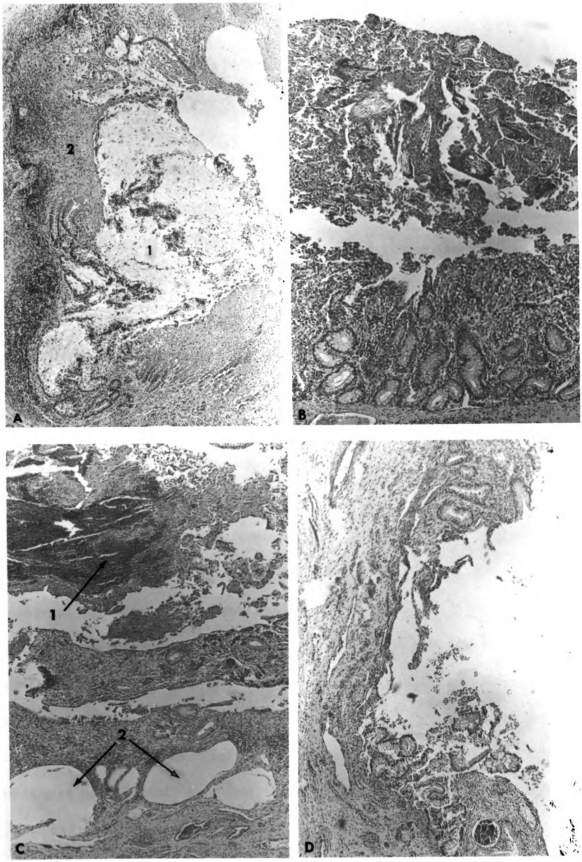
Fig. 32 A. Severe mucous degeneration of the submucosal gland and necrosis of the adjacent lymph follicle (2) of a colon. H and E stain; x 100.

B. Necrotic membrane covering the colonic mucosa. H and E stain; x 120.

C. Blood (1) mixed necrotic membrane covering the cystic (2) rectal mucosa. H and E stain; x 100.

D. Ulceration of the rectal mucosa. H and E stain; x 100.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4. Liver

Gross. Considerable variability occurred in the gross appearance of the liver. The course of sickness greatly influenced the nature of the hepatic alterations. Practically no changes were evinced in animals which succumbed within a few days of sickness. However, animals with a prolonged course usually revealed cloudy swelling to marked fatty changes. Focal and minute areas of necrosis were present in two animals. Hyperemia occurred in some cases. The gall bladder was commonly involved, showing mural changes of increased thickness, serosal opacity, and mucosal congestion. Mucosal erosions did not occur. The gall bladder often contained tenacious and inspissated bile.

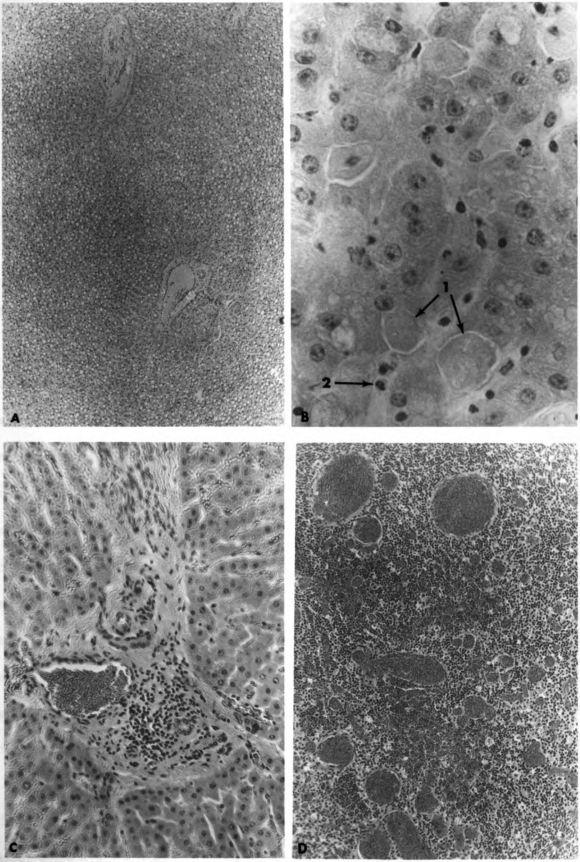
Microscopic. The alterations varied considerably, ranging from mild cloudy swelling to extensive fatty changes (Fig. 33 A). Cloudy swelling was frequently present in animals with a short course, whereas prolonged cases revealed pronounced fatty changes but without any reference to a particular area of the lobule. In a few animals, the parenchymatous cells had intracytoplasmic hyaline-like droplets surrounded by a corona of hydropic cytoplasm. These droplets were negative for PAS, Shorr, Feulgen and iron reactions. Frequently, coagulation necrosis of the individual hepatic cell was seen (Fig. 33 B) and focal caseation necrosis was found in two animals. Acute generalized hyperemia was occasionally apparent. Increased accumulation of leucocytes in the central veins and some sinusoids occurred prominently in a number of cases (Fig. 33 B). Proliferative and infiltrative changes were

Fig. 33 A. Severe and diffuse fatty changes of a liver. H and E stain; x 20.

B. Coagulation necrosis of the hepatic cells (1) and heterophilic infiltration of hepatic sinusoids (2). H and E stain; x 380.

C. Lymphocytic accumulation in the vicinity of portal trinity of a liver. H and E stain; x 120.

D. Hemorrhages and severe congestion of medulla of a mesenteric lymph node. H and E stain; x 80.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characterized by lymphocytic foci in the capsule and in the vicinity of the portal trinities (Fig. 33 C). Submucosal congestion of the gall bladder occurred consistently and prominently.

5. Pancreas

The pancreas did not reveal any discernible changes except for occasional slight hyperemia.

6. Hemopoietic System

a. Lymph Nodes

Gross. The alterations of the lymph nodes draining the alimentary canal were commonly a prominent feature. The changes were considerably variable and consisted of necrosis, edema, hyperemia and/or hemorrhage. Necrosis was manifested as a loss of follicular architecture. Upon sectioning, serum and/or blood drained off from the cut surface of some nodes leaving a collapsed sponge-like structure. Occasionally, the nodes appeared gelatinous on inspection due to edema and concomitant marked lymphoid depletion. Hemorrhage and hyperemia often occurred conspicuously (Fig. 34 A). The nodes were usually swollen and stood out prominently. The alteration of Peyer's patches and solitary lymph follicles of the intestine have previously been discussed under "small intestine."

Microscopic. Variable lymphocytic depletion was always present, disrupting cortical architecture severely in many instances. Occasionally, only discrete areas of depletion were observed in the lymph follicles

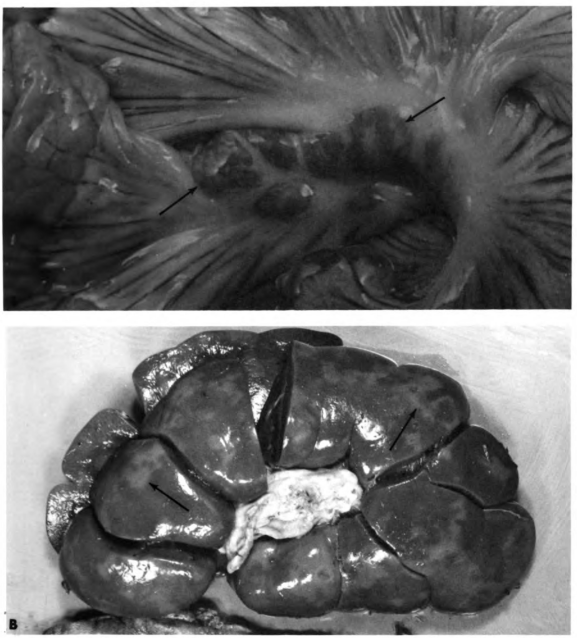

Fig. 34 **A.** Enlargement and congestion of the mesenteric lymph nodes (arrows). B. Typical patchy appearance (arrows) of the kidney.

Fig. 35 A. Lymphocytic depletion, hemorrhages and congestion of the cortex of a mesenteric lymph node. H and E stain; x 72.

B. Extensive lymphocytic karyorrhexis (arrows) in a mesenteric lymph node. H and E stain; x 380.

C. Edema and lymphocytic depletion of the cortex of a retropharyngeal lymph node. H and E stain; x 72.

D. Severe edema of the medulla of a mesenteric lymph node. H and E stain; x 80.

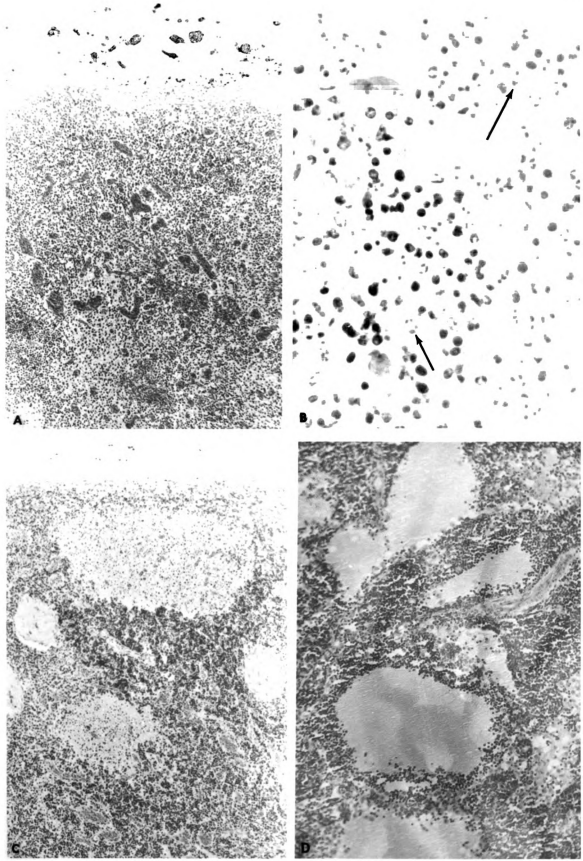
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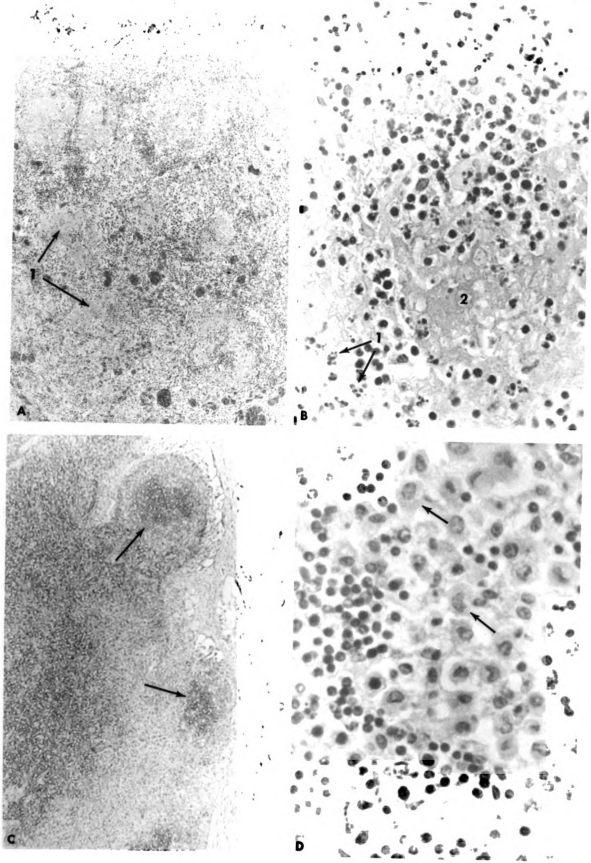
Fig. 36 A. Diffuse caseation necrosis (1) and congestion of the cortex of a mesenteric lymph node. H and E stain; x 60.

B. Higher magnification of "A" showing lymphocytic karyorrhexis (1) and caseation necrosis (2). H and E stain; x 360.

C. Focal caseation necrosis (arrows) of the cortex of a mesenteric lymph node. H and E stain; x 60.

D. Proliferation of macrophages in a mesenteric lymph node. H and E stain; x 360.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(Fig. 35 C). In many instances, the nodes had undergone marked coagulation necrosis showing lymphocytic pyknosis and abundant karyorrhexis (Fig. 35 B). Focal to diffuse caseation necrosis occurred conspicuously in a few cases (Fig. 36 A, B and C). Lymphocytic depletion and necrosis frequently appeared concomitantly. These alterations were often accompanied by dilatation of the sinusoids and potential spaces. In some instances, marked heterophilic infiltration of the lymph spaces and follicles was present. Hemorrhage and congestion were so severe in some cases that the histologic sections had a uniform eosinophilic gross appearance (Fig. 33 D, Fig. 35 A and Fig. 36 A). Patchy to diffuse edema was common (Fig. 35 C and D). Occasionally, the nodes revealed proliferation of macrophages many of which had phagocytized dead cells and tissue debris.

b. Spleen

Gross. The spleen did not reveal any significant alterations consistently; however, marked pericapsular capillary hyperemia was a prominent feature in two animals.

Microscopic. The splenic lesions were primarily confined to the lymph tissue (germinal centers) and closely resembled those evinced by the lymph nodes. The Malpighian corpuscles appeared less prominent than normal due to variable lymphocytic depletion. In severe cases they were beyond recognition, appearing as a network composed of reticulum cells and fibers. Lymphocytic necrosis, leucocytic infiltration and macrophagic proliferation were very similar to those

observed in the lymph nodes. Extensive breakdown of erythrocytes had resulted in marked hemosiderosis in two animals.

c. Bone Marrow

The bone marrow was examined in only a few animals but no significant alterations could be detected.

7. Respiratory System

Gross. The lesions of the upper respiratory tract were inconstant but when present appeared as catarrhal rhinitis, and minute shallow erosions and ulceration adjacent to the nostrils. These erosions were contiguous with those of the muzzle. The larynx, trachea and bronchi were usually devoid of lesions except for a few scattered petechiae. A few animals revealed bilateral pneumonia especially of the anterior lobes and antero-ventral portion of the diaphragmmatic lobes. Scattered areas of consolidation were also occasionally found elsewhere in the lungs.

Microscopic. Focal epithelial desquamation and necrosis resulted in small shallow erosions and ulcerations of the anterior-most portion of the nares (Fig. 37 D). Denuded, hyperemic and often mucus-coated lamina propria formed the base of the ulcers. Secondary bacterial invasion of the ulcers did not occur and, generally, the inflammatory reaction was absent. Secondary bronchopneumonia was present in a few cases and varied from serofibrinous to necrotic or suppurative. The character of the pneumonia was determined by the nature and extent of

secondary bacterial colonization. Catarrhal to suppurative bronchitis often accompanied the pneumonia. Generalized hyperemia and interalveolar edema were a common finding.

8. Urogenital System

a. Kidneys

Gross. The kidneys were often conspicuously affected showing marked cloudy swelling which appeared as irregular, blanched areas (Fig. 34 B). Cut sections of the kidneys invariably revealed considerable medullary congestion. The hyperemia was often more pronounced in the papillary areas. Cortical hyperemia also occurred, but less commonly.

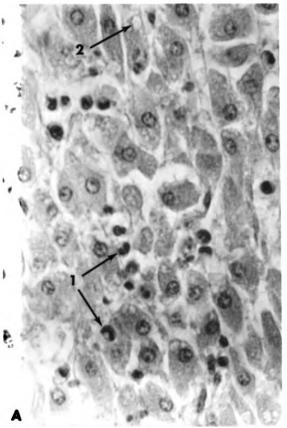
Microscopic. The most consistent change was cloudy swelling of the renal tubular epithelium. Granulation and swelling were particularly conspicuous in the proximal convoluted tubules. In some instances, the epithelial cells were swollen to such an extent as to cause complete disappearance of the lumina of the proximal and distal tubules. Dilatation of the distal tubules and collecting ducts also occurred in many cases resulting in flattening of the lining epithelium. Fatty changes and vacuolation (hydropic degeneration) of tubular epithelium of the Henle loops was another common feature (Fig. 37 B). Occasionally, the renal epithelium had undergone necrosis showing pyknosis, karyorrhexis and karyolysis. Tubular lumina frequently contained granular precipitate and hyaline materials (Fig. 37 B and C). Medullary hyperemia was

Fig. 37 A. Heterophilic infiltration (1) and fatty changes of parenchymatous cells (2) of zona fasiculata of an adrenal cortex. H and E stain; x 380.

B. Dilatation (1) granular casts (2) and epithelial hydropic degeneration (3) of proximal and distal tubules of a kidney. H and E stain; x 80.

C. Dilatation and casts of collecting ducts (1) and congestion (2) of medulla of a kidney. H and E stain; x 12.

D. Small ulcer of anterior most nasal mucosa. H and E stain; x 100.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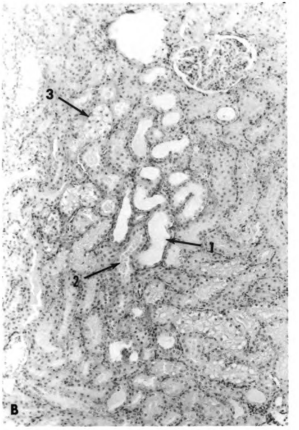
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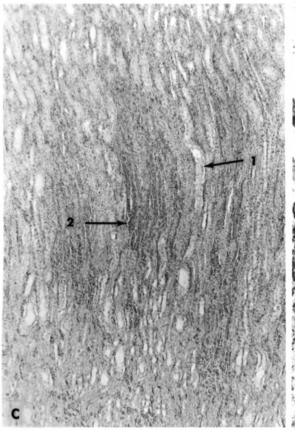
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invariably present but tended to be severe at the cortico-medullary junction (Fig. 37 C). Likewise, cortical hyperemia was not uncommon but was usually less conspicuous. Scattered microfoci of lymphocytic infiltrations and chronic interstitial nephritis appeared prominently in the renal cortex of a few animals.

b. Other Urogenital Organs

The lesions of the vulva and prepuce have been discussed previously under skin; lesions could not be detected elsewhere along the urogenital system.

9. Endocrine System

a. Adrenals

Gross. The adrenals were often variably swollen and friable. Petechial hemorrhages and hyperemia were common in the peripheral portion of the cortex. Occasionally, cortical hyperemia occurred conspicuously surrounding the medulla.

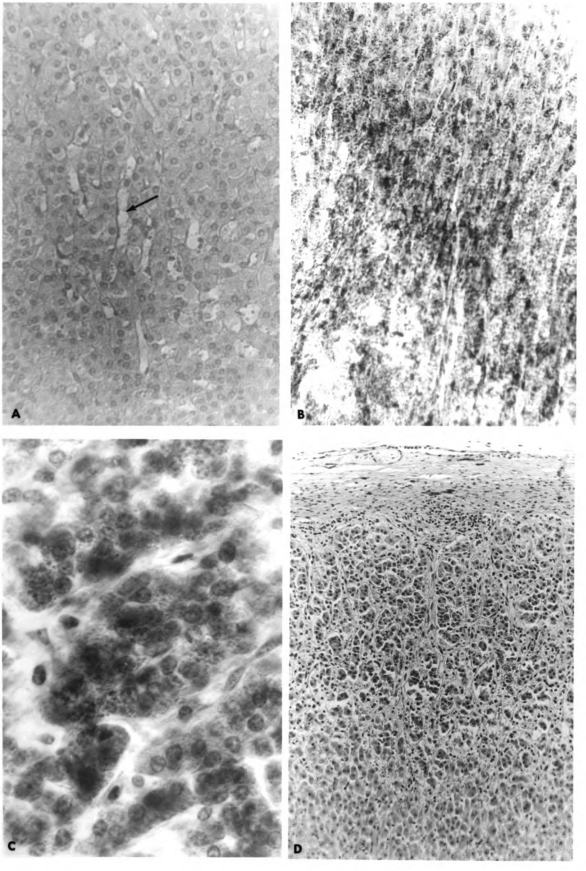
Microscopic. The alterations were usually prominent but considerably variable. Commonly, fatty metamorphosis was the most prominent feature appearing in all the cortical zones as evidenced by the Sudan IV staining procedure (Fig. 38 A, B and C). The process was often most severe in the peripheral portion of the zona fasciculata (Fig. 39 D). The affected parenchymatous cells revealed all gradation of fatty changes varying from slightly foamy appearance to extensive

Fig. 38 A. Fatty changes of parenchymatous cords (arrow) of zona fasciculata of an adrenal gland. H and E stain; x 260.

B. Intracytoplasmic fat droplets in parenchymatous cells of zona fasciculata of an adrenal gland. Sudan IV and hematoxylin stain; x 180.

C. Severe fatty changes of parenchymatous cells of zona glomerulosa of an adrenal gland. Sudan IV and hematoxylin stain; x 380.

D. Coagulation necrosis of parenchymatous cells of zona glomerulosa and fasciculata of an adrenal gland. H and E stain; x 100.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vacuolation of the cytoplasm and concomitant pyknosis and nuclear deformities. The process usually affected a group of consecutive cells in a number of adjacent cords. Hence, in advanced stages the cytoplasmic transformation and persistence of the resistant cellular membrane imparted a ladder-like appearance to the affected portion of the cords (Fig. 38 A). In the event of severe fatty alterations, bursting of the cell membrane had resulted in the merging of the adjacent cells appearing as clear and empty spaces interposed between the relatively normal portions of the affected cord.

Coagulation necrosis of parenchymatous cells often occurred, especially in the zona glomerulosa (Fig. 38). The necrotic cells appeared shrunken and evinced accompanying cytoplasmic eosinophilia and nuclear pyknosis, karyorrhexis or karyolysis. Disappearance of the necrotic cells resulted in sparsity of the parenchyma and decreased width of zona granulosa. The process affected both individual and small groups of cells. The zona fasciculata and zona reticularis were similarly affected but often less severely.

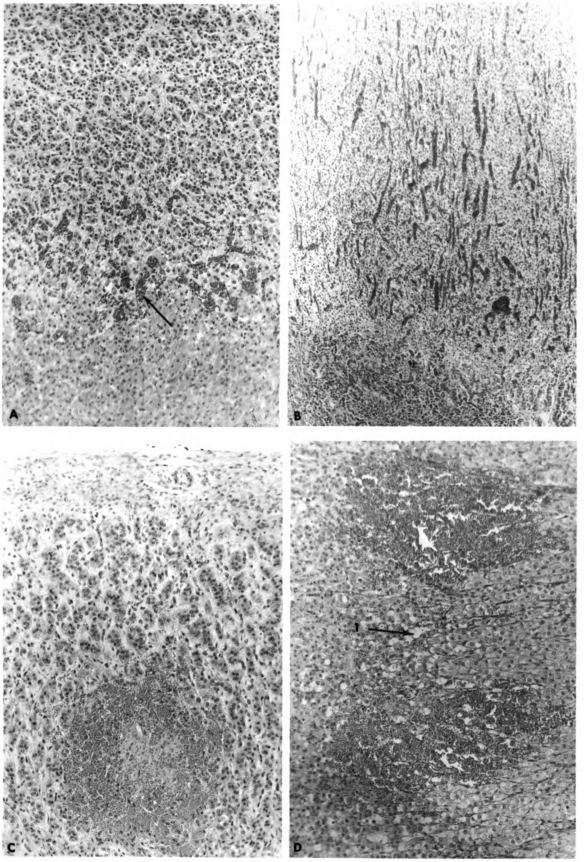
Cross section of the adrenals frequently revealed two to seven petechial hemorrhages which were located principally in the peripheral portion of the zona fasciculata and usually accompanied severe fatty changes in this area (Fig. 39 D). Likewise, petechiation also occurred in the deeper portions of the zona glomerulosa (Fig. 39 C) and zona reticularis. The hemorrhages often accompanied cortical hyperemia especially of the zona reticularis and deeper portions of the zona fasciculata and zona granulosa

Fig. 39 A. Congestion of the adrenal cortex at the junction of zona glomerulosa and zona fasciculata. H and E stain; x 100.

B. Severe congestion of zona reticularis and deeper portion of zona fasciculata of an adrenal gland. H and E stain; x 72.

C. Petechial hemorrhage in zona glomerulosa of an adrenal gland. H and E stain; x 120.

D. Fatty changes of parenchymatous cells (1) and two petechial hemorrhages in peripheral portion of zona fasciculata of an adrenal gland. H and E stain; x 120.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(Fig. 39 A and B). Occasionally, severe congestion surrounding the medulla imparted a radiating appearance to the cortex (Fig. 39 B). Medullary hyperemia and hemorrhage usually did not occur. In a few cases, the cortex was diffusely infiltrated with heterophils and a few eosinophils and plasma cells (Fig. 37 A). Rarely, the medulla revealed focal inflammatory cell infiltration accompanying regional necrosis. Cortical edema was a common feature leading to marked dilatation of the tissue spaces and sinusoids. In severe edema the parenchymatous cords and cells were mechanically pushed apart (Fig. 40 C and D). Commonly, focal edema also occurred in the medulla.

Proliferative and infiltrative changes were observed in about 50 percent of the cases appearing as variable lymphocytic foci distributed principally within and beneath the capsule, in the trabeculae and rarely in the medulla (Fig. 38 D and Fig. 40 A and B). The foci varied considerably in distribution, size and extent. A few eosinophils and plasma cells were often found interspersed in the centers. Generally, the foci occurred without any reference to the blood vessels.

b. Thyroids

Gross. The thyroids were slightly congested in a few cases and were strikingly atrophic in two animals.

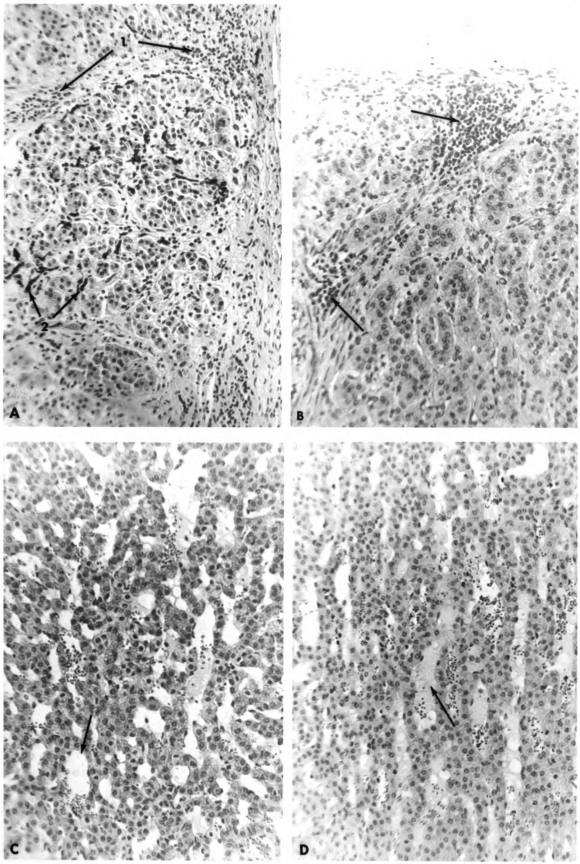
Microscopic. Hyperemia was observed in a few cases. The organs from two animals revealed severe colloid depletion, atrophy and heterophilic infiltration (Fig. 41 A). Since the esophagus was severely ulcerated

Fig. 40 A. Lymphocytic accumulations in the capsule and trabecula (1), and incidental melanosis of zona glomerulosa (2) of an adrenal gland. H and E stain; x 130.

B. Marked lymphocytic accumulations (arrows) in the capsule and trabecula of an adrenal gland. H and E stain; x 240.

C. Sinusoidal dilatation of zona reticularis (arrow) of an adrenal gland. H and E stain; x 240.

D. Edema (arrow) of zona fasciculata of an adrenal gland. H and E stain; x 240.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in these animals, the alterations of the thyroids were considered the result of direct extensions of the acute inflammatory process in the esophagus.

c. Pituitary

Hyperemia was the chief discernible gross and microscopic finding, and this was not constant.

d. Parathyroids

The glands were devoid of any discernible pathological alterations.

10. Cardiovascular System

Gross. Petechial to diffuse subepicardial and/or subendocardial hemorrhages were frequently present. The subepicardial hemorrhages were principally confined to an area adjacent to the coronary groove whereas the endocardial hemorrhages were distributed at random without reference to a particular area. In a few instances, the heart was found to be somewhat flabby, but microscopically the myocardium did not reveal any discernible alterations.

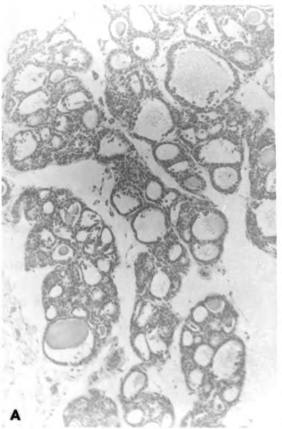
Microscopic. Fibrinoid and hyaline-like degeneration and necrosis of the arteries and arterioles appeared conspicuously adjacent to the infected ulcers of the gastrointestinal tract in some instances. Often these degenerated blood vessels revealed changes simulating periarteritis (Fig. 41 B) and their lumina frequently contained large numbers of leucocytes.

Fig. 41 A. Colloidal depletion and atrophy of a thyroid gland. H and E stain; x 72.

B. Periarteritis in the submucosa of a colon. H and E stain; x 120.

C. Congestion and heterophilic infiltration of a myenteric plexus in the submucosa of cecum. H and E stain; x 120.

D. Fatty changes (1) and hyaline degeneration (2) of skeletal muscle of the tongue. H and E stain; x 120.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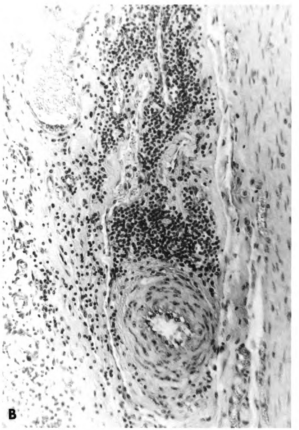
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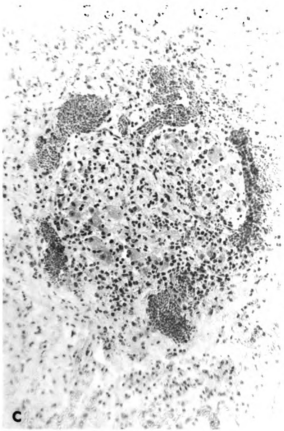
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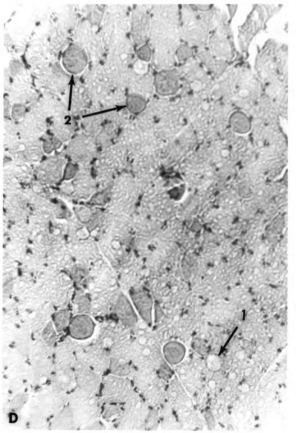
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D

11. Nervous System

Lesions of the central nervous system were not common. However, variable hyperemia, edema and accompanying slight excess of the cerebrospinal fluid occasionally occurred. Deeper penetration of the ulcers of the digestive tract occasionally resulted in coagulation necrosis and acute inflammation of the myenteric ganglia along with Wallerian degeneration of the plexuses of the alimentary canal (Fig. 41 C). Similar changes also appeared in the plexuses of the corium.

12. Musculature

Gross. Skeletal musculature of the tongue, pharynx, esophagus and adjacent to the muzzle was frequently hyperemic.

Microscopic. The musculature adjacent to the highly infected ulcers commonly revealed cloudy swelling, uneven staining, hyaline to fatty degeneration (Fig. 41 D), hyperemia and occasionally marked sarcolemma cell proliferation.

CHAPTER VIII

BACTERIOLOGICAL STUDIES

Materials and Methods

The material for bacteriological studies was taken from 14 Michigan field cases of mucosal disease and consisted in pieces of different tissues or swabs, collected aseptically in sterilized containers at room temperature. The intestinal material, consisting of about six inches in length of cecum or colon, was collected in separate containers. The material was then submitted to the bacteriology diagnostic laboratory of the College of Veterinary Medicine for aerobic and anaerobic bacterial isolations.

Results

The bacteriological findings were inconsistent. The pathogenic bacteria isolated were of the type usually responsible for secondary infection (Table V). The cases did not reveal a particular pathogenic bacterial flora which could be considered typical of mucosal disease. In one-half of the cases, Escherichia coli was isolated from the large intestine. Clostridium perfringens was found in the large intestine in three other cases. In three cases with pneumonia, Micrococcus pyogenes and Pasteurella multocida; β-Streptococcus; and Pasteurella multocida were isolated, respectively, from the lungs. Moraxella bovis was recovered from a case with full-blown "pink-eye" manifestations.

TABLE V. Bacteriological observations

Case number	Date	Source	Results
A 60	7-20-56	Kidney, spleen and mesenteric lymph node	N
A 262	9-26-56	Lung abscess	Micrococcus pyogenes Pasteurella multocida
		Liver abscess	Micrococcus pyogenes
A 948	1-28-57	Colon	Escherichia coli Clostridium perfringens
A 1532	4-24-57	Brain	N
A 1634	5-4-57	Colon	Escherichia coli
B 221	7-16-57	Mesenteric lymph node	N
		Colon	Escherichia coli
B 1305	10-11-57	Colon	Clostridium perfringens
		Lung abscess	β-Streptococcus
B 1615	11-7-57	Colon	Escherichia coli Alcaligenes
B 3098	1-20-58	Liver, spleen and colon	Escherichia coli
B 3173	1-24-58	Cecum	Escherichia coli
B 5133	4-12-58	Colon	Escherichia coli
		Lung	Pasteurella multocida
B 3698	2-14-58	Liver, spleen, mesenteric lymph node and brain	Micrococcus pyogenes
		Colon	Clostridium perfringens
C 1219	9-12-58	Colon, liver and mesenteric lymph node	N
C 2286	11-15-58	Ocular discharge	Moraxella bovis

N = Negative

CHAPTER IX

PARASITOLOGICAL STUDIES

Material and Methods

Studies were made for gastrointestinal parasites on 11 Michigan field cases of mucosal disease. In 9 of the 11 cases, about 2 gm of fecal material was mixed with sugar solution and centrifuged. Slide preparations were then made and examined microscopically for parasite eggs. In remainder of the cases (two), the gastrointestinal tract was heavily infested with parasites; hence, gross examination was made only.

Results

Examination revealed commonly occurring gastrointestinal parasites (Table VI). Strongyle eggs were found in the majority of cases. In three cases, intestinal coccidiosis was evident.

TABLE VI. Parasitological observations

Case number	Date	Source	Results
A 116	8-7-56	F	N
A 390	9-31-56	F	Strongyle eggs++++ Trichuris eggs+++
A 421	10-12-56	I	Strongyles++++
			Nodular worms++++
			Whipworms++++
A 430	10-18-56	F	Stronglye eggs++
A 580	11-14-56	F	Strongyle eggs+++
			Trichuris eggs++
			Coccidia++
A 581	11-14-56	F	Strongyle eggs+++
			Trichuris eggs+++
			Coccidia+
A 1532	4-24-57	F	Strongyle eggs++
B 221	7-16-57	F	Strongyle eggs++++
B 1457	10-24-57	F	N
B 5133	4-12-58	S	Stomach worms++++
		I	Tapeworms++++
C 1219	9-12-58	F	Coccidia++++ (at least 3 species)

F = feces

++++ = heavy

+++ = moderate

++ = light

+ = occasional

N = negative

S = stomach

I = intestine

CHAPTER X

TISSUE CULTURE STUDIES

Material and Methods

The material for tissue culture studies was obtained from seven Michigan field cases of mucosal disease. The material consisted of whole blood from three cases, nasal and oral swabs from one case, and various tissues from three cases. It was collected aseptically in sterilized vials and refrigerated immediately. The material was submitted to the virology laboratory of the College of Veterinary Medicine for studies in embryonic bovine kidney cell tissue cultures.

Results

The tissue culture studies gave negative results (Table VII).

TABLE VII. Tissue culture observations

Case number	Date	Source of materials	Results (Cytopathogenicity)
A 390	9-31-56	Blood	N
A 421	10-12-56	Blood	N
A 430	10-18-56	Blood	N
B 1305	10-11-57	Nasal and oral swabs	N
B 1912	11-29-57	Mesenteric lymph node, liver and nasal and intestinal mucosa	Cytopathogenicity lost after 3rd passage
B 3697	2-24-58	Brain, spleen, mesenteric lymph node and oral mucosa	N
B 3698	2-24-58	Brain, spleen, mesenteric lymph node and oral mucosa	N

N = Negative

CHAPTER XI

EXPERIMENTAL TRANSMISSION STUDIES

Materials and Methods

The material for transmission studies was obtained from two Michigan field cases of mucosal disease. In one case, tissue material from brain, spleen, lymph node and intestine were collected in sterilized screw-top glass jars and immediately frozen. The final tissue preparation consisted in supernatant of 20 per cent organ emulsion in chilled nutrient broth, containing 10, 000 I. U. of penicillin and 10 mgm of streptomycin per ml. The chilled supernatant was parenterally administered into two experimental calves and four adult mice. Three adult mice received the tissue material in drinking water. An experimental calf was transfused with citrated whole blood soon after its withdrawal from a mucosal disease case. The experimental cattle and mice were observed twice daily for body temperature, feed intake and visible signs of the disease for several weeks and necropsy was finally performed after several months of observation.

Results

Attempts at experimental transmission of the disease were largely unsuccessful (Table VIII). However, one calf revealed transient fever, anorexia, and leucopenia but failed to develop full-blown mucosal disease. The experimental animals were devoid of any gross and microscopic lesions.

TABLE VIII. Transmission studies

Test animal date	Source Nature of material	Route of administration	Results
Holstein Male 2 months 8-7-56	A116 Supernatant of brain, spleen, lymph node and intestine emulsion	Subcutaneous - 5 cc Intraperitoneal - 5 cc Prescapular lymph node - 2 cc	No deviation from health
Holstein Male 3 months 8-8-56	A116 Supernatant of brain, spleen, lymph node and intestine emulsion	Subcutaneous - 5 cc Intraperitoneal - 5 cc Prescapular lymph node - 2 cc	No deviation from health
Four adult mice 8-7-56	A116 Supernatant of brain, spleen, lymph node and intestine emulsion	Subcutaneous - 2 cc Intraperitoneal - 2 cc	No deviation from health
Three adult mice 8-7-56	A116 Supernatant of brain, spleen, lymph node and intestine emulsion	Drinking water	No deviation from health
Brown Swiss male 4 mo. 5-4-57	A1634 Citrated blood	Intravenous - 400 cc	5-3-57 - T. 101.6 5-4-57 - T. 101.6 and WBC 6,000 5-5-57 - T. 102.6 and off-feed 5-7-57 - T. 102.8 and WBC 5,000 5-10-57 - T. 105.4 5-11-57 - T. 102.8 5-23-57 - T. 101.8 5-31-57 - T. 101.6, good health and termination

T = Body temperature in ^{o}F.

CHAPTER XII

DISCUSSION

A specific disease entity of cattle, occurring in Michigan, has been described under the term mucosal disease for want of a more suitable name. The designation was originally given to a new dyndrome described in Iowa by Ramsey and Chivers (1953). Necropsy of the affected animals revealed lesions which were prominent along the mucosa of the alimentary canal, and they tentatively designated the syndrome as "mucosal disease." The name is inappropriate for two main reasons; (1) pyrexia, scours and ulceration of the digestive tract which are considered to be characteristic of mucosal disease, are also exhibited by several other bovine diseases and (2) the disease also produces significant lesions in the nonmucosal tissues. The nomenclature "mucosal disease," despite its generic and misleading inference, has been commonly used to identify a specific malady of cattle.

Incidence, Symptomatology, and Clinical Pathology

The disease has occurred state-wide, but it has been definitely diagnosed on 26 farms in 16 counties in the southern part of the state. These counties do not represent particular areas of concentration of the disease. The counties represented are those in which the practicing veterinarians cooperated in supplying the cases.

The disease has shown definite seasonal incidence; the greatest number of cases occurring in fall, suggesting that sudden fluctuations or drop in the environmental temperature may serve as a predisposing factor.

Because the disease occurred sporadically and did not spread rapidly through the herd and because the animals on the adjoining farms or pastures remained unaffected, it seems that the disease is not contagious.

It has become clear that younger animals are particularly susceptible to the disease and that the older animals somehow acquire immunity to the disease.

It was not possible to determine the cause of the disease. The tissue culture and transmission studies gave negative results. The bacteriological studies were not significant, and the pathogenic bacteria isolated from the cases were responsible for the secondary infections. However, evidence obtained from investigations by several researchers has shown that the etiologic agent is infectious, probably a virus. A British worker (Huck, 1957) has isolated a filterable virus which, when introduced into susceptible cattle, produces a typical disease. Likewise, American workers (Noice and Schipper, 1959; Underdahl et al., 1957) have reported the isolation of filterable agents from cattle with mucosal disease. Goret and Pilet (1959), in reviewing the disease, have concluded that it is caused by a virus. Although several agents possessing virus-like features have been isolated from mucosal disease cases, the experimental transmission studies

have yielded inconclusive results. Furthermore it remains to be established if the disease is caused by a specific agent.

Owing to the low incidence in a herd, it seems very likely that certain predisposing factors play a significant role in the disease onset. Common stressors (such as transportation, over-crowding, sudden fluctuations in the environmental temperature, muddy and wet barn floors, inadequate supply of water, malnutrition, gastrointestinal parasitic infestations, exposure to certain chemicals etc.) may serve as a trigger mechanism. The susceptible animals somehow suffer a marked breakdown in their resistance and become vulnerable to the etiologic agent.

The epizootiology and incubation period of the disease have not been determined. One may conjecture that the susceptible animals either harbor the etiologic agent in a dormant state, or it is readily transmissible from the immune carriers through any number of media or avenues. Following a certain incubation period, it then gains access into the blood circulation giving rise to sudden onset of the disease with high fever. Eventually, it localizes in the tissues of predilection, where it produces typical lesions. This is immediately followed by a sharp decline of body temperature to normal. A diphasic rise in body temperature, noted in some cases, seemingly occurs due to secondary bacterial infection. Hypothermia was commonly noted in moribund animals as a prelude to death, but in others it may have been due to profuse diarrhea, anorexia and decreased metabolism.

The peripheral blood picture, being markedly variable in different cases, is of little diagnostic value and may reflect the degree of dehydration and/or the type and intensity of secondary bacterial infection.

Diarrhea and tenesmus, a most constant finding, seem to develop through erosion, ulceration and intense irritation of the gastrointestinal mucosa. Marked dehydration and rapid emaciation prominent in the disease, may appear due to profuse diarrhea and anorexia. The sick animal eventually goes down moribundly due to marked weakness.

Death eventually ensues due to a combination of primary shock (pain stimuli originating from the damaged tissues), secondary shock (toxic breakdown products from the damaged tissues, secondary bacterial infection, hemoconcentration, starvation, kidney damage etc.) and hemorrhagic shock (excessive loss of blood from the gastrointestinal tract).

Pathogenesis of the Lesions

It is readily clear from this study that the disease possesses a special affinity for the epidermis, mucosa of the alimentary canal and hemopoietic system. Lesions also occur in the adrenals, liver, kidneys and lungs but, owing to their nonspecific nature, seem to develop only secondarily. The lesions varied considerably in extent and distribution but were basically constant from case to case regardless of the form of the disease. The lesions of mucosal disease are not considered pathognomonic of the malady but are distinct from those of other bovine

epitheliotropic diseases, thus being of significant diagnostic value. The lesions appear to follow certain consistent patterns which have been elucidated tissue-wise.

1. The Stratified Squamous Epithelium

The disease appears to possess a special propensity for the squamous epithelium as evidenced by a widespread distribution of lesions in this tissue. The essential lesion seems to emerge through hydropic degeneration, reticular colliquation (ballooning degeneration) and acantholysis. The effect of the causative agent is seen initially in the germinal (deep) layer of the stratum spinosum and occasionally also in the basal layer. The affected cells here undergo hydropic degeneration. Initially, only a few solitary or small groups of cells are affected. Later, the process spreads so that more and more adjacent cells are involved. The affected cells become progressively swollen to several times their normal size. Marked swelling of the cells, consequently, results in the closure of intercellular lymph spaces which ultimately disappear completely. At the same time the spinous processes too become obscured through mechanical compression.

The process finally spreads to the superficial layers of the squamous epithelium which then undergo abundant reticular colliquation (ballooning degeneration) due to severe intracellular edema of the affected epithelial cells. The process would seem to result either through starvation of the cells secondary to the disappearance of the

intercellular lymph spaces or from the direct action of the causative agent.

Since the early lesion is almost invariably located in the germinal layer, it may imply that the proliferative cells become affected selectively, and subsequently the lesion extends upward into the superficial layers which then undergo abundant ballooning degeneration.

Erosions and ulcerations are among the most characteristic manifestations of the disease and seemingly emerge through acantholysis and sloughing of the degenerated epithelium. In detail, dissolution of the spinous processes of degenerated epithelial cells results in the loss of coherence of the cells with one another which permits the cells to drift about effecting intralaminal cavitations or erosions and ulcerations.

Intracellular unilocular or multilocular spongiform vesicles are often seen in this disease. Seemingly, these develop through heterophilic infiltration of the reticulated or balloon cells under the influence of either the causative agent, bacterial secondary invaders or certain unknown leukotactic factors.

Frequently, the erosions and ulcerations become infected through solution in the continuity of the stratified squamous epithelium exposing the corium and lamina propria to bacterial secondary invaders which in turn incite inflammatory reaction and in severe cases destroy the dermal papillae and lamina propria.

Spongiosis commonly occurs in the disease but only to a limited extent and does not seem to play a significant role in the development

of the typical lesions. The process is essentially an extension of the edema from the corium or lamina propria into the basal layer and stratum spinosum. Spongiosis may be looked upon as a defensive mechanism attempting to dilute the irritant and a means to transport additional antibodies.

Coagulation necrosis is another limited response affecting solitary or small groups of cells. The process does not seem to play any significant role toward the pathogenesis of the lesions.

There is a lack of agreement among workers concerning the pathogenesis of the lesions of the squamous epithelium. Seibold (1956) considered epithelial necrosis to be mainly responsible for the development of the lesions. Ramsey (1956) regarded necrosis and vacuolar degeneration of the cells as the principal lesion which appears first in the superficial layers and ultimately extends into the deeper layers. Rooney (1957) concluded that hydropic, ballooning degeneration of the epithelial cells is the essential lesion which appears first in the outer third of the stratum spinosum. The entire stratum spinosum is finally involved causing bulging of the stratum corneum which eventually ruptures to produce erosions and ulcerations. Jarrett (1958) described the typical lesion as a "vesicle-ulcer" which emerges through ballooning degeneration of the stratum spinosum.

Certain other bovine diseases are also known to produce lesions of the squamous epithelium. Maurer et al. (1955) have reported that the rinderpest virus produces characteristic lesions in the squamous

epithelium of the alimentary canal. The presence of the virus here is evidenced by necrosis of the epithelial cells in the deeper layer of the stratum spinosum. The necrotic cells exhibit pyknosis, karyorrhexis and irregularly eosinophilic cytoplasm. Extension of the necrotic process superficially and shedding of the necrotic epithelium result in shallow erosions which are bounded and demarcated by essentially normal squamous epithelial cells.

The virus of foot and mouth disease is known to have a necrotizing effect which is characterized by swelling of the cells, pyknosis and karyolysis in the stratum spinosum. Frenkel (1949) reported that vesiculation of the disease occurs through acantholysis and spongiosis. Coalescence of vesicles and detachment of the surface epithelium ultimately result in variable sized erosions and ulcerations.

The primary lesion of vesicular stomatitis is indistinguishable from that of foot and mouth disease. Chow et al. (1951) and Chow (1953) described the lesions of vesicular stomatitis as developing through spongiosis, acantholysis and intercellular vacuolation of the stratum spinosum.

Pritchard et al. (1958) observed a distinct entity, "ulcerative stomatitis of cattle" and found the lesions to be characterized by areas of ballooning degeneration in the stratum spinosum which followed hydropic degeneration and accompanying pyknosis and karyorrhexis of the epithelial cells. Seemingly, vesiculation occurred due to coalescence of the ballooned cells.

In vaccinia infection the first response to the virus is thickening of the epidermal layer due to a brief period of proliferation of the basal layer of cells, after which necrosis sets in. These changes were reported by Bland and Robinow (1939) and Kidd (1950).

Berkman (1958) studied the lesions of bovine malignant catarrhal fever and found initial proliferation of the basal layer, followed in severe cases by necrosis or focal ballooning degeneration and ultimate vesiculation.

Smith and Jones (1957) conclude that ballooning degeneration and reticular colliquation are characteristic of many viral diseases.

2. The Columnar (Glandular) Epithelium

A very common lesion in mucosal disease is focal to diffuse coagulation necrosis of the abomasal mucosa. This type of lesion of the abomasum is known to represent a nonspecific reaction to a variety of noxious stimuli. However, this lesion is a prominent and constant feature of mucosal disease, hence it may represent a specific effect of the etiologic agent. Since similar lesions have been observed in otherwise normal calves and in a host of bovine diseases, Rooney (1957) regarded it to be a nonspecific reaction.

Secretion of mucus occurs rather conspicuously along the intestinal mucosa in the early stages of the disease. This vigorous secretory response may be conjectured as an attempt to dilute the irritant, to push it out of the affected cells by viscous fluid and to help evacuate it. Ramsey (1956) observed a similar reaction which subsequently resulted

in distention of crypts leading to pressure atrophy and necrosis of the lining epithelial cells.

Coagulation necrosis also appears in the intestinal mucosa and may represent a specific lethal effect on the glandular epithelium. Incidentally, the intestinal epithelial necrosis is usually more pronounced in the absence of vigorous mucous secretion and may represent an aftermath following epithelial secretory exhaustion. Seibold (1956) described the intestinal lesion as primarily necrosis of the glandular epithelium. Similarly, Rooney (1957) considered the intestinal lesion to have essentially resulted from coagulation necrosis of the epithelial cells and to have first appeared superficially and ultimately extended into the deeper portions of the mucosa.

The gastrointestinal erosions and ulcerations apparently develop through desquamation and sloughing of the necrotic and degenerated mucosa. However, the intestinal ulcerations at certain locations appear to emerge secondarily to the necrosis of the underlying solitary lymph nodules and Peyer's patches. These lesions grossly conform to the configuration of the local lymphatic tissue of the intestines.

The pathogenesis of the abscessation of gastrointestinal crypts in this disease is not fully understood. The process may be looked upon as a specific response to the disease and/or a nonspecific reaction to the bacterial secondary invaders. Profuse heterophilic infiltration seen in the crypt abscesses may occur under the influence of certain undetermined leukotactic factors. Rooney (1957) proposed that crypt abscesses represent a specific necrotizing effect on the glandular epithelium.

However, he also emphasized that the crypt abscessation is peculiar to the intestinal glands in a number of dissimilar conditions, hence should not be considered pathognomonic of the disease. Similar gastrointestinal crypt abscesses have been reported by Ramsey (1956).

Several other bovine diseases are known to reveal gastrointestinal lesions somewhat similar to those seen in mucosal disease. Maurer et al. (1955) concluded that the virus of rinderpest invades the glandular epithelium and produces the gastrointestinal lesions through necrosis of the epithelial cells. Rooney (1957) described crypt distention with mucus and cell debris in bovine hyperkeratosis. Berkman (1958) theorized that the gastrointestinal erosions and ulcerations observed in malignant catarrhal fever are probably due to anoxia caused by occlusion of the submucosal blood vessels.

3. The Hemopoietic System

Depletion and necrosis of the lymphatic tissue of the hemopoietic system observed in this disease may reflect a defensive response as an attempt to arrest the causative agent, to absorb it and to release additional supplies of antibodies. Drinker and Yoffey (1941) obtained evidence that the meshlike structure of the lymph nodes can arrest small particles, reaching them by the lymph stream, and hence they act as "filters." The lymph sinuses are crossed and recrossed by a fine mesh of reticulum which is an important structure for the filtering function of the nodes. Florey (1958) pointed out that the mechanical filtration by the reticulum

mesh is greatly enhanced by the trabecular phagocytic cells, an important part of the reticuloendothelial system. Widdicombe et al. (1955) and Drinker et al. (1934) showed that the lymph nodes are very efficient in filtering out bacteria. On the contrary, some viruses are not effectively arrested by the lymph nodes but instead are protected and transported to other parts of the body. Yoffey and Sullivan (1939) found that vaccinia virus is not arrested but instead enters the lymphocytes which are constantly leaving the nodes for the blood stream. The virus in the lymphocytes is protected and conveyed to all parts of the body.

The lymph tissue is known to actively participate in maintaining body resistance. Chase et al. (1946) and Harris and Harris (1949) conducted experiments which provided evidence that lymphocytes actively manufacture antibodies.

The heterophilic infiltration which occasionally occurs in the regional lymph nodes may suggest a reaction to bacterial secondary invaders and their toxins, and to other toxic and leukotactic substances which may have been absorbed from the injured alimentary canal.

Since the lymph tissue is often severely damaged in this disease, it may mean that the disease possesses a special affinity for this tissue and that lesions found here represent a specific reaction. Ramsey (1956), describing depletion and necrosis of the lymph tissue in mucosal disease, concluded that the pathogenesis of these changes is not clearly understood. Jarrett (1958) felt that lymphocytolysis is a nonspecific reaction of the lymph tissue in this disease. Rooney (1957) reported

edema and heterophilic infiltration to be a secondary response seen in the capsular and medullary sinuses only in the suprapharyngeal, bronchial and mediastinal lymph nodes.

Similar lesions of the lymph tissue are also known to occur in several other bovine diseases. Maurer et al. (1955) believed that the virus of rinderpest has a special affinity for the lymph tissue where it causes necrotizing lesions. Carlson (1957) studied the lesions of viral diarrhea in Indiana and found depletion and necrosis of the lymph tissue. Berkman (1958) observed disappearance of the follicular architecture due to lymphocytic depletion in a few cases of malignant catarrhal fever.

4. Certain Parenchymatous Organs

Certain parenchymatous organs (adrenals, liver, kidneys) commonly revealed variable cloudy swelling, hydropic degeneration, fatty changes and even necrosis of the epithelial cells in mucosal disease. It is common knowledge that these degenerative changes represent nonspecific reactions in response to diverse forms of noxious stimuli and are commonly encountered in infections (such as streptococcal), intoxications (such as arsenicals, phosphorus), anemias (such as eperythrozoonosis) and circulatory disturbances.

Basically, the degenerative changes of the parenchymatous cells are the result of anoxia, complex physical, biochemical, and toxic injurious agents. These noxious agents or other injurious stimuli injure the cells either through (1) depriving them of certain essential substances such as lipotropic factors (choline: Best, 1941; methionine: Du Vigneaud,

1941; pancreatic methionine-liberating enzyme: Chaikoff and Entman, 1948), (2) disturbance of osmotic equilibrium due to altered membrane permeability and the loss of selectivity (Lucké and McCutcheon, 1932; Robinson, 1952; Leaf, 1956), (3) lack of oxygen, (4) inhibiting various enzymatic activities such as oxidation and reduction by certain poisons which interfere with the tricarboxylic acid cycle at the citrate and malt-ate levels, hence disruption of respiration at that level (Judah et al., 1954), or (5) through interference with the functioning of sulfur-containing amino acids (Miller et al., 1940).

The parenchymatous organs seem to undergo deterioration in response to anorexia, cachexia, probably toxemia, dehydration, and/or anoxia secondary to the damage of the alimentary canal and the hemopoietic system in this disease. The fatty changes of the liver are seemingly due to severe nutritive disturbance and starvation characteristic of this disease. Florey (1958) proposed that with starvation there is a shortage of lipotropic substances and carbohydrates. Hence the little fat which is reaching the cells from the fat depots alone cannot be combined with lipotropic substance, nor adequately metabolized in the cell because of carbohydrate deficiency. Consequently fat accumulates within the parenchymatous cells, and the organs become fatty. Rooney (1957), discussing the pathogenesis of the fatty changes, believed that these changes accompany anorexia and cachexia in this disease. He also considered the focal necrosis as a specific lesion, the result of anoxia or an aftermath of severe fatty changes.

The fatty and other degenerative changes in the adrenal cortex may have been caused by complex forms of stresses. Normally, adrenal cortical parenchymatous cells contain few or no lipid droplets (Nicander, 1952; Verne and Herbert, 1951). However, fatty changes of the adrenals are known to occur in a variety of bovine conditions. Prominent among these are (1) ketosis, due to inadequate availability of carbohydrate (Shaw et al.,1948, 1949), (2) hypocalcemia in parturient paresis (Garm, 1952), (3) during stress of lactation and pregnancy (Bell and Weber, 1959) and (4) experimental disturbance in electrolyte metabolism (Weber et al., 1958).

The renal changes of cloudy swelling, vacuolation and necrosis of the tubular epithelium and corticomedullary congestion may represent reactions to diverse forms of injury similar to that seen in anoxic nephrosis in man (Boyd, 1958), "lower nephron nephrosis" (Lucké, 1946) and toxic tubular nephritis (Smith and Jones, 1957).

5. The Lymphocytic Foci in the Adrenals and Liver

The lymphocytic foci in the adrenals and liver occur particularly in cases with severely damaged lymphatic tissue, especially in older animals and in those with prolonged course. Hence, one may conjecture this reaction as a compensatory autochthonus lymphocytic rejuvenation and proliferation. Florey (1958) obtained evidence that there is a constant demand for lymphatic tissue in the body. This is evidenced by development of compensatory nodules within a few weeks in the portal tracts of the liver and along the bronchi following surgical removal of

the spleen, all the lymph nodes, the Peyer's patches and thymus in rats and rabbits. Whiteman (1960) proposed that lymphocytic accumulations in the adrenals may be looked upon either as an inflammatory reaction or perivascular cuffing (typical of some viral diseases).

CHAPTER XIII

DIFFERENTIAL DIAGNOSIS

Essentially, the mucosal disease observed in Michigan is closely similar to that reported elsewhere. The differences reported among the syndromes (mucosal disease) are merely quantitative rather than qualitative. It is common knowledge that pathologic manifestations of a disease are significantly influenced by husbandry practices, state of nutrition, climatic conditions and age of the animal affected. Moreover, two cases of the same disease are never pathologically alike in every respect and may even exhibit considerable departure in the distribution and extent of lesions. Thus the larger the number of cases studied the clearer the understanding of the lesions of a disease. An unintentional disregard of these determining factors has led many investigators to report the same disease under different names. This, of course, has created a great deal of confusion in the recognition of this disease as one and the same entity. It is hoped that we can look forward to a concrete understanding of mucosal disease.

Ever-increasing international traffic poses a serious threat of introduction of rinderpest and certain vesicular diseases into this country. Hence, this necessitates means for accurate diagnosis and differentiation of various somewhat similar syndromes one from another. Since rinderpest exhibits certain features which are indistinguishable from those of mucosal disease, the importance of differential diagnosis can

be readily appreciated. Moreover, this is true of several other bovine diseases already prevalent in this country. The differential features of individual diseases are included in the following account.

1. Rinderpest

Fortunately, the Americas have not, to date, experienced the devastating epizootics of rinderpest. Constant vigilance and awareness of the disease are the most significant prerequisites to preventing its occurrence and spread in this country. Recently, natural outbreaks of the disease have been studied in Africa by Maurer et al. (1955). The disease is known to possess easy transmissibility, high morbidity and high mortality in contrast to mucosal disease. Coughing, respiratory disturbance and abdominal distress are a conspicuous clinical feature of rinderpest but not of mucosal disease. Rinderpest affects cattle of all ages while mucosal disease occurs chiefly in young animals.

Rinderpest exhibits certain lesions which serve a useful means of differential diagnosis. In rinderpest, skin lesions do not occur, and the lesions of the squamous epithelium of the digestive tract appear as shallow erosions demarcated by normal epithelium. The erosions develop through necrosis of the cells initially in the stratum spinosum which ultimately extends in the superficial layers. In mucosal disease, epidermal erosions are common and the erosions and ulcerations of the alimentary squamous epithelium tend to be irregular and coalescent, and to develop through hydropic and reticular degenerations of the stratum

spinosum which extend from the defects. Extensive erosions and hemorrhages of the nares, larynx and trachea are commonly found in rinderpest but not in mucosal disease. In rinderpest, lesions of the forestomachs seldom occur, whereas lesions here are a constant feature of mucosal disease. Hemorrhages and severe congestion in the anterior portion of the duodenal mucosa along with hemorrhages and erosions in the mucosa of the gallbladder, seen in rinderpest, do not occur characteristically in mucosal disease. Epithelial desquamation of the renal pelvis and urinary bladder with microscopic erosions and macroscopic hemorrhages are frequently seen in rinderpest but are not observed in mucosal disease. In rinderpest, diffuse subendocardial hemorrhage over the papillary muscles of the left ventricle is a constant occurrence while such lesions are not encountered in mucosal disease.

2. Viral Diarrhea

This is perhaps the only disease entity encountered in the U. S. A. which is clinically rather indistinguishable from mucosal disease. The entity was first recognized by Olafson et al. (1946) in New York and further studied by Olafson and Rickard (1947) and Baker et al. (1954). Unlike mucosal disease, this entity is characterized by easy transmissibility, high morbidity, and low mortality. Erosions of the oral cavity, pharynx, esophagus, abomasum and cecum along with diffuse reddening and hemorrhages of the omasum, abomasum and intestines are a characteristic finding of mucosal disease, but erosions and ulcerations of the forestomachs, most of the intestines and the Peyer's patches typical

of the mucosal disease do not occur in viral diarrhea. Hemorrhages of the subcutaneous tissue and vagina are commonly seen in virus diarrhea as opposed to mucosal disease.

A similar but immunologically distinct viral diarrhea has been reported in Indiana by Pritchard et al. (1956) and Carlson et al. (1957). Viral diarrhea of Indiana is almost similar to that observed in New York. The lesions of the Indiana entity have been described in detail by Carlson et al. (1957). Skin lesions do not occur in Indiana viral diarrhea in contrast to erosions and ulcerations observed in mucosal disease. Intestinal erosions and ulcerations are a rare finding in the Indiana disease, but the intestines including Peyer's patches are severely affected in mucosal disease.

Histologically, the erosions of the squamous lamina epithelium develop through necrosis and vacuolar degeneration of the cells at the deep layer of the stratum spinosum and are sharply bounded by normal epithelium, whereas such lesions in mucosal disease are characterized by hydropic and ballooning degeneration which extend a varying distance from the more serious defects. Frank necrosis of the Peyer's patches and other lymph tissue, seen in mucosal disease, does not occur in viral diarrhea. In Indiana viral diarrhea erosions of the gallbladder and the urinary bladder mucosae are a common finding; this is not true of mucosal disease.

3. Malignant Catarrhal Fever

The disease has been studied in this country by Barner and Montgomery (1954), Berkman (1958), Berkman et al. (1960) and Roderick (1958), and elsewhere abroad by Daubney and Hudson (1936), Dobberstein and Hammert-Holswick (1928), Götze (1929), Goss (1947), Mettam (1923), Pattison (1946), Piercy (1954), Plowright (1953) and Stenius (1952). Malignant catarrhal fever causes low morbidity; usually a single animal is affected at a time, while several cases may be seen with mucosal disease in a herd. Older animals may contract malignant catarrhal fever, whereas mucosal disease is seldom encountered in animals over 20 months old. High temperature (around 106°F.) and bilateral corneal opacity are diagnostic features for malignant catarrhal fever but not for mucosal disease. Skin lesions (reddening, papulation, and scabbing), hyperexcitability, and relatively dry feces are characteristic of malignant catarrhal fever; in contrast, mucosal disease manifests relatively normal body temperature, epidermal erosions and diarrhea with mucoid to bloody feces.

The gastric and duodenal ulcers in malignant catarrhal fever are usually raised and slightly yellowish in color whereas in mucosal disease ulceration of the duodenum is not seen and abomasal ulcers have a punched-out appearance. Severe erosion and ulceration of the large intestine and the Peyer's patches, characteristic of mucosal disease, do not occur in malignant catarrhal fever. Diphtheritic membranous covering of the nasal passages, trachea and pharynx are almost constantly

found in malignant catarrhal fever but not in mucosal disease. The urinary bladder mucosa commonly exhibits diffuse hemorrhage and epithelial desquamation in malignant catarrhal fever while such lesions usually are not found in mucosal disease.

Histopathologically, erosions and ulcerations of the squamous epithelium develop in malignant catarrhal fever through proliferation of the basal layer cells and ballooning degeneration leading to vesiculation of upper layers, whereas in mucosal disease erosions primarily are due to hydropic and ballooning degenerations accompanied by acantholysis of the deep layer of the stratum spinosum. A most important differential feature of malignant catarrhal fever is the proliferative and infiltrative changes involving the blood vessels in most organs, but especially in the brain. In addition, lymphocytic and monocytic periportal accumulations in the liver occur conspicuously. These lesions are not found in mucosal disease. Necrosis and crypt abscessation of the gastrointestinal mucosa and lymphocytic necrosis typical of mucosal disease are in contradistinction to submucosal perivascular proliferation in the abomasum and the intestines and reticuloendothelial proliferation in the lymph nodes in malignant catarrhal fever.

4. Hyperkeratosis

Cattle, upon intoxication with chlorinated naphthalenes, suffer from a syndrome called hyperkeratosis (X-disease). The entity has been described by Olafson et al. (1947), Gibbons (1949) and Morrill and Link (1950).

Dry, thickened, and wrinkled skin, serous to mucopurulent ocular discharge and salivation are the clinical manifestation of hyperkeratosis as opposed to epidermal erosions and ulcerations, and absence of both ocular discharge and salivation in mucosal disease. However, Morrill and Link (1950) observed that animals with hyperkeratosis may die without showing skin lesions yet be affected internally.

The lesions appear as marked thickening of the squamous epithelium due to increased cornification. However, shallow ulcerations of the oral cavity, esophagus, and forestomachs may occur in acute intoxication and usually precede thickening in early experimental cases (Gibbons, 1949). In mucosal disease erosions and ulcerations persist, and increased cornification does not occur. Microscopically, the lesions of the squamous epithelium are characterized by thickening due primarily to extensive cornification and some degree of acanthosis in hyperkeratosis. Contrariwise, the erosive and ulcerative lesions of mucosal disease emerge through hydropic degeneration, ballooning degeneration and acantholysis.

In hyperkeratosis, the lesions of the gastrointestinal tract appear as nodules through hyperplasia of the columnar epithelium leading to cysts filled with mucus and cell debris in contrast to erosions and ulcerations, especially of the Peyer's patches, in mucosal disease.

In hyperkeratosis, biliary cirrhosis accompanies the bile duct hyperplasia and metaplasia. Renal tubular hyperplasia is portrayed by enlargement and dilatation primarily of the collecting ducts. Similar

changes may occur in the salivary glands and pancreas. Squamous metaplasia and cornification are commonly seen in the main ducts of salivary glands, in the accessory sex glands, in the secretory ducts of the testes and in the cervix. Of course, these changes are not found in mucosal disease.

5. Foot and Mouth Disease (Aphthous Fever)

Foot and mouth disease has been completely eradicated from this country, but its reintroduction is an ever-present threat. The entity has been described by Daubney (1932), Frenkel (1949) and Smith and Jones (1957). The disease is characterized by easy transmissibility and high morbidity especially in young animals in contrast to mucosal disease. Smacking of the tongue and lips, which is typical of foot and mouth disease, does not occur in mucosal disease. Diarrhea with mucoid to bloody feces is characteristic of mucosal disease but not of aphthous fever. Vesicles (aphthae) along the coronary bands and lightly haired skin areas such as the udder, the vulva and the conjunctivae, are peculiar to foot and mouth disease while in mucosal disease erosions develop over the muzzle, medial surface of the thighs, udder or scrotum, vulva or prepuce, etc.

Vesicular lesions of foot and mouth disease are prominent over the lips, dorsum of the tongue (especially the anterior portion), palate and forestomachs, whereas the entire oral cavity, pharynx, esophagus and forestomachs are severely involved in mucosal disease, showing large

irregular erosions and ulcerations. The vesicles and bullae which are characteristic of foot and mouth disease develop through ballooning degeneration of the stratum spinosum, while vacuolation, ballooning and acantholysis of the deep layer of the stratum spinosum form the basis of the erosions and ulcerations in mucosal disease. Punctate hemorrhages or edema of the gastrointestinal mucosa along with blue-red hyperemia of the large intestine develop in foot and mouth disease as opposed to prominent erosive lesions of the gastrointestinal mucosa and Peyer's patches in mucosal disease.

The lymphatic system involvement is a common feature of mucosal disease but not of foot and mouth disease. Hyaline degeneration and necrosis of the cardiac muscle (the wall and septum of the left ventricle) accompanied by lymphocytic and occasionally heterophilic infiltration, described for foot and mouth disease, do not occur in mucosal disease. Likewise, necrosis of the skeletal muscle, a prominent feature of foot and mouth disease, is not found in mucosal disease.

6. Vesicular Stomatitis

The virus of this disease, like that of foot and mouth disease, possesses a strong affinity for epithelial tissue. The entity has been described by Chow et al. (1951), Chow and McNutt (1953), Cotton (1927), Fellowes et al. (1956), Galloway and Elford (1933), Jacoulet (1915), Oletsky and Long (1928), Stozzi and Ramos-Saco (1953), Theiler (1901) and Wagener (1932). Ease of transmission and very low mortality are

features of vesicular stomatitis in direct contrast to mucosal disease. Diarrhea and erosions of the muzzle are constant clinical features of mucosal disease but not of vesicular stomatitis. Vesiculation of the skin of the lips and the coronary bands observed in vesicular stomatitis are not found in mucosal disease. Erosive lesions of the alimentary canal and of Peyer's patches, typical of mucosal disease, are not a feature of vesicular stomatitis.

In vesicular stomatitis the vesicles of the squamous epithelium appear through spongiosis in the stratum spinosum whereas hydropic degeneration, ballooning degeneration and acontholysis of the cells at the deep layer of the stratum spinosum are primarily responsible for the erosions observed in mucosal disease.

7. Erosive Stomatitides

This complex composes a number of bovine syndromes which have been encountered in various parts of the world, and described in veterinary literature from time to time. These include papulous stomatitis (Ostertag and Bugge, 1906; Germany), Armagh disease (Norris and Mettam, 1913; Ireland), erosive stomatitis (Mason and Neitz, 1957; South Africa), ulcerative stomatitis of calves (Gibbons, 1956; U. S. A.), parotido-stomatitis (Pande and Krishnamurty, 1956; India) and an ulcerative stomatitis of cattle (Pritchard et al., 1958; U. S. A.). These syndromes are characterized by easy transmissibility, 5 to 100 per cent morbidity and little or no mortality in contrast to mucosal disease.

Diarrhea, a conspicuous feature of mucosal disease, does not usually occur in the stomatitis entities.

Pathologically, the lesions are primarily confined to the oral cavity and its surrounding skin, muzzle, external nares, anterior-most turbinates and occasionally the esophagus. In contrast, lesions are widespread along the skin and alimentary canal in mucosal disease. Mycotic stomatitis (Udall, 1947) produces erosions and ulcerations of the udder, teats and coronary bands in addition to those associated with the stomatitides, but the erosions and ulcerations of the forestomachs and gastrointestinal tract which are so characteristic of mucosal disease do not occur.

Histopathologically, the lesions of the squamous epithelium in all resemble closely those of mucosal disease and are characterized by ballooning degeneration of the cells in the stratum spinosum and later coalescence of the affected areas resulting in vesiculation.

CHAPTER XIV

SUMMARY AND CONCLUSIONS

The aim of the present study was to investigate bovine mucosal disease in Michigan. From July, 1956, to December, 1958, a total of 30 cases, originating from 26 farms, was studied. Although the cases came from 16 counties in the southern part of the state, the disease has been observed state-wide.

The greatest incidence was during fall, but cases were noted in all months of the year. Most of the cases were between four and 13 months of age. No particular breed or sex susceptibility was observed.

The course of the disease varied from four to 22 days in cases terminating in death and from three to 71 days in those who were moribund and received euthanasia. Among the herds, the course ranged from four days to seven months.

The morbidity rate was 0.4 to 60 per cent in different herds and the mortality rate, inclusive of the moribund animals who received euthanasia, was 100 per cent.

Clinically, the disease was characterized by sudden onset, initial high fever, variable peripheral blood picture, frequent laminitis, serous to mucopurulent nasal discharge, profuse persistent to intermittent watery to mucoid or bloody diarrhea, erosions and ulcerations of the muzzle and mouth, marked dehydration, rapid cachexia, progressive weakness, and acute, subacute or chronic form.

Necropsy of the 30 animals revealed various characteristic lesions of the disease which were considerably variable in extent and distribution but were essentially identical from case to case regardless of the form of the disease. Areas of extensive erosion and ulceration of the skin (especially of the muzzle, interdigital space, coronary bands, prepuce or vulvar labiae) and alimentary canal were the most constant and conspicuous findings of the disease. The erosions and ulcers were irregular in outline, punched-out in appearance, yellowish-gray to hemorrhagic or brown in color and had a shallow base, frequently covered with serosanguineous exudate or necrotic pseudomembrane.

The disease apparently possesses a special affinity for the squamous epithelium of the skin and digestive tract where the lesions were widespread appearing as typical erosions and ulcers. The squamous epithelium was often covered with a necrotic pseudomembrane diffusely along the mucosa of the digestive tract. Microscopically, the lesions developed through hydropic degeneration of the germinal layer of cells of the stratum spinosum. The process then gradually spreads upward to involve superficial layers which usually revealed abundant ballooning degeneration (reticular colliquation). The erosions and ulcers seemingly emerge through acantholysis and desquamation of the degenerated layers of the squamous epithelium. Inflammatory reaction in the noninfected epithelium, corium and lamina propria was commonly absent or absolutely minimal.

Generally, the abomasal mucosa throughout revealed typical erosions and ulcers. These lesions were essentially due to coagulation

necrosis of the glandular epithelium, and this response has been conjectured as a specific reaction to the disease. Congestion, edema and petechial to ecchymotic hemorrhages of the gastric mucosa were also common.

A very common lesion of the disease was the erosion and ulceration of the intestinal mucosa, usually more severe along the large intestine and posterior portion of the small intestine. These lesions conspicuously conformed to the configuration of Peyer's patches and solitary lymph follicles of the intestine, but elsewhere these were irregularly disposed. Tenacious glairy exudation, congestion, edema, petechial to diffuse hemorrhage and melena of the intestinal mucosa were common. Microscopically, the intestinal lesions in the early stages were noted as severe catarrhal enteritis and coagulation necrosis of the columnar epithelium. The initial vigorous mucous secretory response seems to be a defensive mechanism whereas the coagulation necrosis of the glandular epithelium appears to be a lethal effect of the causative agent. The erosions and ulcerations emerged through marked caseation necrosis of the intestinal mucosa. Abscessation of the gastrointestinal crypts was another prominent finding, and this is believed to be a reaction to the lethal effects of the disease.

The disease, seemingly, also has a strong propensity for the hemopoietic system, particularly for the lymph tissue of the lymph nodes, spleen and intestine (the solitary lymph follicles and Peyer's patches). The lymph nodes draining the digestive tract were often selectively

affected showing swelling, congestion, hemorrhage, edema, lymphocytic depletion and coagulation to caseation necrosis. Similar changes also occurred in the spleen (germinal centers), Peyer's patches and intestinal solitary lymph follicles. The lesions of the lymph tissue apparently represent a specific reaction in this disease.

Lymphocytic foci occurred conspicuously in the adrenals and liver, especially in cases with severe and extensive lymphocytic damage. This response has been interpreted as the development of compensatory nodules to meet a constant demand for lymphocytes in the body.

The blood vascular changes consisted of congestion, edema and hemorrhage primarily of the gastrointestinal tract, lymph nodes, kidneys and adrenals.

Cloudy swelling and fatty metamorphosis frequently noted in the liver, kidneys and adrenals have been conjectured as merely secondary and nonspecific. The central nervous system and musculature did not reveal any significant gross or microscopic alterations.

The lesions described cannot be considered pathognomonic of this disease but are so characteristic as to have significant diagnostic value. A good history together with clinical observations is helpful, but a necropsy and careful evaluation of the microscopic lesions are absolutely essential to make an accurate diagnosis of the disease.

Therapy with antibiotics, sulfonamides, blood transfusion and intestinal astringents has been unfruitful.

The cause of the disease could not be determined. The tissue culture and experimental studies yielded negative results.

A number of pathogenic bacteria were isolated from the mucosal disease cases, and these have been apparently responsible for secondary bacterial infections.

Parasitological examination revealed commonly occurring gastrointestinal parasites, but their role in the disease is merely conjectural.

Differential diagnosis of the disease is difficult but is possible beyond reasonable doubt when based on sound history, clinical findings and pathologic studies.

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