# BOVINE MALIGNANT CATARRHAL FEVER IN MICHIGAN I. OCCURRENCE II. PATHOLOGY III. DIFFERENTIAL DIAGNOSIS IV. COMPARISON WITH SIMILAR SYNDROMES IN OTHER COUNTRIES

By

Robert Nelson Berkman

A THESIS

Submitted to the School for Advanced Graduate Studies of Michigan State University of Agriculture and Applied Science in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Department of Veterinary Pathology

1958

ProQuest Number: 10008584

All rights reserved

INFORMATION TO ALL USERS
The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript
and there are missing pages, these will be noted. Also, if material had to be removed,
a note will indicate the deletion.


ProQuest 10008584

Published by ProQuest LLC (2016). Copyright of the Dissertation is held by the Author.

All rights reserved.
This work is protected against unauthorized copying under Title 17, United States Code
Microform Edition © ProQuest LLC.

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 - 1346

5907

# TABLE OF CONTENTS

PAGE

ACKNOWLEDGMENTS

The author wishes to express his sincere thanks to his major professor, Dr. R. D. Barner, who first recognized the problem of bovine malignant catarrhal fever in Michigan and initiated the studies herein presented. In addition, Dr. Barner has provided a constant supply of ideas, information, and enthusiasm which were invaluable in this undertaking. The author is also indebted to Dr. C. C. Morrill and Dr. R. F. Langham for their help in reviewing the material and suggestions regarding the photography. Much credit is due the veterinarians of Michigan who supplied the cases upon which these studies were based. The author is indebted to the technicians-Mrs. Laurie Felch, Mrs. Joyce Trier, Mrs. Nancy Malik, Miss Marjorie Leopold, and Miss Barbara Myers -for their preparations of the tissue sections and the blood examinations. The author appreciates the research funds supplied under the regional project, "The Mucosal Diseases of Cattle", (NC-34).

# INTRODUCTION

Bovine malignant catarrhal fever (MCF) has a world-wide distribution. The disease has been reported from the continents of Europe, Africa, South America, and North America (Stenius, 1952). Bovine malignant catarrhal fever was first reported in the United States by Marshall et al. (1920) in Pennsylvania. The disease has been reported also from Ohio (Goss et al., 1947), North Dakota (North Dakota Livestock Sanitary Board, 1937), Colorado (Farquharson, 1946), Michigan (Barner and Montgomery, 1954), and New York (Udall, 1956).

Hutyra et al. (1949) state that "the disease has been observed and described from the end of the eighteenth century ...Anker (1832) described it as a typhus of cattle and regarded it, with Spinola, as originating from benign nasal catarrh...Haubner and Roll, and later Lucet, described it as a diphtheroid infection of the mucosa, but it was first described as a specific infectious disease of cattle by Bugnion in 1877."

# STATEMENT OF PROBLEM

Bovine malignant catarrhal fever has not been extensively investigated in this country and it is generally considered to be of minor importance. However, the possibility that the disease occurs in forms other than the clinically obvious "head-and-eye" type appeared to be probable on the basis of preliminary studies. Several investigators have described different types in other countries. It was felt that many

cases were probably misdiagnosed as such things as so called "hemorrhagic septicemia", infectious kerato-conjunctivitis, atypical pneunomia, or as entities of the mucosal disease complex.

The cases which had been observed in Michigan in preliminary studies had indicated that the syndrome was not fully compatible with some features described in other countries. A need for an accurate picture of the disease as it occurs in North America was indicated.

The recent appearance of the several syndromes making up the mucosal disease complex pointed up the need for means of differential diagnosis. Clinically, many of our cases resembled diseases of the complex — particularly the condition first described by Ramsey and Chivers (1953) in Iowa. This condition has been our major problem in differential diagnosis.

We must keep in mind the possibility of exotic diseases which may invade our country through several increasing means as international traffic increases. Foremost among such possible invaders are rinderpest and the vesicular diseases. The accurate diagnosis of these conditions is a necessity if they are to be combatted.

Thus, we find that although the number of reported cases of MCF is small, yet the possibility of unrecognized cases, the need for characterization of the disease as it occurs in this country, and the necessity for its differential diagnosis furnish justification for the studies herein presented.

Many investigators have worked on the transmissibility

of MCF but have reported conflicting results. Mettam (1923) reported the successful transmission through bacteria-free blood to cattle. Daubney and Hudson (1936) reported similar results. Götze (1930), Rinjard (1935), and Magnusson (1940) reported the successful transmission of the disease to cattle in a similar manner. Piercy (1952) utilized several different inocula to achieve successful transmission to cattle in S. Africa. Other workers (Dobberstein and Hemmert-Halswick, 1928; Stolnikoff, 1933; de Kock and Neitz, 1950) failed to transmit the disease to cattle.

The disease has been transmitted to rabbits by Ernst and Hahn (1927), Zwick and Witte (1931), Pattison (1946), and Plowright (1953). Other researchers (Mettam, 1923; Dobberstein and Hemmert-Halswick, 1928; Stolnikoff, 1933; Bisbocci, 1934; Aleska, 1935; Bendixen, 1940) have failed to transmit the disease to rabbits. Götze and Liess (1930) failed to infect rabbits, mice, rats, and guinea pigs. Meissner and Schoop (1934) did not succeed in infecting rabbits and guinea pigs. Pattison (1946) was unsuccessful in infecting rats and guinea pigs. Daubney and Hudson (1936) reported successful transmission to rabbits, mice, and guinea pigs.

The disease is not confined strictly to cattle. Stenius (1952) states that buffalo, sheep, goats, gnu, deer, steenbok, carabou, and the giraffe are susceptible.

Several causative agents of the disease have been suggested. Bassi (1930) believed that MCF was due to poisoning by Polytrichium trifolii. The lack or surplus of calcium

affecting vasomotor responses was suggested by Linkies (1926). Sjollema (1937) reported a deficiency of calcium and vitamin A in diseased animals. Wyssman (1938) believed that meteorological factors were involved. Otte (1925) connected MCF with an invasion of Eristalis larvae and Dictyocaulus viviparus. Numerous investigators have believed the disease to be caused by bacteria (Le Clainche, 1896; Isepponi, 1902; Stolnikoff, 1926; Guizzardi, 1931; Huynen and Logiudice, 1911; Reisinger, 1926). Götze (1940) did not find evidence of a rickettsial infection, but did demonstrate a spirochete. Stenius (1952) could not find spirochetes in 10 cases in which tissues were stained with Levaditi's stain. He also reported that serological tests failed to incriminate Toxoplasma as the causative agent. Mettam (1923) described "snotsiekte" of cattle in S. Africa as caused by an ultramicroscopic agent (this disease is believed to be MCF). Ernst and Hahn (1927) were the first of the European workers to suggest a viral agent. Investigators have subsequently utilized bacteria-free blood and tissue emulsions to transmit the disease as previously mentioned.

This historical review does not cover all the literature on MCF. Literature pertinent to the studies are included in the respective sections.

# I. OCCURRENCE

## MATERIALS AND METHODS

A total of 39 cases of MCF was collected in Michigan beginning in 1954 and extending to the present writing. Of these 39 cases, 31 animals were examined post-mortem and material was collected for histopathological examination. In 8 cases the animals were not secured for necropsy but are included because they were classical pictures of the "head- and -eye" form of MCF occurring on farms with a past history of the disease. The majority of cases came from an enzootic area in southeastern Michigan.

## RESULTS AND DISCUSSION

### SEASONAL INCIDENCE

Previous investigators (North Dakota Livestock Sanitary Board Reports, 1937; Mackey, 1956) have observed the greatest seasonal incidence of the disease in the spring and fall. Marshall et al. (1920) described an outbreak in one herd in Pennsylvania in which cases developed from December through June. Farquharson (1946) reported that the disease may occur during any season but the greatest incidence was found during the winter and early spring months. In Michigan the greatest incidence of the disease occurred during February and March gradually declining through June. One practitioner (Eames, 1956), who has practiced in the heart of the MCF area for 15 years, has noted a correlation of the onset of the condition with the marked fluctuations of temperature during the late winter and early spring. Wyssman (1938) has suggested a

similar correlation with temperature variation. Cases have also occurred in the fall but these numbered only 3 of our 39 cases.

AGE, BREED, AND SEX

Marshall et al. (1920) indicated that the most susceptible animals were those between two and five years of age. Our studies indicated that all age groups may be equally susceptible. The youngest animal affected was four months old. If the cases were divided into three age groups — mature cattle (2-5 years), 1-2 years, and one year or less — it was found that the disease was distributed almost equally among these groups.

No particular breed susceptibility was noted. Both dairy and beef cattle were affected. The disease was observed in females, males, and steers.

ROLE OF SHEEP

Many investigators have suspected sheep as the intermediate carrier of the virus without showing symptoms of the disease themselves (Götze, 1930; Rinjard, 1938; de Kock, 1950; Piercy, 1954). The exact relationship, if existent, has not as yet been satisfactorily demonstrated. Farquharson (1946) has pointed out that there was undeniable clinical evidence that the incidence of the disease in Colorado was much higher on farms and ranches where both sheep and cattle were raised. The greatest incidence of MCF in Michigan occurred in the largest sheep-raising area in southeastern Michigan. Here, commonly, sheep and cattle share the same

barn and often use the same yards and watering troughs. Sheep are raised on 23 percent of the farms in this area as compared to 6 percent for the rest of the state (Hill, 1956). If the greater percentage of farms in this area contain no sheep, why do they not have a corresponding incidence of MCF if other factors are responsible? All of the 39 cases reported occurred on farms where sheep were raised. In one instance, the disease occurred in a Hereford steer on a farm where sheep raising was the main endeavor and no permanent cattle herd was maintained. This animal was purchased as one of 16 feeder animals in October, 1956, and came down with the disease in February, 1957. A similar case had occurred three years previously in a feeder steer. Inasmuch as no permanent cattle herd had been maintained on the farm for several years, the involvement of sheep as a carrier seems indicated; however, this does not preclude the possibility of prior infection or another source of infection. Stenius (1952) confirmed successful transmission from cattle to sheep and sheep to cattle reported previously by Zanzucchi (1934). Stenius further reported that the test animals showed only slight clinical symptoms not typical of malignant catarrhal fever.

SUSCEPTIBILITY OF NEW ADDITIONS

The apparent susceptibility of new additions to the herd has been noted in Finland (Stenius, 1952). Similar observations have been made in this study. New additions to the herd have become infected up to one year after joining the

herd suggesting that previous exposure was not a factor. Farquharson (1946) believed that we must accept the fact that either most cattle are immune or have had subclinical infection. It seems probable that the explanation for the occurrence in animals born and raised on the farm is a matter of individual resistance and stress factors (such as weather changes).

MORTALITY

Marshall et al. (1920) recorded a mortality of 100 percent in an outbreak in Pennsylvania. Farquharson (1946) observed a mortality of at least 90 percent in Colorado. Stenius (1952), citing a total of 120 cases, observed that 27 percent died, 38 percent were slaughtered, and 35 percent recovered. The mortality rate in Michigan has been almost 100 percent. A practitioner with 15 years' experience in the enzootic area reports only one recovery during this period (Eames, 1956). A few cases, in which MCF had been diagnosed clinically, have appeared to be recovering only to suffer relapse and die within a few days.

MORBIDITY

Bovine malignant catarrhal fever is enzootic in nature; varying intervals of time may elapse between cases. Old-timers in the enzootic area recall cases up to 50 years previous to the time of the present episode. Thus, historically, the disease is not a new condition in Michigan. Farquharson (1946) and Stenius (1952) have stated that once the disease occurs on the premises it is likely to recur;

these studies lend support to this statement. Usually only one animal is affected in a herd; rarely, as many as three cases have occurred. A similar morbidity rate has been reported in Colorado (Farquharson, 1946). Seemingly, only in rare instances are several animals simultaneously affected; but it must be born in mind that outbreaks ascribed to so-called "hemorrhagic septicemia", infectious kerato-conjunctivitis, mucosal disease, or pneumonia may be MCF.

AS A CAUSE OF ABORTION

The evidence seems to indicate that malignant catarrhal fever is not a cause of abortions. No history of an unusual abortion rate on infected premises has been reported. In one case a calf was dropped one month prematurely; nevertheless, the calf showed no signs of the disease. The animal was weak but survived with good care suggesting that the abortion was not due to the agent per se, but to the debilitating effects of the disease on the dam. The calf was born a month after the acute episode; the dam later died in the chronic stage of MCF. One fetus in utero was examined post-mortem and showed no gross or microscopic evidence of infection although the dam had died of the acute head-and-eye form of MCF. In Pennsylvania it was noted that several calves dropped during an enzootic outbreak were not affected by the disease (Marshall et al., 1920).

ECONOMIC ASPECTS

The exact economic importance of MCF is difficult to ascertain. Few reports of this disease are made yearly in

Michigan but the cases investigated in this study indicate that the disease may be masquerading under other names such as hemorrhagic septicemia, infectious kerato-conjunctivitis, atypical pneumonia, and mucosal disease. The individual farmer unfortunate enough to have this disease on his premises suffers intermittent financial loss with varying intervening periods of no losses. Marshall et al. (1920), North Dakota investigators (1937), and Farquharson (1946) have reported cases of an enzootic type. The chronic case may cause the owner considerable loss; the animal appears to be improving slightly, thus encouraging the farmer to continue treatment and care, only to relapse and die several months later.

SYMPTOMS OF DISEASE

The onset of the disease is sudden; no indications of impending sickness are seen. Milk production drops sharply to little or nothing. The animal eats and drinks poorly or not at all. A profuse mucopurulent exudate hangs from the nostrils and, in some cases, an accumulation of this material may be seen on the floor or in the manger (fig. 1). A characteristic nasal roar and severe dyspnea develop as the disease progresses; distinct rattling sounds may be heard as exudates collect. The breath has a fetid odor.

During the early phase of the disease a serous fluid drains from the medial canthi of the eyes, coursing its way ventrally down the lateral surfaces of the head leaving swaths of matted hair; after three to four days this fluid becomes mucoid in nature and collects in the corners of the

eyes. A peripheral corneal cloudiness usually begins on the first or second day terminating in complete opacity and blindness in four to five days (fig. 2). This "frosting" of the cornea is a prominent feature of the syndrome. Marked episcleral injection is noted. The eyelids often are mildly swollen with somewhat rounded margins.

The epithelium of the muzzle is at first slightly reddened; later, a thick crusting of necrotic epithelium and exudate may partially mask this change. If this thickened, cracked layer be dislodged, a raw red surface which may bleed profusely is presented. Gradually the nasal epithelium sloughs in small patches. The anterior nasal mucous membrane is covered by a gray pseudomembranous layer which overlies the inflammed and necrotic nasal mucous membrane. On examination of the oral cavity one may find changes varying from a diffuse necrosis of the buccal mucosa to a macular appearance formed by small areas of erosion (figs. 3,4). A diphtheritic coating may be found in some cases, but may have been washed away if the animal has been drinking.

The skin may exhibit certain features of diagnostic importance. The epidermis is dry, leathery, and folded as one would expect in a severely dehydrated animal; in addition, however, a characteristic tufting of the hair in small patches, particularly over the cervical region, has been observed in several cases. Localized thickenings of the skin underlie these tufts; occasionally small contiguous lymph nodes have been swollen. Raised circumscribed areas, measuring approx-

imately five mm. in diameter, have been observed on the udder. Patchy erythema may occur anywhere on the body but has been noted particularly on the udder and lips of the vulva. The teats may be ruborous early in the disease followed by development of a characteristic thickening of the skin crisscrossed by deep fissures exposing the subcutaneous tissue; dark brown scabs may develop on the teats and, less frequently, on the udder and vulva (fig. 5).

Temperature elevation to 106 F. is noted on the first two to three days of illness and gradually declines on the fourth or fifth day to a level of 103 F.-104 F.

The animals are commonly in a state of abject depression, standing motionless with the head lowered and neck extended. Cases have been reported by some investigators in which extreme excitement and viciousness to the point of attacking the handlers have occurred; but in the cases observed in this study only mild symptoms of such nervous excitement — marked uneasiness and shifting of the feet — were seen. Marked hyperthesia was common but this is believed due to the inflammatory processes in the integument rather than a central nervous system disturbance.

Urinary disturbances may be present in some cases, but are not a constant feature. Blood-tinged urine may be passed at the end of micturition accompanied by straining and dribbling of the urine.

FORMS

Götze (1930) described four forms of the disease: viz.,

(1) peracute, (2) head-and-eye, (3) intestinal and (4) benign. Several peracute cases have been diagnosed in Michigan; these cases run a course of two to three days. The majority of cases in this study have been of the head-and-eye form. The course in these cases was generally from four to fourteen days; the most common duration was seven days. One case of the intestinal form has been diagnosed on the basis of histopathological features. A fifth or chronic type of MCF has been observed in Michigan. This type runs a course of up to six months or longer, terminating in death. Some of these cases may be mistakenly assumed to be recovering as the symptoms abate. The animals begin to eat and drink but do not seem otherwise to improve nor deteriorate until they suddenly relapse and die; often large patches of skin will slough in the later stages. Cases of the benign form have not been recognized here.

It must be emphasized that atypical variations of the symptoms previously described were not uncommon. In a few cases the corneal opacity was absent; in others, muzzle and/or oral erosions were not found. In one instance no characteristic clinical features were present except a temperature elevation of 106 F. which did not respond to antibiotics. The diagnosis was made on the basis of post-mortem lesions which will be discussed in the next section.

CLINICAL PATHOLOGY

Examination of blood and urine specimens can be of value in diagnosis. Leukopenia with a shift to the left may be

present in the early stages of the disease. Damage to the urinary tract may be indicated by albuminuria, glucosuria, or hematuria. The latter has been observd clinically toward the end of micturition and apparently indicates hemorrhage in the bladder.

## SUMMARY AND CONCLUSIONS

Bovine malignant catarrhal fever as observed in Michigan is an enzootic disease characterized clinically by fever (106 F.), nasal and ocular discharge, corneal opacity, erosions of the muzzle and oral cavity, marked depression, anorexia, rapid weight loss, erythema of the skin (particularly the udder and vulva) and, occasionally, thickening and cracking of the teats, tufting of the hair, and hematuria. Leukopenia may be present.

A definite seasonal incidence involving late winter and early spring is indicated.

Clinical evidence points to sheep as carriers of the causative agent.

The disease is usually fatal in from 4-14 days although chronic cases may occur.

Atypical cases may be misdiagnosed as atypical pneumonia, infectious kerato-conjunctivitis, hemorrhagic septicemia, or as entities of the mucosal disease complex.

Fig. 1-Cow with head-and-eye form of malignant catarrhal fever showing mucopurulent nasal discharge and excoriation of the muzzle.

Fig. 2-Eye of cow showing marked corneal opacity due to malignant catarrhal fever.

Fig. 3-Mucous membrane of lower lip and gum of cow showing patchy erosions (arrows) in a case of acute malignant catarrhal fever.

Fig. 4-Lateral surface of bovine tongue showing irregular erosions (arrows) of the mucous membrane in an acute case of malignant catarrhal fever.

Fig. 5-Bovine teat showing hyperkeratinization with scaling and cracking due to malignant catarrhal fever.

# II. PATHOLOGY

## INTRODUCTION

Few reports on the pathology of bovine malignant catarrhal fever have been published in the United States. Smith and Jones (1957) in their book, Veterinary Pathology, state that "considerably more study of malignant catarrh is needed, as are better methods for its recognition." The few available reports of the disease in North America are mostly of a clinical nature or have dealt with only the gross lesions (Marshall et al., 1920; North Dakota Livestock Sanitary Board, 1937; Farquharson, 1946; Rines and Barner, 1955). Schofield (1950) described round cell and mononuclear cell infiltrations in the brain, liver, and kidneys in a case in Canada. Goss et al. (1947) described a sero-catarrhal to diphtheritic inflammation involving the mucous membranes; cytoplasmic inclusions were reported in the epithelial cells of the mucous membranes. It is hoped that the studies reported herein, based on material collected from 31 field cases of bovine malignant catarrhal fever, will contribute to the knowledge regarding the nature and diagnosis of this disease, particularly the recognition of relatively atypical cases which, in our experience, were quite common.

## MATERIALS AND METHODS

Tissues were fixed in 10 percent formalin with sodium acetate as described in the Armed Forces Institute of Pathology Manual (1957). The tissues were next dehydrated in a series of graded alcohols, passed through xylene, and embedded

in paraffin. Sections were cut at 6-7 microns and stained with hematoxylin and eosin according to the method described by Malewitz and Smith (1955). Sudan IV was used as a fat stain as described by Mallory (1938). Other special stains used were Lendrum's, Pollak's trichrome, Masson's trichrome, Verhoeff's elastica stain, Mallory's aniline blue collagen stain, and the phloxine methylene blue stain. These stains were used according to methods and formulas in the Armed Forces Institute of Pathology Manual (1957). The phloxine methylene blue stain was modified in that the slides were stained in phloxine for three hours at 56°C. or overnight followed by decolorization in one percent acid alcohol for ten seconds.

## RESULTS

### SKIN

The animals presented for post-mortem examination were usually markedly underweight. The hair coat was dull and roughened; occasionally, tufting of the hair was found (in chronic cases hairless areas were present), particularly in the cervical area. In many cases, thickened crusts, 1-2 mm. in diameter, were observed in the skin, most often in the cervical region, but, occasionally, scattered over the entire body. The vulva was frequently markedly reddened. In many instances, marked lesions of the udder were found: cracking and crusting of the skin of the teats, areas of erythema, and raised papules, 1-2 mm. in diameter. Lesions of the muzzle varied from thickening and scaling to complete

erosion of the muzzle epithelium exposing a raw, reddened surface. Generally, there was a profuse mucopurulent nasal discharge.

The microscopic lesions of the skin as well as other stratified squamous epithelia have been grouped for convenience of description. Representative sections from the muzzle, vulva, udder, eyelids, affected skin areas, and squamous portions of the digestive tract were examined. Specimens from macroscopically normal as well as visibly affected areas were studied. It was discovered that many of the apparently normal tissues contained excellent examples of microscopic lesions. By comparing tissues from these areas with tissues from more severely affected sites, the pathogenesis of the lesions could be reconstructed. Lesions from all cases were remarkably similar although their distribution varied from animal to animal; in other words, the variations were quantitative rather than qualitative. The process appeared to begin as multiplication of cells of the basal layer of the epithelium together with an increase of connective tissue cells and lymphocytes in the dermal papillae (fig. 11). Increased cellular activity was apparent about blood vessels which were markedly congested. The epithelial cells formed loose networks which were interconnected by fine cytoplasmic strands. Occasional ballooning cells with condensed acidophilic cytoplasm were found in the central areas of the rete pegs. Many of the rete pegs were elongated and club-shaped. The basal cell layer was not distinct due to the

loss of polarity of the nuclei and proliferation of the cells (mitotic figures were frequently observed in the basal area). Occasional necrotic epithelial cells, identified by their bright pink cytoplasm and fragmented nuclei, were scattered through the cellular masses in the dermal papillae. Thickened keratin layers often maintained the external continuity of the tissue; in other instances, portions of the keratin layer were elevated by the underlying disease processes. In more severe lesions, large clumps of ballooning cells underwent reticulating colliquation with resultant vesicle formation in the upper epithelium (fig. 13). The vesicles contained cellular debris, protein-containing fluid and, occasionally, abundant polymorphonuclear leucocytes. Russell's bodies were sometimes observed in the epithelial cells. The hypercellular masses in the dermis were often markedly pleomorphic. Many spindle-shaped connective tissue cells with large pale oval nuclei (fibroblasts) were present. Often numerous lymphocytes, many of which were large immature forms, were seen. Eosinophiles, macrophages, plasma cells, and mast cells were usually present in smaller numbers. These changes were not restricted to the upper dermis but were very evident around blood vessels in the deeper portions of the dermis. Hyperplasia in and about blood vessels and capillaries was usually pronounced and, in some cases, obstruction of the vessels occurred due to masses of endothelial cells which projected into the lumen (fig. 14). Hyperplasia of the epithelial cells of the skin adnexae was often prominent

(fig. 15). Occasional lymphocytes and proliferating capillary endothelial cells were observed in these areas. Vessels in the underlying muscle were sometimes involved. Generally, it may be said that in early lesions hyperplasia was paramount; in the more advanced processes infiltration of lymphocytes and sometimes eosinophiles was prominent. Special stains were used to identify the proliferating tissue in the dermis and about the blood vessels. Mallory's collagen stain and Masson's and Pollak's trichrome stain indicated that this was collagenous connective tissue.

EYES

Bilateral corneal opacity was usually marked; however, cases with only slight or no cloudiness were encountered. The conjunctival vessels were generally injected. The eyelids were thickened and rounded. Abundant mucopurulent exudate was often present in the medial canthi.

The corneal opacity observed macroscopically and the nature of its development (initial peripheral cloudiness which gradually spread to the center of the cornea) may be explained by the lesions found on microscopic examination. The most severe changes were found in the area of the corneoscleral junction, but extended into the cornea, becoming less marked as they approached the center of the cornea. Essentially, the pathological process was one of a proliferative and infiltrative nature. The conjunctival epithelium usually showed ballooning degeneration and irregular hyperplastic projections into the lamina propria. In these areas

mitotic activity was evident. In some areas the epithelium was absent. The underlying lamina propria and sclera, particularly in the anterior portions, contained pleomorphic and abundant cellular aggregations composed of mononuclear cells, lymphocytes, and some eosinophiles and plasma cells. Large connective tissue cells were increased in number (fig. 22). Many mitotic figures were observed in large cells of varying shapes which were difficult to classify. Swelling, rounding and hyperplasia of capillary endothelial cells were observed. Blood vessels were affected by proliferative and infiltrative lesions as in the skin. The corneal epithelium showed ballooning degeneration and occasional areas of erosion. Rupture of the substantia propria of the cornea sometimes occurred. The connective tissue in the substantia propria of the cornea was often granular and somewhat disrupted. Polymorphonuclear leucocytes were occasionally abundant in the cornea; the humors of the eye sometimes contained polymorphonuclear leucocytes as well as monocytes, lymphocytes, and cellular debris. Cell accumulations, similar to those described in the conjunctival lamina propria and sclera, were found in the iris, ciliary body, and retina. Occasional vascular lesions occurred in the connective tissue of the optic nerve and periorbital fat and orbital muscles. Congestion of seemingly all parts of the eye was marked.

DIGESTIVE TRACT

Mouth, pharynx, and esophagus. The mucous membranes of the mouth usually showed a severe necrotizing process

which varied from distinct ulcerations of irregular shape and size to diffuse necrosis of the epithelium of almost the entire cavity, in which the epithelium was easily scraped away with a knife. Commonly, a thick grayish-white diphtheritic membrane was found in the pharynx; it often involved the esophagus and trachea also. This diphtheritic membrane covered a necrotic mucous membrane. When distinct ulcerations were present, they might be found in any area of the oral cavity; usually, the remaining intact membrane was dull and gray in appearance. In some cases, petechial hemorrhages were present on the ventral surface of the tip of the tongue. The diphtheritic inflammation in the pharynx usually extended into the proximal squamous portion of the esophagus for a short distance. Occasionally small ulcers or diffuse necrosis were found throughout the length of the esophagus. Flattening of the longitudinal folds and dullness of the esophageal epithelium were observed in some cases.

Microscopically, the stratified squamous portion of the digestive tract contained lesions as previously described. Blood vessels were markedly congested and showed lesions as described for the skin. The salivary glands were often the site of proliferative and infiltrative processes. The epithelial cells of the salivary ducts were often hyperplastic and disarranged; proliferation and infiltration of cells were observed in the lamina propria of the ducts. The secretory units adjacent to the affected areas were compressed.

Forestomachs. Gross lesions were variable in the fore-

stomachs. Occasionally, diffuse areas of hemorrhage and/or erosions were found. In a few cases, the papillae of the rumen showed particularly striking hemorrhages (fig. 6). Microscopically, the lesions involved the squamous epithelia as previously described under "skin" (fig. 12).

Abomasum. The abomasum was commonly the site of extreme congestion, hemorrhage, and often ulcers up to 3 cm. in diameter (fig. 7). Microscopically, scattered areas of epithelial desquamation were observed in many cases. The primary change appeared to involve the blood vessels, particularly those in the submucosa. These vessels were surrounded by cuffs of lymphocytes, monocytes, and occasional eosinophiles snd plasma cells. Adventitial and endothelial cells were often increased in number; the media often contained areas of fibrinoid degeneration, pyknotic nuclei, or foci of proliferating cells which appeared to extend from the adventitia or endothelium. Vascular congestion was generalized. Occasionally, hemorrhages were noted in the mucosa.

Small intestine. The small intestine was rarely severely involved. Abundant mucus was usually present. Rarely, petechiae, congestion, and/or small erosions were found. Microscopically, the lesions resembled those of the abomasum except that they were less frequently found.

Large intestine. In a few instances, the ileocecal valve was markedly hemorrhagic, thickened, and edematous (fig. 9). In several cases the cecum and colon were congested and petechiated; they sometimes contained small erosions.

The rectum displayed similar changes; petechial hemorrhages were usually arranged linearly on the crests of the rectal folds.

Microscopically, severe lesions were found in the large intestine in several cases. Hemorrhage into the mucosa of the ileocecal valve was common; smaller hemorrhages were observed in the mucosae of the colon and rectum. Minor desquamation of the epithelium was seen in scattered areas throughout the large intestine. In several cases blood vessels, particularly in the submucosa, were surrounded by cuffs of lymphocytes, monocytes, eosinophiles and plasma cells. Adventitial and endothelial cell proliferation was usually evident in such cases and often extended into the media. Submucosal edema was generally pronounced in the pathologic portions of the large intestine.

Liver. Prominent gross lesions were not found in the liver. Usually swelling and indications of fatty degeneration were present. Microscopically, conspicuous lesions were consistently found in the periportal areas. These areas were greatly distended by cell accumulations which compressed but did not extend between the hepatic cords (fig. 16). Many of the liver cells which were so compressed by the cell accumulations showed pyknosis or karyorrhexis. The periportal cell collections were composed of several types of cells, but monocytes and lymphocytes were the more prominent (many of which were markedly pleomorphic). More variably found were eosinophiles, plasma cells, and, occasionally, poly-

morphonuclear leucocytes. Mitotic activity in these areas was pronounced. The blood vessel walls were often greatly masked by the collections of cells, being recognized only by a central collection of erythrocytes surrounded by an occasional area of recognizable mural structure. The bile duct epithelium was often hyperplastic as evidenced by an irregular piling up of pleomorphic duct cells. Capillaries in the portal areas were markedly congested and the endothelial cells were enlarged and hyperplastic. Sections from 4 of 31 cases were stained for fat and revealed mild to severe diffusely distributed fatty degeneration of the hepatic cells.

Gallbladder. In a few cases macroscopic evidence of congestion and thickening of the wall of the gallbladder were noted. Microscopically, the changes followed the pattern found in other organs. The epithelium was intact except for an occasional small area. There was an increase of primarily monocytes, fibroblasts, and lymphocytes in the lamina propria. Plasma cells and eosinophiles were observed in small numbers. Proliferative reaction was noted around the blood vessels, particularly the capillaries. All blood vessels were markedly congested. Occasional glands appeared hyperplastic in the areas of proliferative activity in the lamina propria. The muscle layers were disrupted by cellular infiltrates which appeared to emanate from blood vessels affected by the proliferative and infiltrative processes.

Pancreas. Macroscopic lesions of the pancreas were not observed. Microscopic lesions were not prominent.

Mild proliferative activity among fibroblasts was present about occasional ducts; some of the duct cells were somewhat disoriented, suggesting the possibility of an early hyperplastic change. The capillaries were moderately congested and sometimes showed mild hyperplasia of the endothelial cells.

## LYMPHATIC SYSTEM

Lymph nodes. The lymph nodes of the head were usually enlarged, edematous, and congested. In many instances, the lymph nodes throughout the body were similarly affected and contained microscopic lesions. The changes were very consistent and are considered to be of diagnostic value. Blood vessels in the capsule, pulp, and perinodal fat were often markedly affected by proliferation of adventitial and endothelial cells as well as accumulations of lymphocytes, monocytes, plasma cells, and eosinophiles. The cell accumulations extended into the capsule and trabeculae from the vessels masking the normal structure (fig. 19). In some cases the follicular architecture was absent or represented by a few lymphocytes; in other cases, the follicles were hyperplastic. The majority of cases exhibited marked reticulo-endothelial proliferation, particularly along the trabeculae. Numerous mitotic figures were observed. Marked congestion and edema were frequently found; rarely, hemorrhage was present. The parenchyma often bulged against the capsule, in which case clusters of pyknotic lymphocytes were observed along the capsule. Eosinophiles, plasma cells, and polymorphonuclear

leucocytes were variably found in the pulp.

Spleen. The spleen showed no remarkable gross lesions. Microscopic lesions similar to those in the lymph nodes were seen in some cases. Trabecular disruption and degeneration were evident adjacent to involved vessels. Follicular hyperplasia was often evident. Large amounts of hemosiderin were present in some cases.

CARDIOVASCULAR SYSTEM

Heart. Hemorrhages were frequently observed on the epicardium. The microscopic lesions followed the pattern noted in other organs. Perivascular cuffs of adventitial cells, lymphocytes, occasional monocytes, and sometimes minor ininfiltrations of eosinophiles, plasma cells, and polymorphonuclear leucocytes were present. Both fibrinoid degeneration and accumulations of proliferating cells were observed in the media. Proliferation of endothelial cells was seen in some vessels. The lesions occasionally impinged on adjacent muscle fibers but usually extended along the connective tissue tracts from the blood vessels. Mild to severe fatty degeneration was observed in the cardiac muscle fibers in four cases in which special stains were done. Vascular lesions were not present in the hearts from all of the cases and not all vessels in an affected section showed lesions.

Aorta. In one case papular elevations, 1-2 mm. in diameter, were noted on the intimal surface of the aorta. These proved, microscopically, to be focal areas of endothelial proliferation. Whether this should be considered an incidental

finding or a part of the MCF syndrome cannot be decided on the basis of one specimen, although the nature of the lesion suggests that it was a part of the disease process. Accumulations of cells in and about the vasa vasorum of the aorta, similar to those described in the heart, were occasionally observed.

## RESPIRATORY SYSTEM

Nasal passages and trachea. Commonly, a thick, greenish, fetid, fibrino-necrotic membrane covered the congested nasal mucous membranes (fig. 9). Usually the proximal portion and occasionally the entire length of the trachea contained a similar diphtheritic layer. Scattered petechial hemorrhages were observed in both the nasal passages and trachea. The epithelial surface of the trachea was generally dull and yellowish in appearance.

Microscopically, the epithelium of the nasal passages and trachea contained many ballooned cells. Fibrino-necrotic exudate was piled up on the surface. In several cases little or no recognizable epithelium remained. Aggregations of lymphocytes and monocytes were scattered throughout the lamina propria. Connective tissue proliferation in the lamina propria was evident. Capillaries were markedly congested and the endothelial cells were swollen and hyperplastic.

Lungs. The lungs exhibited pleural hemorrhages and areas of firm red hepatization in some cases.

In several cases the lung exhibited marked microscopic lesions which were consistent with the pathological picture

found in other organs. The larger bronchioles were the site of marked proliferative and infiltrative changes, although not all of these bronchioles were affected. The lamina propria contained cellular aggregations of monocytes, lymphocytes, fibroblasts, and occasional eosinophiles, plasma cells, and polymorphonuclear leucocytes which extended into the muscularis (fig. 18). The bronchiolar epithelium was pushed into the lumen by the underlying cell collections; loss of polarity and hyperplasia of the bronchiolar epithelium were usually present in affected bronchioles. Many of the respiratory epithelial cells were ballooned. Often there was poor demarcation between the epithelium and lamina propria. The lumina of the bronchioles contained mucus, cellular debris, and polymorphonuclear leucocytes. Capillary endothelial cells were generally swollen and hyperplastic. The alveolar walls were thickened by an increased number of septal cells. The alveoli were filled with erythrocytes in many areas. Large and small blood vessels exhibited marked adventitial and endothelial proliferation; fibrinoid degeneration was common in the media, although in areas increased numbers of cells were noted which appeared to extend from the proliferative endothelial or adventitial areas. Accumulations of monocytes, lymphocytes, and occasional eosinophiles, plasma cells, and polymorphonuclear leucocytes were present in the adventitial cuffs. All of the blood vessels were extremely congested.

## URINARY SYSTEM

Kidneys. The kidneys were usually congested and often

contained petechial hemorrhages. In one case, white focal areas were present on the cortical surface.

The microscopic changes in the kidney affected the blood vessels and Bowman's capsule. These changes were consistent with lesions in other organs and were essentially proliferative and infiltrative in nature. Blood vessels, surrounded by loose cuffs, which were composed of adventitial cells, lymphocytes, monocytes, and some eosinophiles and plasma cells, were scattered throughout the kidney, although not all vessels were affected. In many cases the glomerular capsule was masked by infiltrations of lymphocytes and monocytes. It was noted that these areas were most frequently seen surrounding the afferent and efferent arterioles, and, in view of the lesions of the vessels in the kidney as well as in other organs, it was felt that the accumulations originated from the arterioles. The lesions were usually semilunar in distribution, but did extend completely around the glomerulus on occasion. The process occasionally extended into the capillary tuft. Compression of the tubules in the areas adjacent to the cell accumulations was evident. Albuminous degeneration was usually present in the tubules. Marked congestion of the intertubular capillaries and, occasionally, hemorrhage were found in both the cortex and medulla. The pathological findings in the kidney were not constant, but were of frequent occurrence. Mild to severe tubular and glomerular fat accumulations were revealed by special stain of sections from 4 of the 31 cases.

Ureters. Grossly, the ureters appeared swollen and congested. Microscopically, the transitional epithelium exhibited ballooning degeneration; little or no recognizable epithelium remained in some areas. Occasional sections of epithelium appeared somewhat hyperplastic and blended with the highly cellular lamina propria. The latter contained numerous monocytes, lymphocytes, and large pale connective tissue cells together with a smaller number of eosinophiles, plasma cells, and occasional mast cells. Blood vessels in the lamina propria and muscularis showed fibrinoid degeneration of the media and accumulations of cells, as previously described under "skin", in the adventitia. Marked congestion in most vessels was evident.

Urinary bladder. Macroscopically, the bladder was severely affected in several cases. The wall was greatly thickened. The mucosa was thrown into large folds; mucosal hemorrhage was often severe (fig. 10) — accounting for the hematuria observed clinically in several cases.

Microscopically, hemorrhage was often pronounced in the submucosa. The epithelium was absent in many cases; in other instances, transitional cells undergoing ballooning degeneration were noted. The lamina propria was markedly hypercellular containing large mononuclear cells, lymphocytes, fibroblasts, and some eosinophiles and plasma cells (fig. 20). In a few areas, the cellular masses in the lamina propria blended with the transitional epithelium. Blood vessels were severely involved, undergoing alterations similar to those previously

described. Capillary endothelial cells were enlarged and hyperplastic. Congestion was marked. The smooth muscle often contained evident vascular lesions which produced disruption of the muscle layers.

## REPRODUCTIVE SYSTEM

Uterus, ovaries, and oviducts. The uterus, ovaries, and oviducts did not present any macroscopic lesions other than congestion.

Sections indicated that severe involvement of the system may occur. Portions of uteri examined revealed lesions in accord with those observed in other organs. Blood vessels throughout the uterus were affected by proliferative, infiltrative, and sometimes degenerative phenomena. Endothelial activity was observed in both capillaries and larger vessels. Cuffs of cells surrounded many vessels; these were composed of adventitial cells and infiltrating cells as previously described. The media was either involved with cellular accumulations or undergoing fibrinoid degeneration or both. Fluid accumulations and cell collections were scattered throughout the uterus. Patchy areas of glandular hyperplasia appeared to contribute to the proliferative picture. Vascular lesions were also found in the ovaries. Many areas of hemorrhage were found in and about the affected vessels. One specimen of placenta and fetus were examined. Vascular lesions were present in the placenta bu none could be found in the fetus. The oviducts contained cell accumulations in the lamina propria as well as vascular lesions.

Mammary glands. Specimens of both lactating and non-lactating mammary tissue exhibited proliferative and infiltrative processes. Endothelial cells of small capillaries in the interstitial tissue were enlarged, rounded, and hyperplastic. Marked congestion of the blood vessels was present. The alveolar cells in many of the secretory units exhibited loss of nuclear polarity and piling up of pleomorphic alveolar cells in a manner which caused them to blend with the activated endothelial cells in the interstitium. In some instances, the lumens of the glands were obliterated by masses of proliferative cells. Similar changes were present in the ducts and teat cisterns. The epithelial cells appeared markedly ballooned and the lamina propria was markedly hypercellular (fig. 21). Monocytes, lymphocytes, and some plasma cells, eosinophiles, and mast cells were present. In some areas the epithelium and lamina propria were poorly demarcated. Vascular changes were the same as observed in other organs. The severe lesions in the mammary gland may account in part, at least, for the sharp decline in milk production in lactating animals which is a prominent clinical feature.

Testes. Macroscopically, the testes from one bull examined were congested. Sections from this case revealed that arteries and veins in both parenchyma and capsule were surrounded by cuffs of proliferating adventitial cells, lymphocytes, and occasional wandering monocytes. The media of many of the vessels exhibited a fibrinoid appearance; cell accumulations sometimes were present in the media. The endothelial

cells in some vessels were enlarged and hyperplastic. Capillaries in the interstitial area contained hyperplastic endothelial cells. Compression of the seminiferous tubules was evident. All of the blood vessels were engorged with blood.

## ENDROCRINE SYSTEM

Thyroid. Macroscopic lesions were not observed in the thyroid. Sections exhibited marked hyperplasia of follicular cells which often obliterated the lumen (fig. 23). The process extended into the interstitial tissue blending with proliferating endothelial cells. Occasional lymphocytes were present in the interstitial areas. Pyknotic follicular cells were frequently observed in the lumens of some of the affected alveoli.

Adrenal glands. Macroscopic changes in the adrenal glands were not observed. Microscopic lesions of the blood vessels, consistent with those found in other organs, were commonly found in the adrenal glands in both the capsular and parenchymal areas (fig. 24). Compression and disruption of the adrenal architecture were apparent in the areas adjacent to the vascular lesions. Fibrinoid degeneration of the media and endothelial and adventitial proliferation were observed. Lymphocytes, monocytes, and some eosinophiles, plasma cells, and mast cells were present in the perivascular tissue extending into the capsule. Occasional areas of hemorrhage were found; blood vessels were markedly congested. Occasional affected vessels were present in the fat surrounding

the adrenal glands.

Pituitary. No macroscopic lesions of the pituitary gland were observed. Microscopic changes were limited to the blood vessels, particularly those in the connective tissue; they were similar to the vascular lesions in other organs.

## NERVOUS SYSTEM

Central nervous system. Gross lesions of the brain were limited to marked congestion and edema of the meninges. The most prominent and consistent microscopic alterations involved the blood vessels, both arteries and veins. The vessels were surrounded by cuffs of predominantly monocytes and lymphocytes (fig. 17). Occasionally, eosinophiles were abundant. The majority of the mononuclear cells were seemingly interconnected by fine pale cytoplasmic strands. The lymphocytes were pleomorphic; large young forms were abundant. Mitotic activity was frequently observed in the cuffs. In some vessels the endothelial cells were enlarged and rounded; occasionally, they were piled up suggesting mild hyperplasia. Free red blood cells were often present in the cuffs and perivascular spaces; they appeared to have leaked through the loose, disarranged structure of the vessel walls. Often the Virchow-Robin spaces were obliterated by the thickened walls and congestion in the vessels; encroachment upon the surrounding brain substance was apparent in many areas. The capillary endothelial cells were generally enlarged and hyperplastic. Sections of the central nervous system examined included meninges, medulla, cerebellum, cerebrum, thalamic area, hippocampus, and spinal

cord, all of which contained lesions. In several cases, the choroid plexus showed both infiltration of numerous mononuclear cells and proliferation of the capillary endothelial cells.

Non-specific changes also were usually present in the brain. Marked congestion and edema were often pronounced. The neurons appeared normal in many cases and degenerative changes, when present, were not marked, but there were varying degrees of neuronal degeneration, as evidenced by eccentricity of the nucleus, chromatolysis, and ghost cells. Satellitosis and neuronophagy were present in some cases but were usually not marked. It is believed that the neuronal changes were due to the impaired circulation and pressure produced by affected vessels rather than to specific infection of the neurons. Both generalized and focal increases in glial cells were observed.

Inclusion bodies as described in Finland (Stenius, 1952) were found in the cytoplasm of the neurons of the vagoglossopharyngeal nucleus in 73 percent of the cases examined. These bodies were observed in two patterns of distribution: viz; single or multiple inclusions were seen scattered throughout the cytoplasm or conglomerates composed of numerous spherical bodies were located adjacent to the nuclear membrane. Distinct halos were often visible about the bodies; the inclusions varied in size from 300-500 millimicrons in diameter. Both degenerated and otherwise apparently normal neurons were affected. The bodies were difficult or impossible to see with the routine hematoxylin-eosin stain. Among the

stains used, Mallory's phloxine-methylene blue stain gave the best results. Not only was excellent differentiation of the bodies obtained (bright red to wine), but the Nissl substance was well stained by this method. Other stains used to demonstrate these bodies were Shorr's III, Masson's trichrome, Pollak's trichrome, and Lendrum's.

In an attempt to demonstrate the diagnostic importance of these striking bodies, sections of medulla from cattle coming routinely to the post-mortem room were examined. Similar bodies were observed in 18 of 47 cases examined. There was no evidence to suggest the presence of malignant catarrhal fever at the time of necropsy in these cases. Therefore, we do not believe that these bodies are of specific diagnostic importance.

Gasserian ganglia. The Gasserian ganglion was removed in several cases for examination for inclusion bodies by special stain. No inclusion bodies were found, though the the observations included several cases wherein such bodies were demonstrated in the medulla. However, microscopic lesions were found consisting of the previously described proliferative and infiltrative changes of the vessel walls which extended into the connective tissue surrounding the cell bodies of the neurons. There did appear to be a mild increase in the capsular cells. Many of the nerve fibers in the affected areas were fragmented.

## DISCUSSION

Grossly and microscopically it is evident that the

causative agent of MCF may produce lesions in all systems of the body and therefore it is pantropic in nature; thus it is no more appropriate to classify this disease as primarily an encephalitis than to so classify hog cholera or canine distemper. The lesions in the brain primarily affect the blood vessels; that neurons are not severely involved is indicated by microscopic examination and by the lack of extreme nervous manifestations clinically in most cases.

The pattern of the lesions is consistent in all systems. Essentially, two different processes are involved: (1) proliferation of connective tissue, endothelial, and epithelial cells is widely distributed in epithelial elements and blood vessels and (2) infiltration is generalized, affecting the lamina propria of many structures as well as the periportal area of the liver and blood vessels. We can logically attribute the necrosis which may occur, particularly in the squamous epithelia, to any one or, more likely, a combination of several causes. First, the surface integrity of structures such as the skin and mucous membranes is disrupted by the ballooning degeneration, vesiculation, and loss of epithelium which exposes the tissue to secondary invaders. Secondly, the involvement of the vasculature by proliferative and infiltrative processes which may obstruct the lumen or disrupt the architecture of the wall, thus affecting the circulation to the area, is certainly important. This mechanism is well illustrated in the abomasum and intestine. Here one finds only primarily a desquamation of epithelium with an involve-

ment of vessels, particularly in the submucosa, which appears to be the logical cause. Even if not obstructed, these vessels cannot contract or dilate normally in response to the tissue demands for blood. Thirdly, the great increase in perivascular cellular elements would seem to produce a pressure which may not only affect the cells directly but probably also shuts off lymphatic and vascular channels. In addition, the functional activity of an organ may be expected to be affected by the lesions in that organ as well as by influences from other involved organs.

We should like to present those features of the disease which, in our experience, have proven to be of the greatest diagnostic value. One must remember that the distribution of many of the lesions is highly variable. Cases of the typical "head-and-eye" form are obvious; however, cases have been encountered wherein only intestinal lesions have been observed. A case is described in Canada in which only inflammation of the trachea and large bronchi and ecchymoses in the heart were found (Schofield, 1950). Historically, contact with sheep and indication of a previous sporadic occurrence (which one may discover only by further questioning of the owner) are helpful features. Clinically, the temperature of approximately 106 F. early in the disease which does not respond to antibiotics, any indication of skin involvement (erythema, papulation, or scabbing), corneal cloudiness, rapid weight loss and death are suggestive of MCF. Suggestive post-mortem findings are: diphtheritic inflammation in the

nasal passages, oral cavity, and trachea; enlarged, edematous and/or hemorrhagic lymph nodes; hemorrhage and/or erosions in the digestive tract and bladder. Microscopically, the most helpful lesions are the constant cellular accumulations (primarily monocytes and lymphocytes) around the blood vessels in the brain and in the periportal areas of the liver. The microscopic lesions in the skin, lymph nodes, kidneys, and adrenal glands may also be of value. We believe that correlation of the history, clinical findings, and post-mortem examination should enable a definite diagnosis to be made even in atypical cases.

## SUMMARY AND CONCLUSIONS

Grossly, the lesions of bovine MCF generally found were marked weight loss, nasal and ocular discharge, corneal opacity, erosions of the muzzle, erythema of the udder and vulva and, in a few cases, encrusting of the skin, tufting of the hair, and thickening and cracking of the epithelium of the teats. Severe oral erosions were found in most cases. Diphtheritic membranes were frequently observed in the nasal passages, pharynx and trachea. Scattered areas of congestion, hemorrhage, and/or erosion were variably found in the digestive tract-usually most pronounced in the abomasum and large intestine when present. Lymph nodes, particularly those of the head, but often of more general distribution were enlarged, edematous, and/or hemorrhagic. Hemorrhage and erosion in the bladder were observed in some cases.

Microscopically, MCF was characterized by proliferative

and infiltrative changes. In the case of squamous epithelial surfaces these were followed by necrosis. The proliferative lesions were widely distributed, affecting vascular and epithelial structures. Marked elongation of the rete pegs was regularly observed in the squamous epithelium; adnexal skin structures often displayed marked hyperplasia. The dermal papillae contained abundant and pleomorphic cellular aggregations composed of monocytes, fibroblasts, lymphocytes, eosinophiles, plasma cells, and mast cells. Similar proliferative and infiltrative processes were also noted in the lamina propria of the eye, bronchioles, urinary bladder, gallbladder, ureters, and teat cistern; the epithelium of some of these structures appeared to be hyperplastic. Vascular proliferative and infiltrative lesions were present and marked in the liver and brain in each case; they were less constantly found in most other organs. Proliferation in blood vessels was most commonly seen in the adventitia, but the media and endothelium were not infrequently involved. Mild to marked infiltrations of lymphocytes, monocytes, eosinophiles, plasma cells, and mast cells were usually observed in and around the affected blood vessels.

Vesicles were frequently found in the squamous epithelium, sometimes containing heterophiles; they appeared to originate from coalescence of necrotic and ballooning cells in the stratum Malpighii.

The lesions described are believed to be consistent and characteristic enough to be of diagnostic value. Intracyto-

plasmic inclusions in the neurons, previously reported in Finland, were observed in the majority of cases; however, their specificity is questioned.

Fig. 6-Hemorrhage in the papillae of the rumen in an acute case of MCF

Fig. 7-Circumscribed (A) and linear (B) erosions in the abomasum in an acute case of MCF.


A-1176

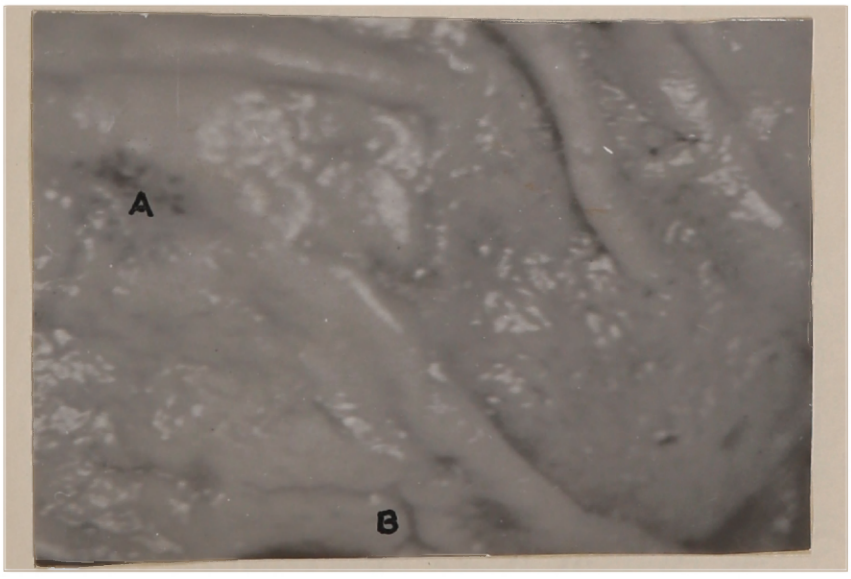
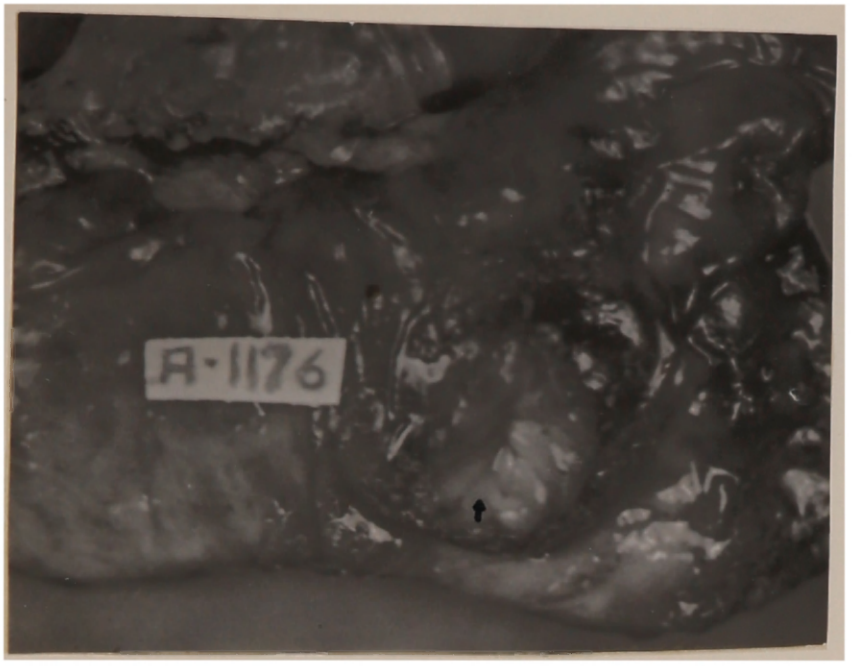

A
B

Fig. 8-Diffuse hemorrhage and edema in the ileocecal valve (arrow) and adjacent area in an acute case of MCF.

Fig. 9-Diphtheritic membrane (A) and hemorrhage (B) in the nasal sinus in an acute case of MCF.


A-1176

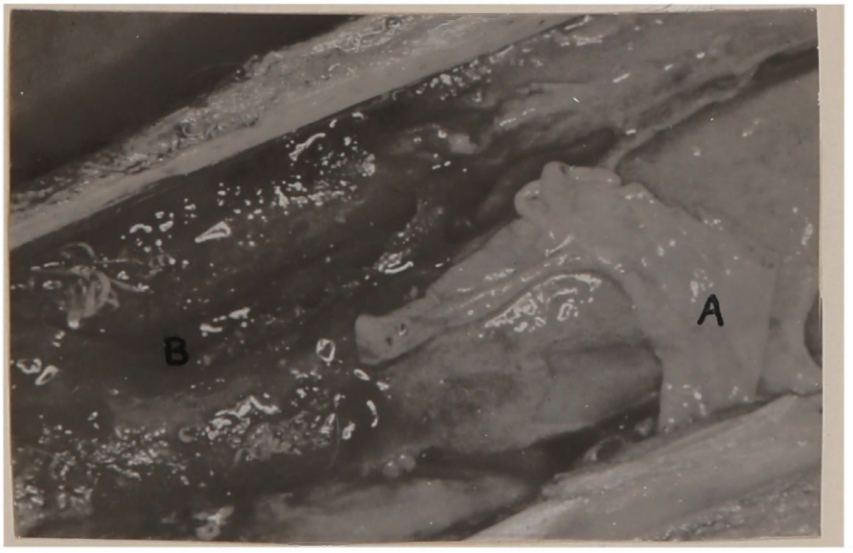

A
B

Fig. 10-Hemorrhage and thickening of the wall of the urinary bladder in an acute case of MCF.

Fig. 11-Early lesion in the tongue demonstrating clubbing of the rete pegs due to hyperplasia (A) and cell accumulations in the papillae (B). X135.


A-1198

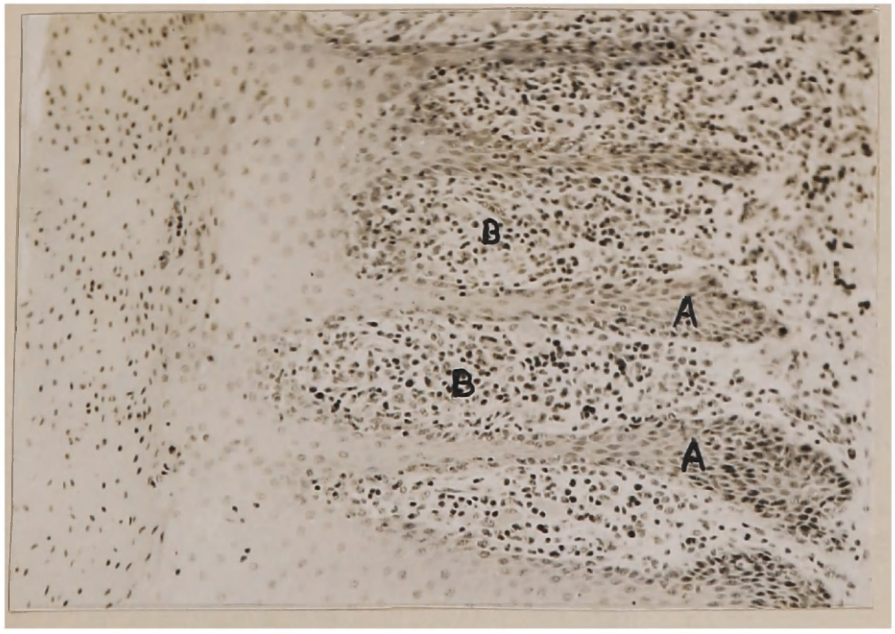
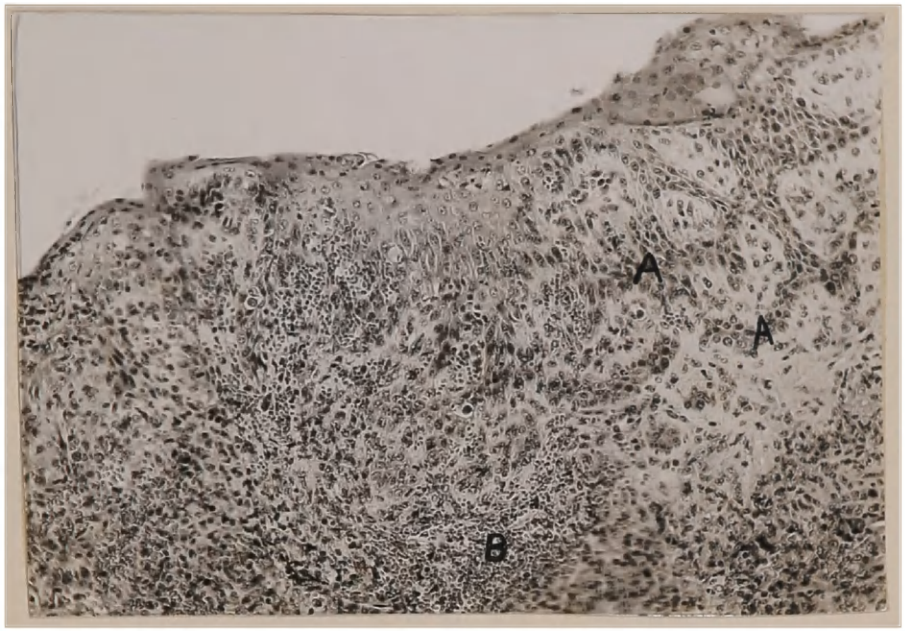

B
A
B
A

Fig. 12-Epithelial hyperplasia (A) and hemorrhage (B) in a papilla of the rumen. X135.

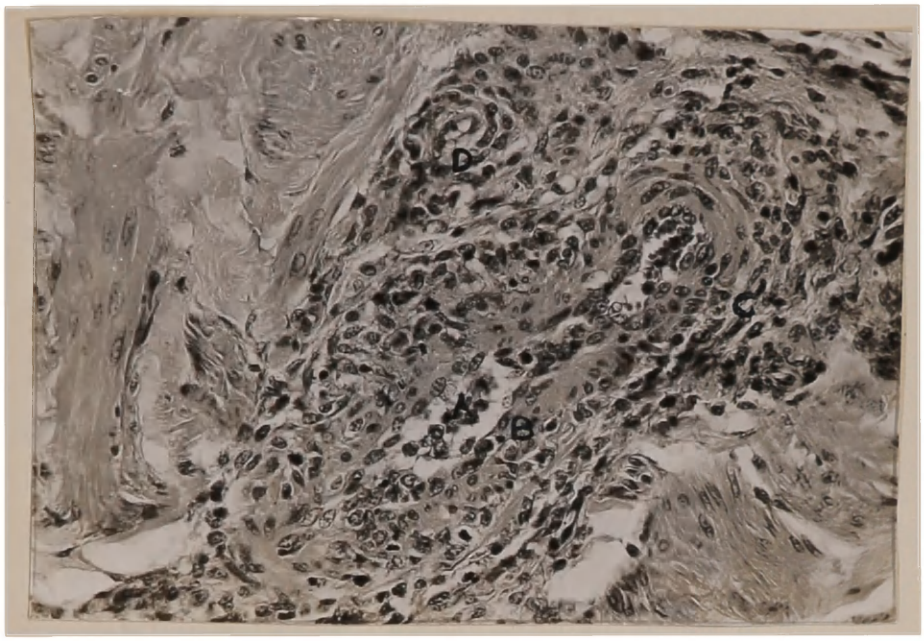
Fig. 13-Vesiculation (A) and scaling of hyperkeratinized layer (B) in epithelium of the teat. X135.


A
A
B


A
B

Fig. 14-Artery in dermis of teat showing endothelial (A) medial (B) and adventitial (C) proliferation. Area of proliferation about a capillary (D). X250.

Fig. 15-Hyperplasia of epithelial cells in meibomian glands of eyelid. Remnant of gland (A) and area of hyperplasia (B). X250.


D
C
A
B

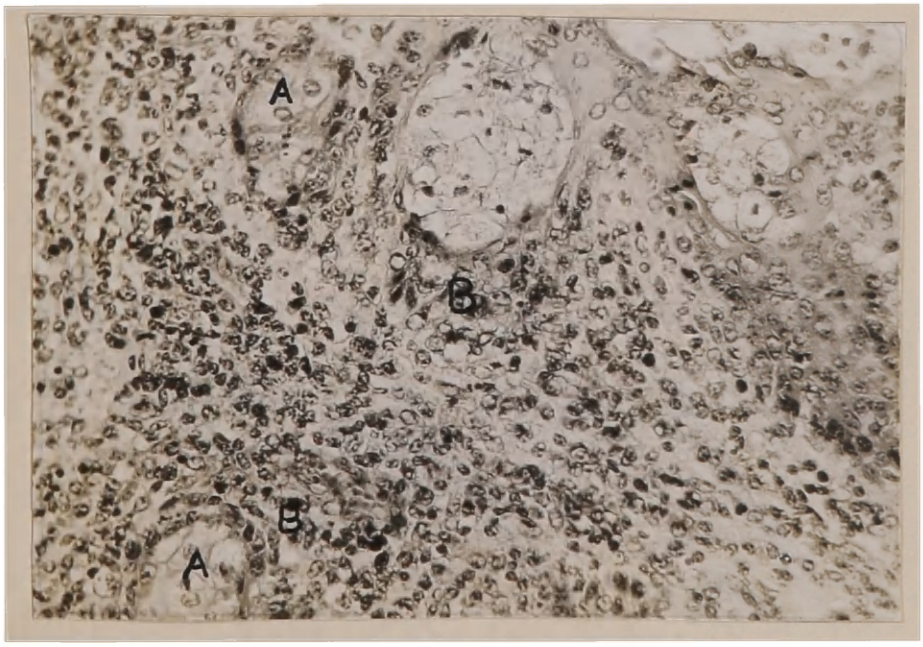
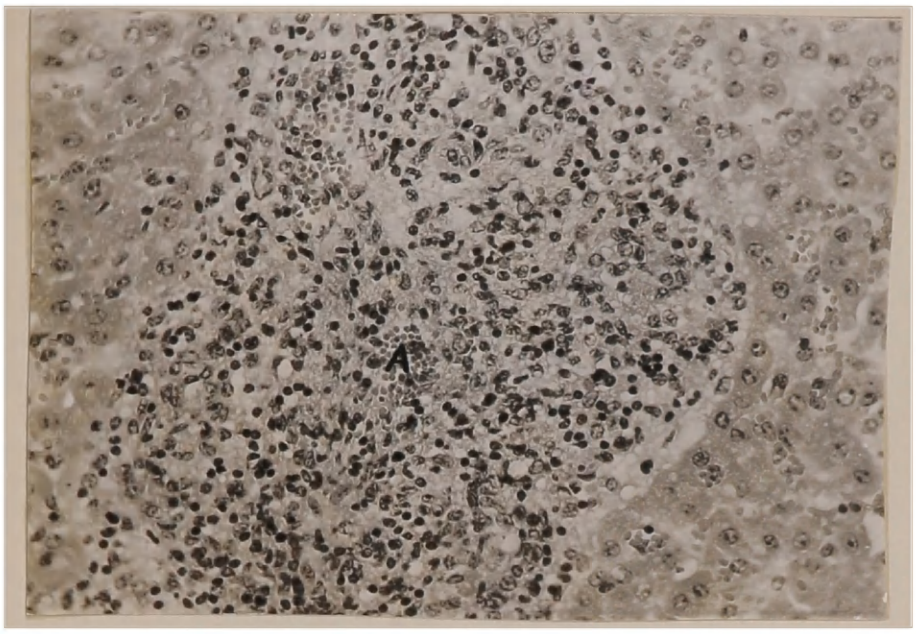

A
B
B
A

Fig. 16-Cell accumulation limited to portal area of the liver. Lumen of vessel with wall masked by cell collections (A). X250.

Fig. 17-Perivascular cuffing of vessel in medulla oblongata. X250.


A

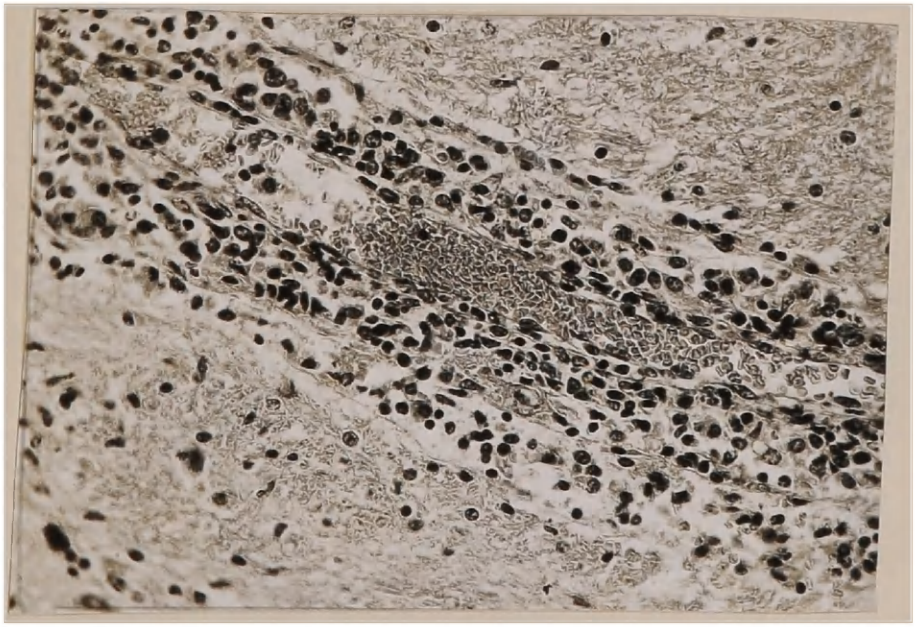
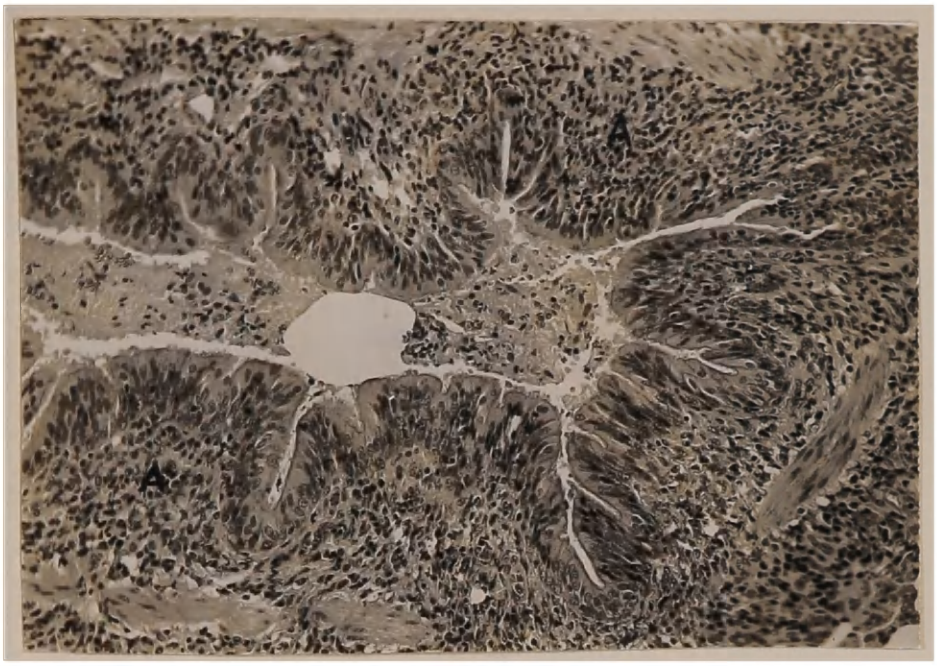


Fig. 18-Cell accumulations in the lamina propria of a bronchiole (A). X250.

Fig. 19-Lymph node showing reticulum cell hyperplasia (A) degeneration of connective tissue in a trabecula (B) and infiltration of a trabecula (C). X135.


A
A

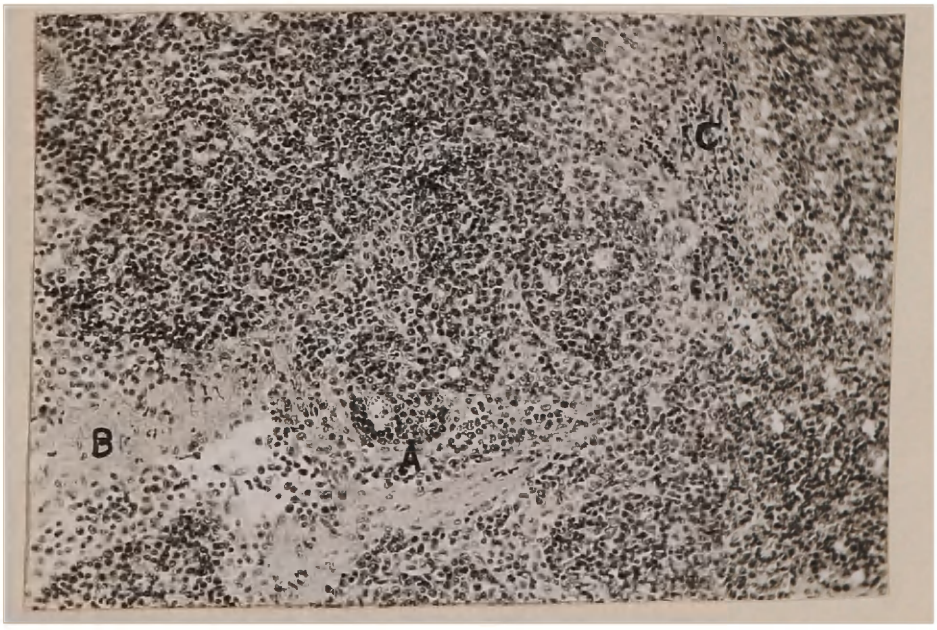
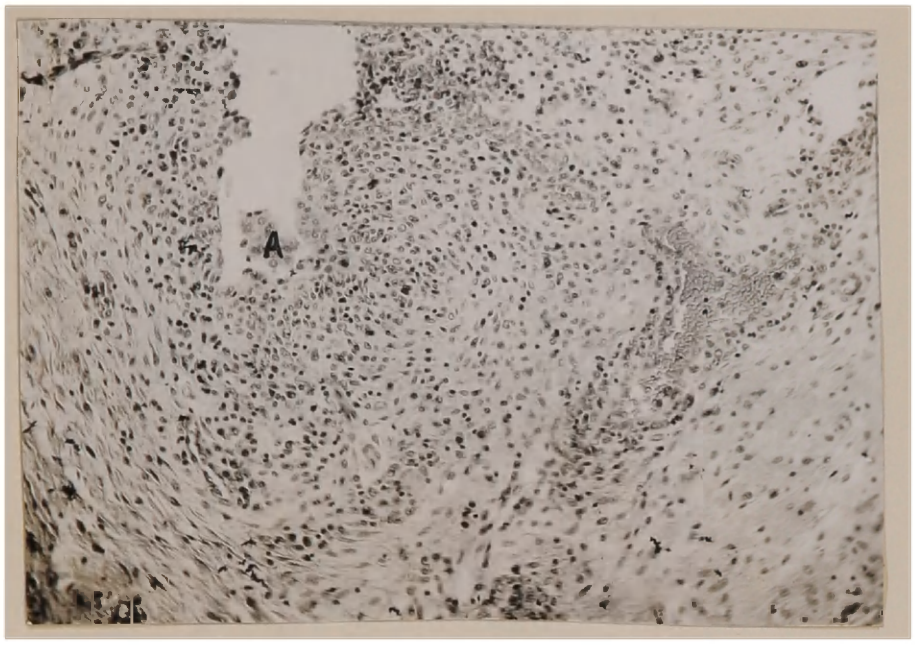

C
B
A

Fig. 20-Loss of transitional epithelium and cell accumulations in the lamina propria of the urinary bladder. Epithelial remnant (A). X135.

Fig. 21-Cell accumulations in lamina propria of the teat cistern (A) ballooning degeneration of epithelial cells lining the cistern (B) and reaction about a duct (C). X135.


A

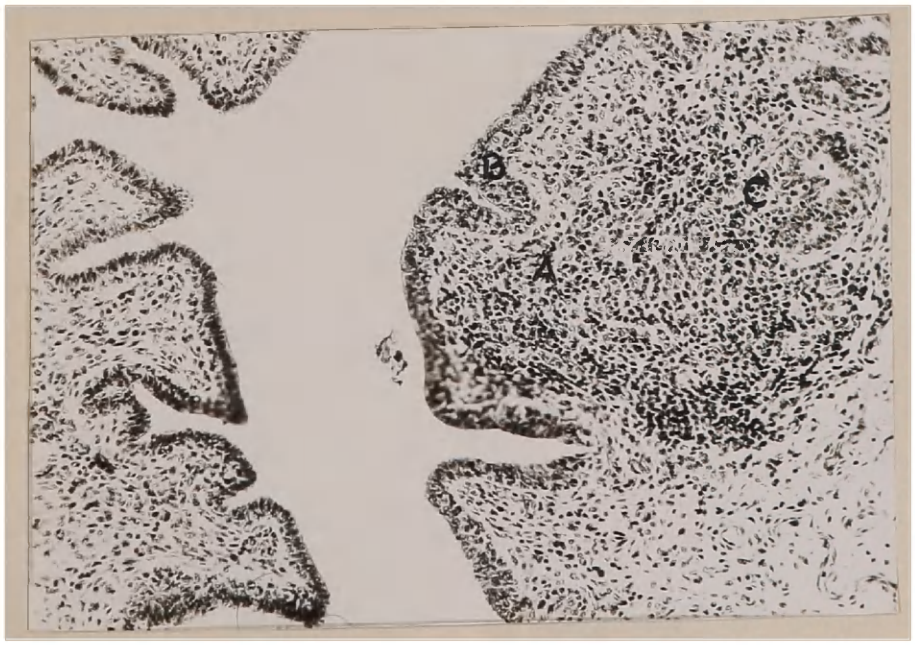

B
A
C

Fig. 22-Cell accumulations in the conjunctival lamina propria (A) and sclera (B) in the area of the corneoscleral junction of the eye. Note hyperplasia of the conjunctival epithelium (C). X135.

Fig. 23-Hyperplasia of follicular cells in the thyroid (A) and pyknotic cells in the lumens of the follicles (B). X250.


B
A
C

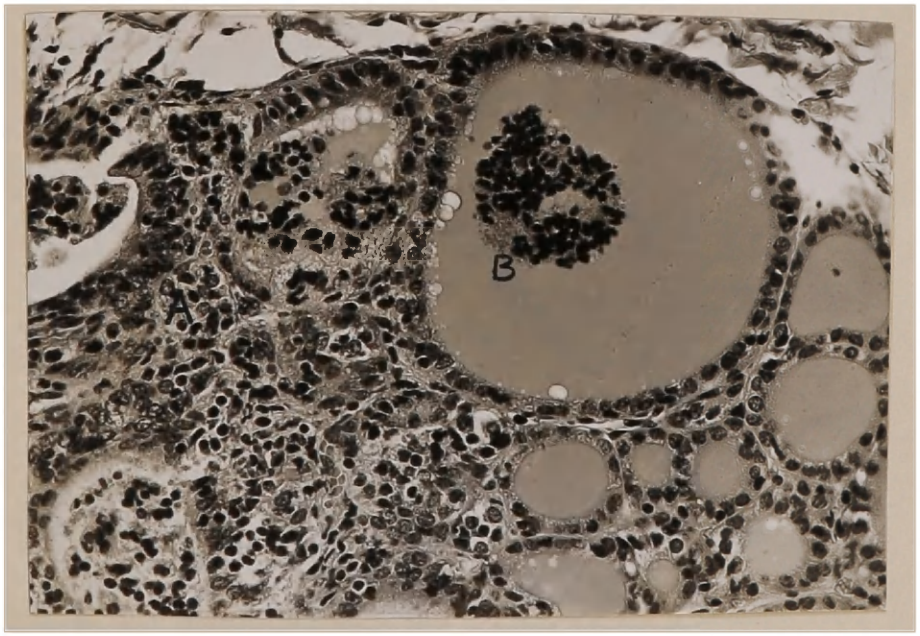
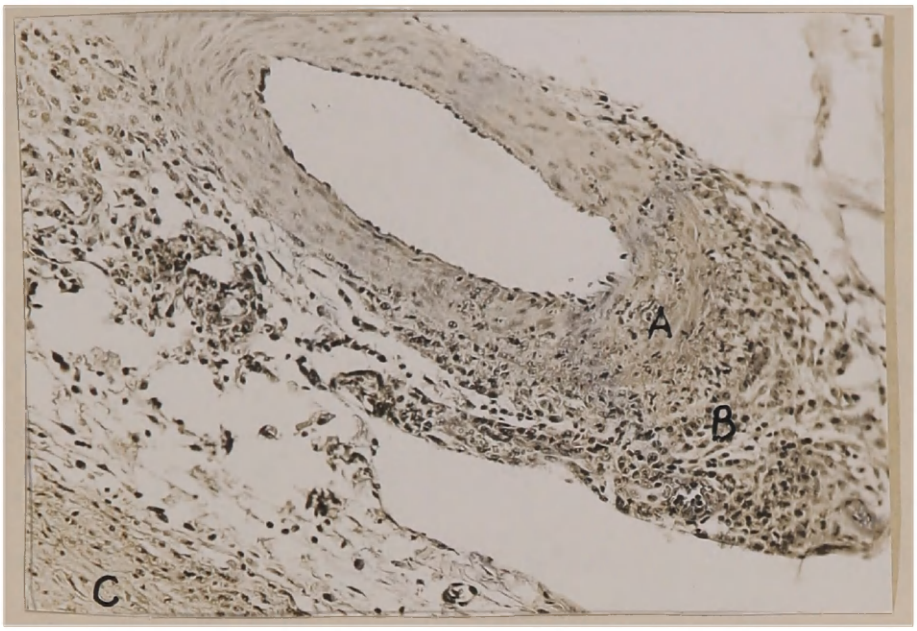

B
A

Fig. 24-Medial degeneration (A) and adventitial cell accumulations (B) in a periadrenal artery. Capsule of adrenal gland (C). X135.


A
B
C

# III. DIFFERENTIAL DIAGNOSIS

The recent attention to the syndromes composing the mucosal disease complex has indicated the need for means of differential diagnosis of the entities. Clinically, several of our cases of bovine malignant catarrhal fever have closely resembled mucosal disease as first described in Iowa. The increase in international traffic necessitates means of diagnosis of MCF from epitheliotropic diseases such as rinderpest and the vesicular diseases. Several diseases which have features in common with MCF are included in this discussion, although in most instances differential diagnosis should not be a problem.

## RINDERPEST

Although rinderpest is not present in the western hemisphere, the possibility of an outbreak is ever present. Thus, the need for distinguishing MCF from this disease is of importance, particularly since the lesions of the mucous membranes are very similar. In contrast to MCF, rinderpest has been described as a disease of easy transmissibility and high infectivity (Maurer, 1956). The presence of diarrhea which is frequently hemorrhagic, coughing and respiratory distress, and gastritis and enteritis which may cause abdominal tenderness are distinguishing clinical features from MCF.

Certain lesions described for rinderpest (Maurer, 1956; Smith and Jones, 1957) are of differential significance. A marked necrosis of lymphocytes is seen in the lymph nodes,

spleen, and Peyer's patches. These lesions are not found in MCF; rather, the lymphatic follicles may be hyperactive or may appear depleted of lymphocytes; hyperplasia of reticulum cells is often marked and proliferative and infiltrative vascular lesions (primarily lymphocytic and monocytic infiltrations and endothelial and adventitial proliferation) are usually present. In rinderpest the squamous epithelium contains sharply demarcated shallow erosions which are bounded by normal epithelium and do not penetrate the basal layer; vesicles are not found. In contrast, vascular lesions, aggregations of cells in the dermal papillae, hyperplasia of epithelial cells (including those of adnexal structures), and ballooning degeneration of cells in the rete pegs leading to vesiculation are regularly observed in MCF.

In rinderpest marked erosions and hemorrhages are commonly found in the abomasum and large intestine; they are less frequent and severe in the small intestine. Necrosis of Peyer's patches is a very prominent feature in rinderpest. Although hemorrhage and erosion are often found in the digestive tract (particularly the abomasum and large intestine) in MCF, the lesions are not as severe nor is the necrosis of Peyer's patches a prominent feature of this disease.

The constant portal accumulations of primarily lymphocytes and monocytes in the liver in MCF provide a diagnostic aid, since only chronic passive congestion is observed in rinderpest. The respiratory system is frequently involved in both diseases; however, the diphtheritic membrane found

in the nasal passages and trachea in MCF is not a feature of rinderpest. Hemorrhage and erosion are found in both diseases in the nasal passages and trachea. Whereas the lungs are involved only secondarily in rinderpest, primary vascular and bronchiolar lesions (mainly accumulations of lymphocytes and monocytes in the lamina propria) are found in many cases of MCF. Differential features may also be noted in the urinary system. Hemorrhage and erosion may occur in the bladder in both diseases; however, lymphocytic and monocytic cell accumulations and proliferation of fibroblasts in the lamina propria are seen in MCF. In addition, vascular lesions (proliferation of endothelial and adventitial cells and lymphocytic and monocytic cell infiltrations) which may involve the muscle layers are characteristic of MCF. Edema and, occasionally, desquamation of renal pelvic epithelium are described in rinderpest. In MCF vascular lesions and glomerular accumulations of lymphocytes and monocytes are seen in the kidney. Furthermore, vascular lesions are variably present in many other organs in MCF. The perivascular cuffing in the brain in MCF is of diagnostic importance; brain lesions are not described in rinderpest.

## MUCOSAL DISEASE (IOWA TYPE)

Mucosal disease, the syndrome first described by Ramsey and Chivers (1953) in Iowa, has many features in common with MCF and clinical differentiation of the two diseases may be difficult in some cases.

A history of association with sheep may be of diagnostic

importance since, in our experience, this has always been the case in MCF. The morbidity is greater in mucosal disease; in our cases, rarely more than one animal was stricken at a time. In addition, MCF often has an enzootic aspect in that it tends to recur with varying intervals between cases on the same farm. Bilateral corneal opacity, which spreads from the peripheral area of the cornea, was a characteristic finding in MCF, whereas corneal opacity has not been observed in our cases of mucosal disease. Corneal opacity occasionally occurs in mucosal disease but it originates centrally rather than peripherally as in MCF (Ramsey, 1956). A temperature elevation to 106 F. was characteristic of MCF; in mucosal disease the temperature is elevated little if at all. Skin lesions observed in MCF (reddening, papulation, and scabbing) have not been noted in mucosal disease. Lesions of the feet were not evident grossly in MCF, although microscopic lesions were found; in mucosal disease, lameness and marked interdigital ulcerations are common. Diarrhea, often bloody, which is a common feature in mucosal disease, was not a feature of MCF. Although viciousness and hyperexcitability in MCF have been described, a profound lethargic state was almost always present in our cases from the onset of the disease. Animals with mucosal disease are usually bright and active until 1-2 days before death.

There are some gross post-mortem findings which may be of diagnostic value. A yellowish diphtheritic membrane is usually present in the nasal passages, trachea, and pharynx

in MCF. The large well-demarcated ulcers (up to 5 cm. in diameter) with yellow borders seen in some cases of mucosal disease were not found in MCF; but, rather the erosions were irregular and not sharply demarcated. Erosions which were scattered the entire length of the esophagus were common in mucosal disease but were not common nor as marked in MCF. Lesions of the upper digestive tract were not significantly dissimilar. The marked hemorrhage, necrosis of Peyer's patches, and cystic lesions in the lower digestive tract, which were common in mucosal disease, were not found in MCF. Hemorrhage and erosion were occasionally observed in the large intestine, but were not as severe as the marked lesions often found in mucosal disease.

No macroscopic lesions occur in the urogenital system in mucosal diseas, whereas, in MCF diffuse hemorrhage and loss of epithelium in the bladder are found in many cases.

Histopathologic examination is of great value in differentiating the two disease. Probably the most important differential features are the marked proliferative and infiltrative lesions involving the vessels in the brain and the accumulations of lymphocytes and monocytes in the periportal areas of the liver in MCF. The vascular lesions may be found variably in several other organs in MCF; however, since Ramsey(1956) has reported a necrosis and monoclear cell infiltration of vessels in mucosal disease, care must be taken in interpreting such lesions. It appears that the vascular lesions are much more widely distributed and prominent in MCF.

Also, necrosis in the media is not as marked in MCF, but rather there is a proliferation of the adventitia and, often, endothelial and medial cell accumulations are found.

In mucosal disease a decrease in monoclear cells and sometimes coagulation necrosis in the lymph nodes have been reported (Ramsey, 1956); reticulo-endothelial proliferation and sometimes hyperactive lymphatic follicles are observed in MCF.

The capsular accumulations of monocytes and lymphocytes around the glomeruli of the kidneys in MCF may be of value. Possible aid may be found in the slight or absent inflammatory infiltration of the lamina propria of the oral epithelium in mucosal disease (Ramsey, 1956); marked accumulations of cells are found in the dermal papillae in MCF. The stratified squamous epithelia in mucosal disease undergo a focal necrosis; in MCF proliferation of epithelial structures and ballooning degeneration leading to vesicle formation are seen. Necrosis and crypt abcesses which occur in the digestive tract in mucosal disease are not seen in MCF. Secondary complications are rare in MCF and rather common in mucosal disease.

Rooney (1957) described a mucosal disease in Virginia very similar to the syndrome described in Iowa except that morbidity approached 100 percent. Ballooning degeneration of stratified squamous epithelia was observed.

## VIRUS DIARRHEA

Olafson *et al.* (1946), Olafson and Rickard (1947) and Baker *et al.* (1954) have described virus diarrhea in New

York as characterized by easy transmissibility , high morbidity, and low mortality. These features are opposite to the difficult transmissibility, low morbidity, and high mortality observed in MCF. The principal gross lesions of virus diarrhea are erosions of the muzzle, oral cavity, esophagus, abomasum, and cecum. Hemorrhages may be found in the omasum, abomasum, small intestine, cecum, subcutaneous tissues, epicardium, and vagina. It appears that the major lesions are limited to the digestive tract in virus diarrhea whereas they are widely distributed in MCF. Corneal opacity and skin lesions (papulation, reddening, and scabbing), commonly observed in MCF, are not features of virus diarrhea. Clinically, the rarity of diarrhea in MCF is important.

Virus diarrhea (Indiana), described by Pritchard et al. (1956) and Carlson et al. (1957), appears to be very similar to the disease described in New York, although immunologically different. Carlson et al. (1957) described the pathology of the disease in Indiana. The histopathological comparison of lesions in the squamous epithelia is indeed interesting. In virus diarrhea, sharply defined areas of necrosis and vacuolation of the epithelium and mild cellular infiltration of polymorphonuclear leucocytes in the papillae occur. This contrasts to the marked cellular accumulations of lymphocytes, monocytes, fibroblasts, and proliferating capillary endothelial cells in the papillae and hyperplasia and ballooning degeneration (which may lead to vesiculation) in the epithelium in MCF. The wide distribution of lesions in MCF should rule

York as characterized by easy transmissibility , high morbidity, and low mortality. These features are opposite to the difficult transmissibility, low morbidity, and high mortality observed in MCF. The principal gross lesions of virus diarrhea are erosions of the muzzle, oral cavity, esophagus, abomasum, and cecum. Hemorrhages may be found in the omasum, abomasum, small intestine, cecum, subcutaneous tissues, epicardium, and vagina. It appears that the major lesions are limited to the digestive tract in virus diarrhea whereas they are widely distributed in MCF. Corneal opacity and skin lesions (papulation, reddening, and scabbing), commonly observed in MCF, are not features of virus diarrhea. Clinically, the rarity of diarrhea in MCF is important.

Virus diarrhea (Indiana), described by Pritchard et al. (1956) and Carlson et al. (1957), appears to be very similar to the disease described in New York, although immunologically different. Carlson et al. (1957) described the pathology of the disease in Indiana. The histopathological comparison of lesions in the squamous epithelia is indeed interesting. In virus diarrhea, sharply defined areas of necrosis and vacuolation of the epithelium and mild cellular infiltration of polymorphonuclear leucocytes in the papillae occur. This contrasts to the marked cellular accumulations of lymphocytes, monocytes, fibroblasts, and proliferating capillary endothelial cells in the papillae and hyperplasia and ballooning degeneration (which may lead to vesiculation) in the epithelium in MCF. The wide distribution of lesions in MCF should rule

erosion in the forestomachs and large intestine, and, occasionally, hemorrhage and erosion in the bladder. Since one or more of these features may be absent in any given case, histopathological examination may be of value. Lesions of affected mucosae in IBR are characterized by a surface accumulation of exudate with or without erosion of the epithelium. The submucosa is edematous and infiltrated with polymorphonuclear leucocytes, lymphocytes, and monoclear phagocytes. Hyperemia and hemorrhage are common. Lesions of the nasal passages in MCF are somewhat similar. In contrast to IBR, lesions of the stratified squamous epithelia in MCF consist of proliferation of epithelial cells, dense subepithelial cell accumulations (not containing polymorphonuclear leucocytes) in the dermal papillae and perivascular areas, and ballooning degeneration and vesicle formation of the epithelium followed by erosion. Elsewhere, the constant portal lesions in the liver, perivascular cell accumulations in the brain, and irregularly distributed vascular lesions found in MCF should make a definite differentiation possible.

HYPERKERATOSIS

Olafson et al. (1947) has described hyperkeratosis or X-disease as a chronic disease characterized by depression, emaciation, anorexia, and a thick, dry, wrinkled skin. Pathologic changes observed were papillary proliferation and fibrosis of small bile ducts, thickening of the intestinal mucosa, and cystic dilatation of the renal tubules. The skin lesions are due to hyperkeratosis. Gibbons (1949)

described an acute form characterized by ulcerative stomatitis. Salivation, lacrimation or mucopurulent ocular discharge were present. Morrill and Link (1950) reported that animals may die without showing skin lesions and yet be affected internally. It was further reported that ulcerative lesions may occur in the mouth, esophagus, and true stomach. Nephritis may be a feature of hyperkeratosis. The skin lesions observed in MCF consist of scabbing and erythema in many external areas. Diffuse thickening of the integument was not observed in MCF. Cases of the "head-and-eye" form should not present a diagnostic problem. The temperature elevation (106 F.) is characteristic of MCF; temperature elevation is not a feature of hyperkeratosis. Hemorrhage, congestion, and ulcerations in the forestomachs and large intestine are suggestive of MCF. Erosions and hemorrhage in the bladder and enlarged hemorrhagic lymph nodes, which may be found in MCF, have not been observed in hyperkeratosis. Microscopically, there are no similarities between the two diseases. Epithelial hyperplasia in the renal tubules and columnar epithelial structures in the digestive tract and squamous metaplasia in the genital organs have been described as features of hyperkeratosis (Olafson et al., 1947; Gibbons, 1949; Morrill and Link, 1950; Smith and Jones, 1957), but have not been observed in MCF.

## FOOT AND MOUTH DISEASE

Foot and mouth disease (FMD) is an ever present threat in this country. Since there are certain points of similarity

between FMD and MCF which may cause confusion, it is well to consider the differential features. Clinically, FMD is an epizootic disease; MCF is enzootic. In cattle, the vesicular lesions of FMD have a characteristic distribution over the lips, dorsum of the tongue, palate, coronary band, vulva, teat, conjunctiva, and forestomachs (Smith and Jones, 1957). Although microscopic vesicles have been observed frequently in MCF, macroscopic vesicles have not been observed in any of our cases. It is interesting to note that in both diseases the vesicles originate from ballooning cells in the epithelium. The oral cavity usually shows a widespread necrosis rather than a characteristic distribution as in FMD. Histopathologically, the accumulation of cells about the blood vessels and in the dermal papillae in MCF would seem to be a differential feature. Evidence of proliferation of squamous epithelium and epithelial cells of adnexal structures may be noted in MCF. The intestinal tract may be involved in both diseases; however, in FMD the lesions consist of punctate hemorrhages and edema in the abomasum and small intestine, whereas in MCF erosions may also be found.

The hyaline degeneration and necrosis of cardiac muscle along with infiltrations of lymphocytes and, occasionally, neutrophiles described in FMD are not found in MCF; rather, vascular proliferative and infiltrative lesions are observed. Necrosis is also found in the skeletal muscles in FMD; again, in MCF occasional vascular lesions are found but necrosis of muscle fibers is not observed. Additional differential aids

in MCF are the regularly observed vascular lesions in the brain and periportal cell accumulations in the liver; the lamina propria and vasculature of many other organs are more variably affected by proliferative and infiltrative processes.

## VESICULAR STOMATITIS

Vesicular stomatitis (VS), another of the epitheliotropic diseases, may resemble MCF. The epizootic nature and low mortality of vesicular stomatitis are contrasted to the enzootic occurrence and high mortality of MCF. The nasal and ocular discharge and corneal opacity, common in MCF, are not seen in VS. As with foot-and-mouth disease, vesicles are observed in VS of cattle but are of short duration; they quickly rupture leaving denuded areas (Chow et al.,1951). In contrast to MCF, the vesicles arise primarily by a process of spongiosis rather than ballooning degeneration. Differentiation of these two disease should not be a problem due to the systemic distribution of lesions in MCF. Skin lesions in themselves may be of differential diagnostic value since in MCF there may be proliferation of epithelial cells in the skin and adnexae as well as prominent cellular accumulations in the dermal papillae and around the blood vessels.

## LISTERIOSIS

The differential diagnosis of those diseases in which encephalitis is feature will be considered next. Of the common symptoms of listeriosis (Gray, 1954), pushing against objects, circling, incoordination, torticollis and uncontrolled running motions have not been observed in MCF. On the other

hand, the following lesions commonly observed in MCF are not features of listeriosis; bilateral corneal opacity, skin lesions, reddening and erosion of muzzle, reddening of the udder and vulva, and papules, particularly of the neck and udder. Few gross lesions are observed in listeriosis on post-mortem examination. Occasionally, there may be slight clouding of the meninges or pin-point grayish white foci in the brain; rarely, fatty liver, duodenitis, and pulmonary edema are seen. In contrast to this, one often finds marked lesions involving several systems. Commonly, the digestive, reproductive, respiratory, urinary, and lymphatic systems are involved macroscopically, Microscopically, the brain lesions of listeriosis are characterized by perivascular cuffing with lymphocytes and monocytes and areas of focal necrosis containing also a few heterophiles; in some instances these foci border on or actually show early suppuration. The brain lesions in listeriosis tend to be confined to the brain stem; in MCF they are generalized. One cannot always differentiate the vascular lesions in the brain in MCF from listeriosis with certainty; neither focal necrosis nor focal suppuration, however, have been observed in MCF. The pantropic distribution of lesions in MCF coupled with perivascular brain lesions appears to be a solid basis for diagnosis. Particularly valuable are the constant periportal cell accumulation and the less constantly found lesions in the lymph nodes, adrenal glands, kidneys, and stratified epithelia.

## SPORADIC BOVINE ENCEPHALOMYELITIS

Sporadic bovine encephalitis (SBE) bears many similarities to MCF. McNutt and Waller (1940), Menges et al. (1953), and Harshfield (1957) have described SBE. In both diseases temperature elevation, marked depression, discharge from the nose and eyes, and course (1-3 weeks) may cause confusion. Of course, a typical case of MCF with corneal opacity and muzzle, oral and skin lesions should not present a problem. Even in the less obvious cases of MCF, scattered erosions, congestion and hemorrhage in the digestive tract, and erosions and hemorrhage in the bladder are of diagnostic assistance. Fibrinous pleuritis, peritonitis, pericarditis, and epicarditis are commonly observed in SBE and not in MCF. The mortality rate in SBE varies from 40 to 70 percent whereas it approaches 100 percent in MCF. Enlarged edematous lymph nodes are described for SBE by McNutt and Waller (1940) and Harshfield (1957); similar lesions are observed in MCF. Microscopically, the serosal inflammation in SBE consists of infiltration of mononuclear cells, occasional neutrophiles, and eosinophiles; fibroblastic and endothelial proliferation are also observed. McNutt and Waller (1940) reported that the liver and kidney sometimes contain monocytic foci; Harshfield (1957) described liver and kidney lesions in which lymphocytes predominated. In MCF, cell accumulations were commonly around the glomeruli and vessels of the kidney (mainly lymphocytes and monocytes); liver lesions were confined to the portal trinity rather than being located in the parenchyma as in SBE. In either

case, the vascular involvement in the liver and kidneys would seem to be of diagnostic value in MCF. McNutt and Waller (1940) described the microscopic brain lesions in SBE as primarily perivascular monocytic cuffing, focal areas of monocytic infiltration, and some areas of liquifaction necrosis. Menges et al. (1953) and Harshfield (1957) reported additionally that the cuffing cells were occasionally polymorphonuclear leucocytes and that the endothelium showed proliferative changes. In MCF the cuffing cells were predominatly lymphocytes and monocytes. Focal areas of monocytic infiltration and necrosis were not features of MCF. Important histopathological differential features of MCF are the proliferative and infiltrative lesions involving blood vessels, which are distributed variably throughout the body, and also the proliferative and infiltrative lesions of squamous epithelium; in some cases ballooning degeneration and vesicle formation may be noted (grossly normal epithelium may show these microscopic features). Demonstration of the elementary bodies in the brain and serosal exudates in SBE is, of course, of value.

## RABIES

A situation might arise wherein the differentiation of MCF and rabies is necessary (e.g. where the head alone is submitted for examination or an atypical case of MCF is presented). Certainly, nervous symptoms may be evident in both diseases. Smith and Jones (1957) state that the lesions of rabies are microscopic and limited to the central nervous

system. Lesions of MCF usually involve several systems. In the event that only the head were available microscopic lesions in the oral cavity and muzzle may be found even though gross lesions are not recognized. The microscopic lesions of rabies in the central nervous system are described as varying from early necrosis of neurons to a diffuse encephalitis consisting of perivascular cuffing, neuronophagic nodules, and other indications of destruction of neurons. Acidophilic intracytoplasmic inclusion bodies in the neurons are considered pathognomonic of rabies. The changes are most prominent in the brain stem, hippocampus and Gasserian ganglia. In MCF, marked and diffusely distributed perivascular lesions with little evidence of neuron destruction are the prominent findings. The formation of "Babes nodules" in the Gasserian ganglion — a replacement of the nerve cells by nodules of proliferating cells — was described by Lapi et al. (1954). The most prominent changes were a marked proliferation of capsular cells and, in some cases, mild infiltration of lymphocytes and plasma cells in rabies. Examination of sections of Gasserian ganglia in cases of MCF indicated that, in some cases, proliferation and infiltration involving the blood vessels occurs; however, the profuse proliferation of capsular cells forming cellular nodules as in rabies was not a feature. In most instances, the history, clinical findings, and systemic distribution of the lesions in MCF should constitute an adequate basis for diagnosis.

## LEPTOSPIROSIS

Inasmuch as the presence of Leptospira catarrhalis has been reported in the digestive tract of animals affected with MCF (Götze, 1940) and in view of the fact that certain lesions of leptospirosis resemble lesions found in MCF, it is well to consider the diagnostic features of these two diseases. The clinical picture of leptospirosis may vary greatly. The principal symptoms of bovine leptospirosis are listed as fever, anorexia, depression, diarrhea, anemia, icterus, hemoglobinemia, hemoglobinuria, oligogalactia or agalactia, emaciation, and abortion (Reinhard, 1951; Reinhard and Hadlow, 1954). Of these, diarrhea, anemia, icterus, hemoglobinemia, hemoglobinuria, and fatal abortions are not features of MCF although hematuria, probably due to hemorrhage in the bladder, is not uncommonly observed. The pathology of acute hemolytic leptospirosis includes; icterus, subepithelial, submucosal, and subserosal hemorrhages, and enlarged spleen (Reinhard, 1951; Reinhard and Hadlow, 1954). Generally, the liver is discolored and the kidneys present a mottled or white spotted appearance-apparently very similar to lesions observed in Africa in cases of MCF.

Histopathological features of leptospirosis have been described by several authors (Jungherr, 1944; Mathews, 1946; Ungar and Bernkopf, 1947; Baker and Little, 1948; Reinhard, 1951; Cordy and Jasper, 1952; Reinhard and Hadlow, 1954; Hadlow and Stoenner, 1955). Changes in the liver include necrosis and hemorrhage, infiltration with neutrophiles

and mononuclear cells, hepatic cord disorganization, cholangitis, and distention of Kupffer cells with blood pigment. Lesions described for the kidney included tubular necrosis, lymphoid and mononuclear cell infiltration, foci of tubular hypertrophy, albuminous degeneration, pigmentation of the renal tubular epithelium, syncytial aggregates of eosinophilic cells, proliferating tubular cells, and multinucleated giant cells. Mucosal hemorrhage, necrosis, and ulcer formation were found in the abomasum. Splenic hemosiderosis was sometimes a prominent feature. As differential features found in MCF, one may therefore cite the constant vascular lesions in the brain which were more variably distributed in other organs, collections of lymphocytes and monocytes and bile duct proliferation limited to the portal area of the liver, epithelial proliferation, ballooning degeneration and vesicle formation in the squamous epithelium, and the cellular accumulations in the lamina propria of many organs. It is evident that macroscopic differentiation would not be a problem in the typical "head-and-eye" form. Skin lesions found in some cases of MCF are of diagnostic value. Although culture and demonstration of the leptospiras may be utilized, differentiation may well be made on clinical, historical, and pathological features.

## INFECTIOUS KERATO-CONJUNCTIVITIS (PINK-EYE)

Inasmuch as the eye lesions observed in MCF are very similar to those in infectious kerato-conjunctivitis, it is well to consider a few features of diagnostic importance.

Clinically, MCF has a high mortality and a low morbidity in contrast to "pink-eye". The eye lesions in "pink-eye" may be unilateral which is not true of MCF. Signs such as epidermal involvement, oral erosions, and temperature elevation to about 106 F. should aid in eliminating the former. On post-mortem examination indications of systemic involvement will rule out infectious kerato-conjunctivitis.

## SUMMARY AND CONCLUSIONS

The epizootiologic, clinical, and pathologic features of MCF, as observed in this study, are singular enough to make possible a differential diagnosis from rinderpest, diseases of the mucosal disease complex, the vesicular diseases, listeriosis, sporadic bovine encephalomyelitis, rabies, leptospirosis, and infectious kerato-conjunctivitis. The pathological features are particularly characteristic, if not unique, in nature and distribution. An important diagnostic combination of microscopic lesions which are constantly found are the cellular accumulations around the portal trinity of the liver and the perivascular cuffing with lymphocytes and monocytes in the brain; other diagnostically important lesions are the epithelial hyperplasia of the epidermis and adnexae, ballooning degeneration and vesiculation of the squamous epithelia, proliferative and infiltrative lesions in the lamina propria of several organs, and the vascular lesions variably distributed throughout the body.

## IV. COMPARISON WITH SIMILAR SYNDROMES IN OTHER COUNTRIES

There has been much controversy as to the identity of "snotsiekte", as described in the Union of South Africa, and MCF as reported by other investigators. We should like to examine the work dealing with snotsiekte as well as the reports of researchers in other countries who have investigated MCF in order to establish, if possible, the relationship of these syndromes with MCF as observed in our studies.

### UNION OF SOUTH AFRICA

Mettam (1923) described a disease of cattle in S. Africa which he called "snotsiekte", as "an acute specific infectious disease of cattle caused by an ultramicroscopic but non-filterable organism and characterized by a general hyperplasia of lymphoid tissue throughout the body, less frequently by inflammation, erosion, and necrosis of the various mucosa." He believed that snotsiekte and MCF were separate entities and made the following distinctions; (1) MCF occurs sporadically, (2) there is an absence of marked lymphatic changes in MCF, (3) the horns often fall off in MCF, (4) there is a vesicular or papular exanthema in MCF and, (5) snotsiekte can be reproduced after a 2-5 week incubation period. That MCF occurs only sporadically and often enzootically is born out by our experience. Mettam described the marked lymphatic changes as a generalized enlargement of the lymph nodes up to the size of a clenched fist; the nodes were creamy-pink to a diffuse port wine color; cortical elevations up to 1.6 cm.

in diameter were present. Mettam believed these changes to be pathognomonic. Histologically, the germinal centers were overcrowded with lymphocytes. We observed changes somewhat similar to those described by Mettam except that they were not as marked. The nodes exhibited mild to moderate swelling; no cortical elevations were noted. Microscopically, hyperactive follicles were observed in some cases; in other instances, the nodes were deficient in lymphocytes. Marked reticulum cell hyperplasia was often evident in our cases.

Grossly, skin lesions were commonly observed in our cases whereas Mettam did not observe such lesions. Microscopically, Mettam described colonies of small lymphocytes in the dermis and around blood vessels in the epithelium. The cellular accumulations were of a more varied composition in our cases and proliferation of epithelial cells was very prominent in early lesions; in addition, vesicles were observed in the squamous epithelia. However, since Mettam may have observed only the more advanced cases, proliferation and vesiculation may not have been present due to necrosis and sloughing of the epithelium.

Lesions in the oral cavity and digestive tract in snotsiekte were grossly similar to those observed in MCF. Microscopically, activation of lymphoid elements was stressed by Mettam. In our cases, the lesions were related to vascular structures and consisted of cell accumulations which were primarily lymphocytes and monocytes; in addition, endothelial and adventitial proliferation were often present.

Grossly, the lungs in the cases of snotsiekte displayed numerous grayish dots which, microscopically, proved to be lymphocytic foci around the vessels and near the bronchial cartilages. Gross lesions were not prominent in our cases, but, microscopically, proliferative and infiltrative lesions were found in the lamina propria of the bronchial mucosa and involving the blood vessels.

Mettam described pinkish-white granules in a few cases in the heart which, microscopically, proved to be colonies of small lymphocytes most noticeable near the capillaries. No gross lesions were found in our cases, but, in some cases, lymphocytic and monocytic cell accumulations involving the blood vessels were noted microscopically.

In the S. African cases the pancreas presented a pink granular appearance; microscopically, the interstitial connective tissue contained lymphocytic foci. No gross lesions were observed in our cases; however, mild hyperplasia of the duct epithelium and underlying tissue and activation of capillary endothelial cells were occasionally observed.

The liver was severely affected in every case according to Mettam. This organ was described, grossly, as greatly enlarged, deeply bronzed or yellow, and containing soft putty-colored areas. A pink granular or mottled appearance was listed as a pronounced feature. Microscopic examination revealed numerous colonies of lymphocytes in the connective tissue of the portal system which, in some instances, covered the whole microscopic field and pushed between the hepatic

cells. The description differs somewhat from changes found in our cases inasmuch as, macroscopically, the liver showed only parenchymatous changes. Microscopically, sections in our cases contained cell accumulations limited to the periportal spaces. This hypercellular mass was composed of mainly monocytes and lymphocytes although eosinophiles were sometimes prominent. Hyperplasia of biliary epithelium was not infrequently observed.

In the spleen, Mettam observed "split pea size" Malpighian bodies which, again, proved to be dense accumulations of lymphocytes. Small colonies of lymphocytes were found near the blood vessels of the trabeculae and capsule. Large numbers of Unna's plasma cells and polymorphonuclear leucocytes were present. In our cases, this marked lymphocytic activity was not observed; occasionally, the capsule and trabeculae were infiltrated with lymphocytes and monocytes.

Mettam described lesions in the kidney which were at variance with our findings. He stated that the capsule stripped with difficulty; the surface was mottled with soft yellow areas and numerous white foci up to 3 mm. in diameter. Histologically, compressed strips of kidney tissue were found between lymphocytic foci which sometimes covered the whole microscopic field. Lymphoid cells and many plasma cells were found in the capsule. In our cases, such gross lesions were not observed. Microscopically, cellular accumulations of lymphocytes and monocytes were found infiltrating and surrounding the blood vessels and glomerular capsules.

The lesions were not as widespread or severe as those described by Mettam.

Mettam noted that the urinary bladder was often swollen and deep red; in some cases small erosions were found. The ureters were normal. Microscopic lesions were not reported. Marked thickening and diffuse hemorrhagic inflammation of the bladder were frequently observed in our cases. The entire walls of the bladder and of the ureters were often edematous and contained cell accumulations composed of lymphocytes, plasma cells, macrophages, and eosinophiles; fibroblasts were increased in number.

Mettam described the sexual organs as deep red in color with small pinkish areas which, microscopically, were foci of lymphocytes. He also reported erosions of the mucosa of the sheath of the male and the floor of the vulva of the female. Reddening and occasional erosions were observed in the external female genitalia in our cases. Microscopically, we observed infiltrating cell accumulations primarily of monocytes and lymphocytes and proliferation of adventitial and endothelial cells in blood vessels in the sexual organs of both sexes.

Mettam described perivascular cuffing with lymphocytes in the brain. Cell accumulations affecting the blood vessels in the brain were composed primarily of lymphocytes and monocytes in our cases.

Bilateral corneal opacity was reported by Mettam. Microscopically, he found an increase of small lymphocytes in

the substantia propria. In our cases corneal opacity was common. Again, we found a more varied collection of cells, which were primarily lymphocytes and monocytes, although significant numbers of eosinophiles and plasma cells were present. Connective tissue cells were increased in number. Lesions in our cases involved the eyelids, conjunctiva, cornea, lamina propria, sclera, iris, ciliary bodies, and optic nerve. Lesions were often prominent about blood vessels.

In summary, we may say that the distribution of lesions is similar in the disease as described in both countries. There do appear to be some macroscopic variations such as the mottling of the liver and kidneys and the marked lymphatic activity which are features of snotsiekte.

Microscopically, the cell accumulations found in MCF are more varied. Mettam stated that "the foci are mostly formed of cells which are analogous to the small lymphocytes of the blood. Rarely are found neutrophile leucocytes, monocytes, large lymphocytes and plasma cells." The marked cell pleomorphism encountered in our cases was not mentioned in Mettam's work.

KENYA

Daubney and Hudson (1936), workers in Kenya, described a disease which they called bovine malignant catarrh. Their description closely parallels Mettam's description of snotsiekte. In many of the cases reported, there was no possibility of contact between the affected cattle and wildebeest — which had occurred in Mettam's cases. In transmission studies, they

found that the transmissibility varied greatly between isolates which helps to reconcile the conflicting results which have been obtained in the transmission studies of other workers.

Grossly, the intestinal tract did not show any great variation from the lesions found in our cases. Microscopic findings in the intestine were not reported. An almost constant finding was a mottling of the liver which, microscopically, proved to be collections primarily of lymphocytes distributed perivascularly in the portal canal. The kidneys always were mottled with large white or yellow infarcts. Large collections of lymphocytes were observed. The gross lesions in the liver observed by these workers were not seen in our cases. White focal areas were observed in the kidney in one of our cases. Microscopically, we observed collections of lymphocytes and monocytes constantly in the periportal areas of the liver and more variably around the blood vessels and glomerular capsules in the kidneys.

The urinary bladder in the E. African cases was described as intensely hemorrhagic, the hemorrhages varying from petechiae to extensive extravasations. These lesions closely resembled those observed in our cases. No microscopic findings were reported. Grossly, the macroscopic changes in the respiratory system described in Kenya were very similar to those observed in our cases. Daubney and Hudson did not report on the microscopic findings.

Daubney and Hudson reemphasized the marked enlargement of the lymph nodes observed by Mettam. In addition to congestion

and hemorrhage, protuberant lymphatic follicles were described. This marked lymphocytic activity was not a feature of our cases; in some cases moderate activity was present and in others, lymphocytic exhaustion occurred. The marked reticuloendothelial activity observed in most of our cases was not described by Daubney and Hudson. Observations of follicular enlargement in the spleen were also reported, which, again, were not observed in our cases.

These workers summarized the histological findings as a perivascular infiltration of all organs with lymphocytes and marked production of small lymphocytes in the lymph nodes. No proliferative lesions of vascular or epithelial structures as found in our cases were mentioned.

Plowright (1953) described the pathology of MCF in Kenya also. He reported a rapid depletion of small lymphocytes from the spleen, lymphatic glands, and, possibly, the intestinal lymphatic tissue. Also present was an intense stimulation to proliferative activity of lymphocytogenous elements; reticulum cells of the hemapoietic system and primitive cells throughout the body formed lymphocytes and intermediate cells which were difficult to classify. The predominantly perivascular distribution of lesions outside the lymphatic tissue was attributed to the occurrence of undifferentiated cells in these areas. Plowright further described dense mononuclear cell infiltrations of blood vessels; this stands in contrast to the observations of Mettam who stated that "rarely are found neutrophile leucocytes, monocytes, large lymphocytes,

and plasma cells." Skin lesions, which were frequently encountered in our cases, were never encountered in the Kenya cases. The parenchymatous organs contained lymphocytic and macrophage accumulations. Gross lesions were not described in the liver. Vesicular foci with hemorrhagic borders were observed in the kidneys. In our cases, prominent liver lesions were not observed macroscopically, White focal areas were found in the kidneys in one of our cases.

Plowright observed degeneration, diffuse necrosis, and macrophage infiltrations in the adrenal glands. We found predominantly vascular lesions most evident in the capsule but also observed in the periadrenal and parenchymal tissue. The adjacent tissues were often disrupted by accumulations of predominantly lymphocytes and monocytes. Plowright reported that destruction of connective tissue and smooth muscle was observed not only in the blood vessels, but also in the capsule and trabeculae of the spleen and lymph nodes, in loose subepithelial connective tissues, in the meninges, and in the smooth muscle of the wall of hollow viscera. This process followed a heavy infiltration of lymphocytes. Very similar disruption and destruction of connective tissue and smooth muscle occurred occurred in our cases.

Plowright reported subepithelial and perivascular lymphoid cell accumulations in the surface epithelia. In our cases, more varied cell accumulations were observed although lymphocytes were often plentiful.

Meningoencephalitis was common in the cases observed

by Plowright; the microscopic lesions were primarily vascular and perivascular. He observed mononuclear cell infiltration of the choroid plexus in rabbits; we observed similar lesions in field cases in cattle. Meningoencephalitis was present in all of our cases.

EUROPE

Many European worker have described the pathology of MCF. Ackerman (1922) reported proliferation, necrosis, and vesiculation in the cornea. Frank (1924) confirmed these findings although, he was not able to demonstrate epithelial defects. In our cases, the lesions closely paralleled the findings of Frank and Ackerman; we did not note vesicle formation in the eye but vesicles were found in other squamous epithelia. Dobberstein and Hemmert-Halswick (1928) described the lesions found in the oral cavity. An inflammatory cell infiltration was regularly observed in the tunica propria, in the vicinity of small blood vessels, and in the interstitium of the mucous glands. The cell collections were composed mainly of lymphocytes, plasma cells, and histiocytes. Eosinophiles, heterophiles, and mast cells were present in smaller numbers. Endothelial cells displayed a distinct stimulation. Epithelial cells were undergoing ballooning and reticulating degeneration leading to formation of vesicles which often contained heterophiles. Russell's bodies were seen. It is evident that this description closely parallels our findings with the addition that some epithelial hyperplasia was observed, particularly in early lesions.

## PALESTINE

Pattison (1946) believed the histopathological features of MCF as it occurred in Palestine sufficiently different to warrant a description of his findings and a comparison to the reports of other investigators. The features which he described closely parallel those observed in our cases.

Infiltrations observed in the liver were composed of lymphocytes, mononuclear cells, plasma cells, occasional eosinophiles, and rare heterophiles confined within the portal areas. Pattison noted that Mettam (1923) and Daubney and Hudson (1936) had stressed the lymphocytic infiltrations of this organ. Pattison reported infiltrations of lymphocytes, monoclear cells, and, occasionally, plasma cells related to the blood vessels and glomeruli in the kidneys. His findings closely resemble ours.

He did not observe the marked lymphocytic activity reported by Mettam and Daubney and Hudson. Pattison commented on this observation as compared to the marked increase in lymphocytes observed by the African investigators. He failed to find any marked lymphocytic activity in the spleen.

A widespread non-purulent encephalitis was present in all 8 cases investigated, primarily evidenced by vascular infiltrations which were composed of lymphocytes, larger monoclears, and plasma cells. Only slight degeneration of occasional nerve cells was noted.

## FINLAND

Stenius (1952) presented an extensive study of MCF in

Finland. The description closely parallels our findings. The disease observed in Finland was of sporadic occurrence. Skin lesions similar to those seen in our cases were found. Slight to moderate swelling of the lymph glands was observed; marked enlargement and follicular protuberances, as described by Mettam (1923) and Daubney and Hudson (1936), were not described. Stenius observed small grayish foci in the liver in the majority of cases and, occasionally, in the kidneys. In our cases, the foci in the liver were not observed. In one cases we found grayish foci in the kidneys.

Stenius reported the lesions of the oral mucosal membranes as an exudative and proliferative process in the propria mucosae. The infiltrating cells were listed as leucocytes (eosinophilic and neutrophilic), lymphoid cells, isolated plasma cells, and histoid elements. These cells were found in the perivascular lymphatic spaces, connective tissue papillae, and interstitium of the mucous glands. Blood vessels were the site of endothelial swelling and cell division phenomena. In some areas, a newly-reproduced granulation tissue consisting of eosinophilic and neutrophilic leucocytes, histoid cells, and fibroblasts was observed. Very similar changes were found in our cases.

Stenius found edema, infiltration with leucocytic cell elements, and proliferating histogenous cells in the propria mucosae of the nasal mucous membranes. Lymphoid cells surrounded arterioles and smaller veins and regressive alteration in the endothelial cells were noted. Similar

changes were observed in our cases.

Hyperemia, edema, and infiltration of leucocytic cells adjoining the corneal limbus were described in the eye. Ballooning and reticulating degeneration and, occasionally, small vesicles in the stratum spinosum were found.

Exudative and proliferative lesions were described in the portal areas of the liver. Eosinophilic leucocytes were predominant in some cases. The marked lymphoid cell infiltrations described in Africa were not observed. Perivascular infiltrates consisting of lympoid cells, leucocytes, and a few plasma cells as well as proliferation of adventitial cells in the kidneys were described. Again, the marked lymphocytic foci observed in Africa were not reported. The lesions in the liver and kidneys are very similar to those found in our cases; in addition, we found capsular accumulations of cells.

Marked lymphocytic activity as described in the lymph nodes by Mettam and Daubney and Hudson were not reported by Stenius. He did note reticuloendothelial proliferation in the lymph nodes. We also observed marked reticuloendothelial proliferation; in addition, marked vascular involvement with capsular and trabecular extensions was noted in our cases.

Stenius found infiltrates of lymphoid cells, leucocytes, and proliferation of adventitial cells in the heart. Lesions in our cases were similar.

Stenius observed a disseminated non-purulent meningoencephalitis in every cases. Perivascular cuffs of lymphocytes, plasma cells, isolated leucocytes, and adventitial cells were

found. Focal glial proliferation was observed in some areas. He also described marked degenerative changes in the nerve cells. Central nervous system lesions were essentially the same as in our cases with the exception that we did not see pronounced neuronal degeneration,

## DISCUSSION

Mettam's view that MCF and snotsiekte were different diseases was disputed by du Toit and Alexander (1938), S. African investigators. They stated that Daubney and Hudson (1936) reported the occurrence of a disease in young cattle indistinguishable from Götze's (1930) mild form of MCF. Extensive skin lesions and marked swelling of the lymph glands were found by Daubney and Hudson. This disease was transmitted to a variable percentage of cattle with difficulty. Du Toit and Alexander also referred to Wyssman (1938) and others who have stated that pronounced lymphatic changes do occur in MCF which, histologically, were not distinguishable from the changes found in the S. African "snotsiekte".

Du Toit and Alexander cited the success of Götze (1930) and Rinjard (1935) in transmitting the disease, although with some difficulty. Thus, they believed that Mettam's major criteria for separation of African "snotsiekte" and MCF (skin lesions, enlargement of lymphatic glands, and ability to transmit the disease) were negated. The sporadic nature of MCF as pointed out by Mettam was not discussed. In conclusion, these authors stated that "none of the characteristics

on which the separation was based in reality constitute a well defined barrier. Probably the correct conception is to regard the two conditions as being produced by different strains or types of the same excitant modified by adaptation to different environment in the two countries. The S. African strain has established a reservoir in the wildebeest, it seems to be more easily transmissible than the European form, and it also seems to present some special clinical features." Wyssman (1938) also felt that in spite of a few discrepancies the European and African diseases were identical or closely related.

There are features of the African form which differ from the disease as observed in N. America. Beginning with Mettam's findings, we should like to point out the following apparent distinctions; Mettam emphasized exclusively lymphocytic infiltrations and pronounced activity of lymphoid tissues with great enlargement of the lymph nodes. We have not found the prominent liver and kidney lesions which Mettam noted. Schofield (1941), reporting on the disease in Canada, did not observe the prominent mottling of the liver and kidney due to cell infiltrations described in Africa. The epizootic form described in Africa is uncommon in this country. Skin lesions are rare in the African form (found only in a few cases by Daubney and Hudson). Transmission of the African form appears to be much more easily accomplished. Transmission to calves has as yet not been successful in our cases. Despite these differences, however, we feel that basically the diseases are

the same or closely related. Many features of history, clinical course, and the distribution and character of the lesions indicate this relationship. Plowright (1953), in describing the intermediate cells and monocytes as well as lymphocytes in the lesions, established another link in the chain of evidence indicating the identity of the diseases. The reports from Palestine and Europe are essentially identical to MCF as we have observed it in this study.

## SUMMARY AND CONCLUSIONS

A comparison of disease syndromes occurring in Africa, Palestine, Europe, and N. America has been made. Certain differential features have been pointed out in the disease as described in Africa; however, generally, the features of the disease are very similar to those observed in our studies. There appears to be little if any variations in the syndromes reported from Europe, Palestine, and N. America. The differences are more quantitative than qualitative.

# REFERENCES


Ackerman, J. 1922. Cited by Dobberstein, J. and Hemmert-Halswick. Beitrage zur pathologischen Histologie des bösartigen Katarrhalfiebers. Zeitschrift für Infektionskrankheiten 39:160-182.

Aleska. 1935. Cited by Pattison, I. Observations on bovine malignant catarrh. Brit. Vet. J. 108:35-47.

Armed Forces Institute of Pathology. 1957. Manual of Histologic and Special Staining Technics.

Baker, J. A., and Little, R. B. 1948. Leptospirosis in cattle. J. Exp. Med. 88:295-308.

Baker, J. A., York, C. J., Gillespie, J. H. and Mitchell, G. B. 1954. Am. J. Vet. Res. 15:525-331.

Barner, R. and Montgomery, 1. 1954. Malignant catarrhal fever. M. S. C. Vet. 14:64-66.

Bassi. 1930. Cited by Stenius, P. I. Bovine malignant catarrh. A statistical histopathological and experimental study. Inst. Path. Vet. College, Helsinki.

Bendixen. 1940. Quoted from Magnusson by Pattison, I. Observations on bovine malignant catarrh. Brit. Vet. J. 108:35-47.

Bisbocci, G. 1934. Cited by Pattison, I. Observations on bovine malignant catarrh. Brit. Vet. J. 108:35-47.

Carlson, R. G., Pritchard, W. R. and Doyle, L. P. 1957. The pathology of virus diarrhea of cattle in Indiana. Am. J. Vet. Res. 18:560-568.

Chow, T. L., Hansen, R. R. and McNutt, S. H. 1951. Pathology of vesicular stomatitis in cattle. Pro. Am. Vet. Med. Assn. 119-124.

Cordy, D. R. and Jasper, D. E. 1952. The pathology of an acute hemolytic anemia of cattle in California associated with Leptospira. J. Am. Vet. Med. Assn. 120:175-178.

Daubney, R. and Hudson, J. 1936. Transmission experiments with bovine malignant catarrh. J. Comp. Path. Therap. 49:63-89.

De Kock, G. and Neitz, W. O. 1950. Sheep as a reservoir of snotsiekte (or bovine malignant catarrhal fever) of cattle in S. Africa. S. Afr. J. Sci. 46:176-180.

Dobberstein, J. and Hemmert-Halswick, A. 1928. Beiträge zur pathologischen Histologie des bösartigen Katarrhalfiebers. Zeitschrift für Infektionskrankheiten 39:160-182.

du Toit, P. J. and Alexander, R. A. 1938. Malignant catarrhal fever and similar diseases. 13th Int. Vet. Cong. 15-19.

Eames, H. 1956. Personal communication.

Ernst, W. and Hahn, H. 1927. Cited by Stenius, P. I. Bovine malignant catarrh. A statistical histopathological and experimental study. Inst. Path. Vet. College, Helsinki.

Farquharson, J. 1946. Malignant catarrhal fever. Vet. J. 102:127-130.

Frank, A. 1924. Cited by Dobberstein, J. and Hemmert-Halswick. Beiträge zur pathologischen Histologie des bösartigen Katarrhalfiebers. Zeitschrift für Infektionskrankheiten 39:160-182.

Gibbons, W. J. 1949. X-disease of cattle. Auburn Vet. 5: 2-8.

Goss, L. W., Cole, C. R. and Kissling, R. E. 1947. The pathology of malignant catarrhal fever (bovine epitheliosis. Am. J. Path. 23:837-841.

Götze, R. 1930. Untersuchungen über das bösartigen Katarrhalfiever des Rindes. Deutsche Tierärztl. Wchnschr. 38:487-491.

Götze, T. 1940. Cited by Stenius, P. I. Bovine malignant catarrh. A statistical histopathological and experimental study. Inst. Path. Vet. College, Helsinki.

Gray, M. L. 1954. Listeria monocytogenes. A review and colonial dissociation. Doctoral dissertation. Michigan State College. 120 num. leaves.

Guizzardi, M. 1931. Cited by Stenius, P. I. Bovine malignant catarrh. A statistical histopathological and experimental study. Inst. Path. Vet. College, Helsinki.

Hadlow, W. J. and Stoenner, H. G. 1955. Histopathologic findings in cows naturally infected with Leptospira pomona. Am J. Vet. Res. 16:45-56.

Harshfield, G. S. 1957. Sporadic bovine encephalitis. S. Dakota State College Agri. and Mech. Arts. Bulletin 18.

Hill, E. B. 1956. Michigan census, 1954. Ag. Econ. Dept. Mich. State Univ.

Hutyra, F., Marek, J. and Manninger, R. 1949. Special Pathology and Therapeutics of the Diseases of Domestic Animals. Alexander Eger, Inc. Chicago, Ill.

Huynen and Logiudice. 1911. Cited by Stenius, P. I. Bovine malignant catarrh. A statistical histopathological and experimental study. Inst. Path. Vet. College, Helsinki.

Isepponi. 1902. Cited by Stenius, P. I. Bovine malignant catarrh. A statistical histopathological and experimental study. Inst. Path. Vet. College, Helsinki.

Jensen, R., Griner, L. A., Chow, T. L. and Brown, W. W. 1955. Infectious rhinotracheitis in feedlot cattle. I. Pathology and symptoms. Proc. 59th An. Meeting U. S. Livestock San. Assn. 189-199.

Jungherr, E. 1944. Bovine leptospirosis. J. Am. Vet. Med. Assn. 105:276-282.

Lapi, A., Davis, C. L. and Anderson, W. A. 1954. The Gasserian ganglion in animals dead of rabies. J. Am. Vet. Med. Assn. 120:379-384.

Leclainche, E. 1896. Cited by Stenius, P. I. Bovine malignant catarrh. A statistical histopathological and experimental study. Inst. Path. Vet. College, Helsinki.

Linkies, G. 1926. Cited by Stenius, P. I. Bovine malignant catarrh. A statistical histopathological and experimental study. Inst. Path. Vet. College, Helsinki.

Mackey, D. 1956. Diseases of Cattle. American Veterinary Publications, Inc. Evanston, Ill.

Magnusson, H. 1940. Cited by Pattison, I. Observations on bovine malignant catarrh in Palestine. J. Comp. Path. Therap. 56:254-265.

Mallory, F. B. 1938. Pathological Technique. W. B. Saunders Co. Philadelphia, Pa.

Malewitz, T. D. and Smith, E. M. 1955. A nuclear stain employing dilute Harris' hematoxylin. Stain Tech. 30: 311.

Marshall, C. J., Munce, T. E., Barnes, M. F. and Boerner, F. 1920. Malignant catarrhal fever. J. Am. Vet. Med. Assn. 56:570-580.

Mathews, E. P. 1946. A contagious disease of cattle associated with Leptospira. Am. J. Vet. Res. 7:78-93.

Maurer, F. D. 1956. Diseases of Cattle. American Veterinary Publications, Inc. Evanston, Ill.

McKercher, D. G., Moulton, J. E. and Jasper. 1954. Virus and virus-like entities new to California. Proc. 58th An. Meeting U. S. Livestock San. Assn. 260-269.

McKercher, D. G., Moulton, J. E., Madin, S. H. and Kendrick, J. W. 1957. Infectious bovine rhinotracheitis recognized virus disease of cattle. Am. J. Vet. Res. 18:246-256.

McNutt, S. H. and Waller, E. F. 1940. Sporadic bovine encephalomyelitis (Buss disease). Cornell Vet. 30:437-448.

Meissner, H. and Schoop, G. 1934. Cited by Pattison, I. Observations on bovine malignant catarrh in Palestine. J. Comp. Path. Therap. 56:254-265.

Menges, R. W., Harshfield, G. S. and Wenner, H. A. 1953. Sporadic bovine encephalomyelitis. Studies on pathogenesis and etiology of the disease. J. Am. Vet. Med. Assn. 122:294-299.

Mettam, R. 1923. Snotsiekte in cattle. 9th and 10th Rep. Dir. Vet. Ed. Sth. Afr. 393-433.

Miller, N. J. 1955. Infectious necrotic rhinotracheitis of cattle. J. Am. Vet. Med. Assn. 126:463-467.

Morrill, C. C. and Link, R. P. 1950. Hyperkeratosis (X-disease) in Illinois. J. Am. Vet. Med. Assn. 116:356-359.

North Dakota. 1937. Malignant catarrhal fever. 31st An. Rep. of the State Livestock San. Board. 15-24.

Noskov, N. M., Surnachev, A. V. and Kanecski, V. N. 1952. A study of the role of sheep in the epizootiology of malignant catarrhal fever of cattle. Veterinaryia 29:34-37. Abstract J. Am. Vet. Med. Assn. 121:212, 1952.

Olafson, P., Mac Callum, A. D. and Fox, F. H. 1946. An apparently new transmissible disease of cattle. Cornell Vet. 36:205-213.

Olafson, P. 1947. Hyperkeratosis (X-disease) of cattle. Cornell Vet. 37, 279-291.

Olafson, P. and Rickard, G. 1947. Further observations on the virus diarrhea (new transmissible disease) of cattle. Cornell Vet. 37:104-106.

Otte, W. 1925. Cited by Stenius, P. I. Bovine malignant catarrh. A statistical histopathological and experimental study. Inst. Path. Vet. College, Helsinki.

Pattison, I. 1946. Observations on bovine malignant catarrh in Palestine. J. Comp. Path. Therap. 56:254-265.

Piercy, S. E. 1952. Studies in bovine malignant catarrh. I. Experimental infection in cattle. Brit. Vet. J. 108: 35-47.

Piercy, S. E. 1953. Investigations into infectious bovine malignant catarrh. Proc. 15th Int. Vet. Cong. 328-332.

Piercy, S. E. 1954. Studies in bovine malignant catarrh. Brit. Vet. J. 110:508-516.

Plowright, W. 1953. The pathology of infectious bovine malignant catarrh in cattle and rabbits. 15th Int. Vet. Cong. 323-328.

Plowright, W. 1953. The blood leucocytes in infectious malignant catarrh of the ox and rabbit. J. Comp. Path. Therap. 63:318-334.

Pritchard, W. R., Bunnell, P., Moses, H. E. and Doyle, L. P. 1956. A transmissible disease affecting the mucosae of cattle. J. Am. Vet. Med. Assn. 128:1-5.

Ramsey, F. K and Chivers, W. H. 1953. Mucosal disease of cattle. N. Am. Vet. 36:629-633.

Ramsey, F. 1956. The pathology of a mucosal disease of cattle. Division of Vet. Med., Iowa State College. Ames, Iowa.

Reinhard, K. R. 1951. A clinical pathological study of experimental leptospirosis in calves. Am. J. Vet. Res. 12:282-291.

Reinhard, K. R. and Hadlow, W. J. 1954. Experimental bovine leptospirosis — pathological, hematological, bacteriological and serological studies. Proc. Am. Vet. Med. Assn. 203-216.

Reisinger, L. 1926. Cited by Stenius, P. I. Bovine malignant catarrh. A statistical histopathological and experimental study. Inst. Path. Vet. College, Helsinki.

Rines, M. P. and Barner, R. D. 1955. A prolonged case of malignant catarrhal fever. M. S. C. Vet. 15:108-109.

Rinjard, P. 1935. Cited by du Toit, P. J. and Alexander, R. A. Malignant catarrhal fever and similar diseases. 13th Int. Vet. Cong. 15-19.

Rooney, J. R. 1957. Pathology of a bovine mucosal-type disease. Am. J. Vet. Res. 18:283-291.

Schofield, F. W. and Bain, A. F. 1941. Malignant catarrhal fever. Am. J. Comp. Med. 5:294-297.

Schofield, F. W. 1950. The value of a histopathological study of the brain in an atypical case of bovine malignant catarrh. Rep. Ontario Vet. College, Ontario Dept. Agri. 104-106, Toronto, Canada.

Schroeder, R. J. and Moys, M. D. 1954. An acute upper respiratory infection of dairy cattle. J. Am. Vet. Med. Assn. 125:471-472.

Sjollema, B. 1937. Cited by Stenius, P. I. Bovine malignant catarrh. A statistical histopathological and experimental study. Inst. Path. Vet. College, Helsinki.

Smith, H. and Jones, T. 1957. Veterinary Pathology. Lea and Feabiger. Philadelphia, Pa.

Stenius, P. I. 1952. Bovine malignant catarrh. A statistical histopathological and experimental study. Inst. Path. Vet. College, Helsinki.

Stolnikoff, V. 1926. Cited by Stenius, P. I. Bovine malignant catarrh. A statistical histopathological and experimental study. Inst. Path. Vet. College, Helsinki.

Stolnikoff, W. G. 1933. Cited by Daubney, R. and Hudson, J. Transmission experiments with bovine malignant catarrh. J. Comp. Path. Therap. 49:63-89.

Udall, D. 1956. The Practice of Veterinary Medicine. Published by the author. Ithaca, New York.

Ungar, H. and Bernkopf, H. 1947. Bovine leptospirosis. Observations on experimentally infected calves. Arch. Path. 44:59-70.

Wyssman, E. 1938. Bösartiges Katarrhalfieber und Ähnliche Krankheiten. 13th Int. Vet. Cong. 22-29.

Zanzucchi, A. 1934. Ricerche epidemiologishe etiopatogenetiche. Cliniche ed anatomopathologiche sulla Febbre Catarrale Maligna. La Clinica Veterinaria 57:689-721.

Zwick, W. and Witte, J. 1931. Cited by Stenius, P. I. Bovine malignant catarrh. A statistical histopathological and experimental study. Inst. Path. Vet. College, Helsinki.

# BOVINE MALIGNANT CATARRHAL FEVER IN MICHIGAN I. OCCURRENCE II. PATHOLOGY III. DIFFERENTIAL DIAGNOSIS IV. COMPARISON WITH SIMILAR SYNDROMES IN OTHER COUNTRIES

By

Robert Nelson Berkman

AN ABSTRACT

Submitted to the School for Advanced Graduate Studies of Michigan State University of Agriculture and Applied Science in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Department of Veterinary Pathology

Year 1958

Approved R. D. Barner

This study was based on a collection of 39 cases of bovine malignant catarrhal fever (MCF) occurring in Michigan. Of these 39 cases, 31 were examined postmortem for determination of the gross and microscopic lesions.

Clinically, MCF was characterized by fever (106 F.), nasal and conjunctival discharge, corneal opacity, erosions of the muzzle and oral cavity, marked depression, anorexia, rapid weight loss, sharp drop in milk production in lactating animals, erythema of the skin (particularly of the udder and vulva) and, occasionally, thickening and cracking of the epithelium of the teats, tufting of the hair, and hematuria. Leucopenia may be present. A definite seasonal incidence during the late winter and early spring was observed. Clinical evidence suggested that sheep may be carriers of the causative agent. The disease was usually fatal in 4 to 14 days, although chronic cases were encountered. Atypical cases may be misdiagnosed as atypical pneumonia, infectious kerato-conjunctivitis, pasteurellosis, or as entities of the mucosal disease complex.

Postmortem examination revealed several gross findings of diagnostic importance. Diphtheritic membranes were generally present in the nasal passages, pharynx, and trachea. Scattered areas of congestion, hemorrhage, and erosion were variably found in the digestive tract and usually most pronounced in the abomasum and large intestine. Lymph nodes, particularly of the head but often generally, were enlarged, edematous, and hemorrhagic. Hemorrhage and erosion in the bladder were observed in a minority of cases; rarely, white foci were observed in the kidneys.

The histopathologic changes were characterized by proliferative and infiltrative changes. In the case of squamous epithelia these were followed by necrosis. The proliferative lesions were widely distributed, affecting vascular and epithelial structures. Infiltration of monocytes, lymphocytes, eosinophiles, plasma cells, and mast cells were found in the lamina propria of several structures. An increase in the number of fibroblasts was often present also. Ballooning degeneration leading to vesiculation was also seen in the squamous epithelia. This followed an earlier proliferation of epithelial cells of the squamous epithelia and adnexae. Inclusion bodies, previously described in Finland, were found in the majority of cases; however, their specificity is questioned.

The historical, clinical, and pathological features of MCF, as observed in this study, are believed to be characteristic enough to permit a differential diagnosis from rinderpest, other diseases of the mucosal complex, the vesicular diseases, listeriosis, sporadic bovine encephalomyelitis, leptospirosis, and infectious kerato-conjunctivitis. Important diagnostic microscopic lesions are the constant cell accumulations found in the periportal areas of the liver and the perivascular cuffing in the brain. The wide distribution of lesions is also an aid in differential diagnosis.

A comparison of the disease observed in Michigan with similar syndromes in other countries indicated that although

minor differences exist (particularly in the African form) the changes are quantitative rather than qualitative; therefore, it is felt that these syndromes should be regarded as the same entity on the basis of present knowledge.