HISTOPATHOLOGY OF PULMONARY ADENOMATOSIS IN IOWA CATTLE

by

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A Thesis Submitted to the
Graduate Faculty in Partial Fulfillment of
The Requirements for the Degree of
MASTER OF SCIENCE

Major Subject: Veterinary Pathology

Iowa State College
1957

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INTRODUCTION

Pulmonary adenomatosis in cattle was first reported in Texas in 1953 (23). This severe respiratory disease had been observed in the fall of 1952 in cattle being fed mouldy corn stalks, sweet potatoes, milo, ligari and other mouldy feeds. Several outbreaks of the disease followed and all cases were associated with the feeding of mouldy feeds.

Clinically the malady was characterized by a marked dyspnea which became progressively more severe. The neck was extended, the mouth was open, the respiratory rate was increased and the expiratory grunt could be heard for some distance. Several of the animals affected showed a subcutaneous emphysema in the dorsal thoracic and cervical region.

The temperature of the animals was normal or only slightly elevated. The heart rate was more rapid than normal. Death usually occurred in less than one week.

Necropsy examination revealed that the lesions were confined to the respiratory system and to the lungs in particular. Pulmonary emphysema was extensive. The lungs were extremely large, "meaty" in appearance, firm, and on cut surface resembled thymus gland in color and consistency.

Histological examination of the lungs revealed both an alveolar and interstitial emphysema. The primary lesion, however, was the great hyperplasia and hypertrophy of the respiratory epithelium.

Pulmonary adenomatosis was first reported in Iowa cattle in 1955 (24). It had been observed in the Veterinary Division of Iowa State College for at least three years previously. The histories, symptoms and lesions of these animals had been so consistent and characteristic that the distinct

disease entity had been recognized again. All outbreaks of the disease in Iowa, however, had not been associated with mouldy feeds.

Practicing veterinarians who referred these cases to the Veterinary Division often termed the condition an atypical pneumonia of unknown etiology. They reported that the clinical response to the usual courses of pneumonitis therapy had been consistently poor and in most cases had been entirely lacking. This inability to effect clinical response in the animals had been encountered in the Texas outbreaks also.

Some aspects of pulmonary adenomatosis in cattle have been found to be similar to Montana progressive pneumonia in the ovine (4), jagziekte in the ovine (4), maedi in the ovine (29), epizootic adenomatosis in the Icelandic ovine (8), jagziekte-like disease in the equine (32), pulmonary emphysema in the bovine (29), and "silo-filler's disease" in man (5). Isolated cases of pulmonary adenomatosis have been observed in chronic pneumonias of several species and in cases of chronic ovine parasitic pneumonia (9).

Since 1952, pulmonary adenomatosis has been recognized in at least four states. Clinical and laboratory evidence indicates that the disease is not infectious. Limited transmission experiments have not been successful.

Clinical observations, etiologic studies, case histories, and the macroscopic and microscopic findings are presented here as an addition to the existing knowledge of pulmonary adenomatosis in the bovine.

METHODS OF PROCEDURE

History

Questionnaires (Appendix) designed to obtain information as to individual and herd history were used on each case under study. Data acquired by this method included: age, breed, sex, time of year, location of farm, number of animals in the herd and number affected, duration of the disease in the individual and in the herd, previous respiratory disturbances in the herd, origin of affected animals, rations, length of time on this ration, changes in feeding routine, weather changes, new additions to the herd, symptoms, treatment, response to treatment and post mortem findings.

Clinical Observations

Clinical observations were recorded daily on hospitalized cases and on some field cases when the information was available. Records were kept on the general condition of the individual, temperature range, heart rate, auscultation of thorax, respiratory movements, temperament change, discharges, skin changes, subcutaneous emphysema, digestive disturbances, and feed consumption.

Field Observations

Field trips over the state to the farms reporting outbreaks of pulmonary adenomatosis made it possible to obtain information on the management, sanitation, and general husbandry of the affected herds.

Etiologic Studies

Routine aerobic bacteriologic studies were conducted on tissues of all animals studied. Attempts to transmit the disease by intratracheal and subcutaneous injections of lung and tissue fluids were made in two adult cows. Several guinea pigs, mice, and a bovine were administered oxides of nitrogen by inhalation. One bovine was exposed intrarumenally to the oxides of nitrogen.

Morbid Anatomy

Macroscopic studies

Detailed necropsy examinations were performed on ten animals from ten different herds. Pulmonary tissues of affected cattle from thirty-one additional herds were studied. The post-mortem examinations were conducted immediately or within a few hours after death. None of the animals were sacrificed and all died of the disease.

Microscopic studies

Blocks of tissue were routinely obtained from the lungs, trachea, larynx, nasal turbinates, bronchial and mediastinal lymph nodes, salivary glands, esophagus, rumen, reticulum, omasum, abomasum, small intestine, large intestine, pancreas, liver, gall bladder, spleen, somatic lymph nodes, kidney, urinary bladder, skeletal and cardiac muscle, brain, spinal cord, and adrenal glands. Ovaries or testicles, mammary glands, thyroid and thymus were obtained for study when possible.

Histological examinations of these organs were conducted on ten animals.

The blocks of tissue were cut at approximately 0.5 cm. thickness and placed in about twenty times their volume of ten per cent formalin. After 24-48 hours the tissues were treated as follows:

1. Placed in 70 per cent ethyl alcohol for 12 hours.
2. Placed in 95 per cent ethyl alcohol for 24 hours.
3. Placed in absolute ethyl alcohol for 8 hours.
4. Placed in chloroform for 12 hours.
5. Placed in chloroform - Altman's mixture (paraffin, beeswax and stearin) for 4 hours in a 56° C. oven.
6. Placed in Altman's mixture alone for 4 hours in a 56° C. oven.
7. Embedded in Altman's mixture with the surface to be sectioned facing downward.
8. Blocks trimmed so that opposite edges were parallel and leaving a narrow margin of paraffin.
9. The blocks were mounted on wooden spindles whose surfaces were covered with melted paraffin and then allowed to cool.
10. Sections were cut at seven microns thickness.
11. Sections were floated on the surface of water which was heated to approximately 42.0° C.
12. Section was floated onto a clean glass slide coated with Mayer's albumin glycerol fixative.
13. Slides were dried in a 56° C. oven for at least one-half hour.

All tissues were stained with Mayer's hematoxylin and .25 per cent alcoholic solution of ethyl eosin in an Autotechnicon.

Mayer's hematoxylin solution consisted of the following (12):

Hematoxylin	1.0 gm.
Distilled water	1000.0 cc.
Sodium iodate	0.2 gm.
Ammonium or potassium alum	50.0 gm.
Citric acid	1.0 gm.
Chloral hydrate	50.0 gm.

The routine hematoxylin and eosin staining procedure was as follows:

1.	Xylene	3 min.
2.	Absolute ethyl alcohol	3 min.
3.	95% ethyl alcohol	2 min.
4.	70% ethyl alcohol	2 min.
5.	Tap water	2 min.
6.	Mayer's hematoxylin	2 min.
7.	Tap water	2 min.
8.	.25% ethyl eosin	1 min.
9.	70% ethyl alcohol	1 min.
10.	95% ethyl alcohol	1 min.
11.	Absolute ethyl alcohol	1 min.
12.	Xylene	3 min.

The sections were mounted in a synthetic resin mounting medium.

Weigert's fibrin stain (17) was used on selected cases. The solutions used were as follows:

Lithium Carmine Solution

Carmine	4 gm.
Lithium carbonate, saturated aqueous	100 cc.
Thymol	1 gm.

Crystal Violet Solution

Absolute ethyl alcohol	33 cc.
Aniline oil	9 cc.
Crystal violet to saturate	in excess

Solution B

Crystal violet	2 gm.
Distilled water	100 cc.

Working Solution

Solution A	3 cc.
Solution B	100 cc.

Gram's Iodine Solution

Iodine	1 gm.
Potassium iodide	2 gm.
Distilled water	300 cc.

The technic used was as follows:

1. Xylene---------- 3 min.
2. Absolute ethyl alcohol---------- 3 min.
3. 95% ethyl alcohol---------- 2 min.
4. Distilled water---------- 2 min.
5. Lithium carmine solution---------- 5 min.
6. Washed thoroughly in water.
7. Stained with the working solution of crystal violet 5-10 min.
8. Drained and blotted with filter paper.
9. Mordanted with Gram's iodine poured over sections and allowed to stand for 5-10 min.
10. Drained and blotted with filter paper.
11. Differentiated in a mixture of equal parts of aniline oil and xylene.
12. Blotted and xylene poured over slide to remove excess aniline.
13. Mounted in synthetic resin mounting medium.
    Fibrin stains blue to black.

Gomori's methenamine - silver nitrate technic (13) was used as a fungus stain. The solutions used were as follows:

1. Five per cent aqueous chromic acid.

2. Methenamine - silver nitrate
   5% silver nitrate---------- 5 ml.
   3% methenamine----------100 ml.

3. One per cent aqueous sodium bisulfite.

4. Five per cent aqueous borax.

5. One-tenth per cent aqueous gold chloride.

6. Two per cent aqueous sodium thiosulfate.

The technic used was as follows:

1. Xylene---------- 3 min.
2. Absolute ethyl alcohol---------- 3 min.
3. 95% ethyl alcohol---------- 2 min.
4. 70% ethyl alcohol---------- 2 min.
5. Distilled water---------- 2 min.
6. 5% chromic acid---------- 1 hr.
7. Washed in tap water---------- 10 min.
8. 1% sodium bisulfite---------- 1 min.
9. Tap water---------- 5 min.
10. Washed in 3 changes of distilled water.

11. Silvered at 45 to 50° C. in a working solution prepared by adding 25 ml. of stock methenamine - silver nitrate to an equal portion of distilled water containing one to two ml. of 5% borax.
12. Rinsed slides in distilled water two or three times.
13. Tinted with 0.1% gold chloride---------- 5 min.
14. Rinsed in distilled water and removed unreduced silver by treating with a two per cent sodium thiosulfate solution for one or two minutes.
15. 70% ethyl alcohol---------- 1 min.
16. 95% ethyl alcohol---------- 1 min.
17. Absolute ethyl alcohol---------- 1 min.
18. Xylene---------- 3 min.

Mounted in synthetic resin mounting medium.
Fungi stain black.

RESULTS

Definition

Pulmonary adenomatosis is an acute, non-infectious respiratory disease of the bovine characterized by sudden onset and short duration, varying degrees of pulmonary emphysema and edema and by the hypertrophy and hyperplasia of the respiratory epithelium. This latter tissue change gives rise to the term adenomatosis due to the tumor-like proliferation of cells lining a gland-like cavity (alveolus) in the stroma of the lungs.

Etiologic Studies

Although the primary objective of this problem was to describe the histopathology, limited etiologic studies were conducted.

Routine aerobic bacteriologic studies of the tissues including blood did not reveal the presence of bacteria except in a few cases which were complicated by a secondary pneumonitis. In all instances the organisms were identified biochemically and morphologically as either a Pasteurella sp. or a diplococcus.

Transmission experiments by direct contact were not conducted. No attempt was made to isolate the affected animals from other patients in the clinic, however, and it is interesting to note that the disease did not develop in cows in adjacent stalls. No evidence of contact transmission was associated with field cases of the disease.

Due to limited facilities, only two adult cows were used in transmission experiments. These two animals were inoculated intratracheally with

one cubic centimeter and subcutaneously in the cervical region with two cubic centimeters of a lung emulsion and pulmonary tissue fluids obtained from case number four of the ten cases studied.

No evidence of transmission of the disease was observed. Each animal's rectal temperature was recorded daily. These recordings varied from 101.5° F. to 102.1° F. and thus were in the range considered to be normal for the bovine. Auscultation of the thorax did not reveal pulmonary rales. Neither the rate nor the depth of the respirations was altered.

Nitrogen dioxide studies

Seaton (28) reported the following: The similarity between the pulmonary lesions in the pulmonary adenomatosis of cattle and those found in human beings with "silo-filler's disease" has suggested that both diseases have a similar etiology. "Silo-filler's disease" has been proved to be the result of the inhalation of nitrogen dioxide (18). In view of this fact an attempt was made to produce pulmonary adenomatosis in animals with the use of nitrogen dioxide.

Tests on mice and guinea pigs

Nitrogen dioxide and associated oxides of nitrogen were produced by reducing concentrated nitric acid with copper wire. Mice and guinea pigs were exposed to the gases in a bell jar for two minutes. During exposure to the gases the animals blinked and squinted their eyes, held their breath, scratched their noses, and later gasped for air, indicating that the gases were irritating. After the animals were removed from the bell jar and placed in their cages, no evidence of respiratory disturbance was observed within the next 24 hours. After 24 hours, however, dyspnea was observed and became progressively worse until the animals died, 72 hours after exposure.

Postmortem examination of the mice and guinea pigs disclosed tremendously enlarged, firm, cyanotic and edematous lungs as well as general passive hyperemia of the viscera. Histologic examination of the lungs from these small laboratory animals revealed hyperemia, edema and pronounced hyperplasia, as well as hypertrophy of the alveolar and bronchial epithelium. The lesions in the lungs of these rodents were similar to those observed in cattle with pulmonary adenomatosis.

Gas tests on a cow

A mature cow with no history of pulmonary disease was obtained and was placed in a closed room that measured 12 x 12 x 12 feet. A container of nitric acid into which copper wire had been placed was set in the same room. Since the toxic dose of nitrogen dioxide for the cow was not known, no attempt was made to measure the amount of gas inhaled by the animal. The toxic gases were allowed to escape into the room, and the cow was exposed to fumes for 30 minutes. When the subject was removed from the gas chamber no evidence of altered respiration was noted. The cow was observed for 96 hours during which time no evidence of respiratory distress appeared.

Second test on a cow

Owing to the concentration and distribution of the gas in the room during the first test, doubt arose as to whether or not the animal had been exposed long enough. Ninety-six hours after the initial exposure a second attempt was made to gas the animal. The same cow was placed in a restraining stock. The bottom was cut out of a burlap feed sack and the sack was placed over the top of an earthen crock containing concentrated nitric acid. The top of the sack was placed over the muzzle and face of the cow up to the level of the eyes, and was held in position by a cord that passed behind the ears and the poll. Copper wire was placed in the container and heavy brown fumes of nitrogen dioxide were evolved. The purpose of the sack was to concentrade and contain the vapors in such position that the cow would be forced to inhale them. The gases apparently were extremely irritating, for the cow struggled violently during the five minutes that she was exposed to them. The gassing device was then removed, and the cow was returned to her stall. At this time the rate of respiration slightly increased, possibly owing to exertion. Eighteen hours later there was still no clinical evidence of illness. When examined 24 hours after the second exposure, a mild dyspnea that was characterized by a slight expiratory grunt was observed. The respiratory symptoms become progressively more severe until the cow died, 94 hours after exposure to the gas. In the course of this illness the typical clinical symptoms of pulmonary adenomatosis were to be observed. The rate of respiration was increased and the depth of respiration was greater than normal; the expiratory grunt also became progressively more audible, until it could be heard throughout the stable. There was an excessive discharge of thick mucus from the nostrils.

Results of autopsy

Postmortem examination of the cow disclosed that both lungs were uniformly involved with the typical gross lesions that occur in pulmonary adenomatosis. Both lungs were greatly enlarged, com-

pletely filling the thoracic cavity, and the imprint of the ribs was clearly visible on the external surface. The lungs, unlike normal lungs, cut with ease. They were edematous, had a "meaty" consistency, and were slightly cyanotic. The bronchi contained a small amount of pink foam. Extensive alveolar and pulmonary emphysema was to be observed. Large bullae were present in the interlobular septa. The consolidation and the vascular changes associated with pneumonia were not present. Multiple petechial hemorrhages were observed in the mucosa of the trachea and the bronchi. The nasal passages were very hyperemic, but there was no evidence of other injury that would have been traceable to the inhalation of the toxic gas. Generalized passive hyperemia was noted in the remainder of the cadaver.

Histologic observations

Histologic examination of the lungs disclosed the typical lesions of pulmonary adenomatosis. The walls of the alveoli were paved with hyperplastic and hypertrophic alveolar epithelium. Obviously this layer of epithelial cells seriously hampered the gaseous exchange within the lungs. Hyperplasia and hypertrophy of the bronchial epithelium were also noted. The lumina of the alveoli and bronchi were filled with edematous fluid, fibrin, desquamated epithelial cells, and a few erythrocytes. The histologic alterations usually associated with either bacterial or viral pneumonia were absent.

In an effort to explain the occurrence of field cases of this disease, attempts were made to initiate the disease by way of the rumen.

In those trials, nitrogen dioxide was produced by the addition of concentrated nitric acid to a glass container in which copper wire had been placed. The container was a closed jar with three openings at its top. The center opening was used to support a separatory funnel containing the acid. A rubber tube extending from inside the jar through a lateral opening to the piston type pump served as an intake. The other lateral opening permitted a rubber tube to conduct overflow vapors to another vessel. This was done to prevent excessive gas pressure from forming in the glass jar. The exhaust from the air pump was attached to a stomach tube which passed through an Emont's speculum down the esophagus and into the rumen of the experimental animal.

An Angus type steer which weighed approximately six hundred pounds was exposed to the gas three times each week for two weeks in succession. The amount of gas administered thusly was not measured but was given in a concentrated vapor until tympany was prominent. The animal eructated frequently as the intrarumenal pressure increased. By the time that the rumen was distended to near its greatest capacity, the animal had usually eructated eleven to fifteen times in unsuccessful efforts to relieve the pressure. Immediately following the administration in this manner, the steer manifested dyspnea and a degree of incoordination such as is seen in naturally occurring cases of tympanites. Within two to four hours, after each treatment, the respirations and coordination of the animal returned to normal.

Beginning on the third week, the exposures were made daily. This continued through the fourth week until eighteen such exposures had been conducted. On two occasions during the third week, the animal experienced anorexia for a 24 hour period each. At no time did the animal experience a constipation or a diarrhea. Approximately 18 hours after the last exposure the animal was sacrificed. Lesions of pulmonary adenomatosis were not found grossly nor histologically. Due to a complete lack of knowledge concerning the toxic dose of nitrogen dioxide gas in the bovine as well as the lack of knowledge of an atrium capable of producing the disease, the results in this animal are difficult to evaluate.

Case History Studies

The disease in Iowa is widespread and the prevalance appears to have increased during the last five years as evidenced by reports from all sec-

tions of the state. Histological diagnoses of pulmonary adenomatosis have been made in cattle originating in the states of Texas, Minnesota and Kentucky as well as Iowa. It seemed probable that the disease was present although undiagnosed in other midwestern states.

Age was not a factor in the incidence of pulmonary adenomatosis. Most of the cases studied were in animals from six to thirty-six months old. The youngest studied was in a two months old calf and the oldest was a cow thirteen years old. Both beef and dairy breeds were affected. Males and females appeared to be equally susceptible.

The seasonal incidence was greatest in late summer and fall, however, it did occur the year around. As many cases occurred in home raised cattle as in those purchased.

The duration of the illness ranged from six hours to five days in those cases terminated by death. Typically, death occurred on the third day after onset of dyspnea. In recovered cases, the symptoms lasted from two days to ten days.

The morbidity rate in a herd was found to be low and the mortality rate was high. In the herds reported, the average morbidity was 5.36 per cent. The highest was 11.90 per cent in a herd of 67 head and lowest was 1.20 per cent in a herd of 80 head. The mortality rate was over 90 per cent in cases not experiencing a change in ration.

In herds in which more than one animal was affected, the onset of symptoms was not always simultaneous. In such instances, dyspnea in the succeeding animals often appeared 12-48 hours later. In one instance seven weeks lapsed before a second animal sickened.

Two animals in different herds were reported to have had the disease

twice. One recovered from an attack and became asymptomatic only to succumb to a second attack six months later. In another instance an animal of the Guernsey breed recovered from the disease clinically and one week later died from a recurrence.

One farm on which Angus cattle were raised reported the illness in the herd for three successive years. In almost all instances on this farm, calves six months old and younger were affected.

The temperatures ranged from 102.6° F. to 106.0° F. It is believed that the higher temperatures may be due to faulty aeration and inadequate cooling of the blood stream by severely incapacitated lungs. A rapid dehydration of the animals was a constant finding.

The therapy employed in these cases has included many different agents. Antibiotics, sulfonamides, anti-histamines, rumenatorics, antiserums, stimulants, expectorants, blood transfusions, vitamins and fluid supportive therapy have all been used to no avail.

Rations of the diseased animals were highly variable. Alfalfa hay was the only food ingredient found in the rations of all animals affected. Primarily, corn, oats and alfalfa hay had been fed. Some animals were being fed corn silage as well. The two to six month old calves were nursing their dams but did have access to creep feeders containing oats, corn and chopped alfalfa hay.

One herd, in which three animals out of 35 became sick, was being pastured on alfalfa alone. All three animals developed respiratory trouble simultaneously. These cows had been grazing in the field ten days prior to symptoms. Additional observations of the herd histories were as follows:

The length of time the affected herds had been fed their particular rations prior to symptoms was variable.

Weather conditions had no apparent effect on occurrence of the disease but may have been a factor in cases complicated by secondary pneumonia.

The animals were usually in good condition and usually were feed-lot animals or dairy cattle being fed for production.

As the disease progressed, the animal's facial expression was usually one of mild anxiety.

Auscultation of the thorax revealed either no sound, indicating a non-functional lung, or dry rales. The sounds were most prominent in the dorsal thoracic region or in the diaphragmatic lobes of the lungs.

Tachycardia was always noted and was often recorded as frequent as 120 cardiac impacts per minute.

Discharges from body openings were confined to excessive mucus in the nasal cavities and froth about the mouth. Both were interpreted as the result of the dyspnea.

Only in one herd studied was subcutaneous emphysema prominent. Two of the three cows affected in the herd had extensive emphysematous areas in the dorsal thoracic and cervical region.

The feces remained normal. Neither a conjunctivitis, rhinitis, nor dermatititis was ever observed.

Morbid Anatomy

Macroscopic studies

The integument had not undergone pathological alterations.

Upon opening the cadaver a subcutaneous emphysema over the thoracic cavity, the thoracic limb and ventral cervical region was encountered in two individuals. All the superficial somatic lymph nodes appeared to be unaltered.

The most important macroscopic lesions in this disease were confined primarily to the respiratory system. The lungs were greatly enlarged, firm, heavier than normal and completely filled the thoracic cavity (Fig. 1). The imprint of the ribs was often clearly visible on the lungs. All cases exhibited pulmonary edema and both alveolar and interstitial emphysema (Fig. 2). Large bullae were present in the interlobular septa. These lesions involved the entire lung. Due to the increased firmness, the lungs were easier to incise than normal. After incising the lung parenchyma, the cut surface resembled thymus gland. No evidence of a suppurative pneumonitis, multiple abscesses, nor exudates were present. The larynx and trachea were not changed but did often contain white froth and mucus. The nares, nasal cavities and nasal turbinates displayed only a mild hyperemia.

Parrott (26), in discussing atria of infection indicated that the lymph nodes of the lungs reflected the lesions occurring in the parenchyma of the lungs like a mirror. This was found applicable in pulmonary adenomatosis.

The mediastinal and bronchial lymph nodes were edematous, emphysematous, and hyperplastic. As a result, they were greatly enlarged. Many of the nodes were four to five times their normal size. No evidence of a suppurative lymphadenitis was present.

The blood vascular system manifested an acute, general, passive

hyperemia throughout the cadaver, thereby reflecting the disturbance in pulmonary circulation. A moderate cardiac dilatation of the right venticle was frequently found. The lymphatic vessels, as a result of the acute, general, passive, hyperemia of the blood vascular system, were greatly distended especially in the subpleural and interstitial tissues.

The organs of the digestive tract contained normal appearing ingesta in the various stages of digestion. An acute, general, passive hyperemia was observed in the following organs: salivary glands, oral mucosa, esophagus, proventicles, abomasum, intestines, liver, pancreas, kidneys, urinary bladder, ovaries, uterus, mammary glands, testicles, brain, spinal cord and skeletal muscles.

Microscopic studies

Microscopically, the lungs had undergone characteristic changes. The hypertrophy and hyperplasia of the pulmonary epithelium and muscles were the more prominent alterations (Fig. 3). These lesions were focal in some cases but diffuse in most cases (Fig. 4). The alveolar phagocytes or septal cells were enlarged and present in much greater numbers than in unaffected lung. These septal cells varied from cuboidal to columnar in morphology and many assumed a foamy or lace-like effect in their cytoplasm. The septal cells became so numerous that many alveoli became lined with them. In several instances the pulmonary epithelium acquired a giant cell appearance due to extremely rapid proliferation (Fig. 5). The arrangement of cells lining the alveolar walls simulated a glandular architecture (Fig. 6). The continued response of the lung to the inciting irritant stimulated the production of septal cells further. The alveolar walls

became thickened by the addition of a second layer of septal cells (Fig. 7). In the cases of several days duration, the alveoli were filled with new layers of septal cells and their desquamated predecessors (Fig. 8). This action gave credence to the belief that the alveolar phagocytes or septal cells were derived from the alveolar epithelium and were not wandering cells of extrarespiratory origin. The bronchial epithelium was hyperplastic and hypertrophic as evidenced by the extension of epithelial rugae into the lumina of the bronchioles (Fig. 9). Desquamated alveolar and bronchiolar epithelium often nearly filled the bronchioles (Fig. 10).

The alveolar capillaries were distended with blood. Small amounts of fibrin were deposited and both an alveolar and an interstitial edema occurred. The subpleural and interstitial lymphatics were distended.

In peracute cases in which death occurred in six hours or less the alveolar walls were often pavemented with an eosin staining protein substance (Fig. 11). Septal cell proliferation in these cases was not pronounced.

A perivascular and peribronchiolar lymphoid hyperplasia was noted in several cases. The pulmonary musculature appeared mildly hyperplastic in most cases. A moderate increase in the number of eosinophiles in the lungs was found in only two cases. The eosinophilia was sub-pleural in one instance and intraseptal in the other.

The larynx, trachea and nasal turbinates were hyperemic.

The bronchial and mediastinal lymph nodes displayed an acute, general, passive, hyperemia and hyperplasia (Fig. 12). The subcapsular or cortical sinusoids were distended with blood. Macrophages and lymphocytes appeared in the sinuses of both the cortex and medulla. The afferent lymphatics

were distended. Extensive edema and emphysema of the nodes was commonplace (Fig. 13). No evidence of a suppurative lymphadenitis was found.

The cardiac muscle had undergone focal coagulation necrosis. The necrotic cells had lost their angularity, the striations were disappearing and the cells were stained heavily with eosin. Sarcosporidia were observed in several hearts. The salivary glands, eosophagus, proventricles and abomasum exhibited no major alteration but did present a marked acute, general, passive hyperemia. A passive hyperemia of the small intestine and pancreas was a constant finding (Fig. 14). Several cases demonstrated a moderate increase in the number of lymphocytes and eosinophiles in the intestinal mucosa and tunica propria. The colon often displayed a lymphocytic infiltration of the tunica propria. The interpretation of these cellular infiltrations in the digestive tract should take into consideration a physiological cellular increase following food ingestion. A mucoid degeneration of the epithelium with a marked increase in the number of goblet cells was especially evident in one case.

The liver clearly demonstrated acute passive hyperemia. The central veins were greatly distended with blood (Fig. 15). An extensive centrolobular necrosis was evident in many livers. Areas of fatty degeneration were commonplace. Occasionally, a hyperplasia of the Kupffer cells was evident. The hepatic triads revealed a lymphocytic infiltration in a few cases. The gall bladders were hyperemic. The kidneys were hyperemic and a lymphocytic infiltration into the glomerular tufts was discernible. An albuminuria in the glomerular spaces occurred in certain cases. Many kidneys had microconcretions in the renal tubules which served as an index of the rapid clinical dehydration. An acute passive hyperemia of the

urinary bladder was present.

The nervous system manifested an acute, passive, hyperemia as the only lesion.

The tongues, thymi, thyroids, adrenals, ovaries, testicles, mammary glands, and uteri were all in a state of passive hyperemia.

DISCUSSION

Several respiratory diseases of domestic animals which were similar in certain aspects to pulmonary adenomatosis in the bovine have been reported in the veterinary literature. They were similar clinically, and in macroscopic and microscopic pathology. These conditions were Montana progressive pneumonia in the ovine, jagziekte in the ovine, epizootic adenomatosis in the Icelandic ovine, maedi in the ovine, a jagziekte-like disease in the equine, and pulmonary emphysema in the bovine or bovine asthma. One respiratory disease in the human, "silo-filler's disease," had similar macroscopic and microscopic lesions and limited experiments suggested a common etiology with pulmonary adenomatosis.

Jagziekte and Montana Progressive Pneumonia

Jagziekte has been reported as a pulmonary disease of sheep in which the lesions were proliferative in character. The illness usually appeared in sheep which were fatigued by long drives, hence the Dutch name jagziekte. Cowdry and Marsh (4) in comparing South African jagziekte and Montana progressive pneumonia in sheep wrote that the mortality rates were nearly the same. The diseases occurred throughout the year and generally sheep over two years old were affected but that all ages could be. Jagziekte occurred mainly in range sheep and the Montana disease did likewise. In neither condition was water nor grazing area considered to be determinative factors. They felt that both diseases were transmitted by contact.

The diseases extended over a period of several months, with the animals showing little temperature rise but severe emaciation. The respiratory

distress was accompanied by a catarrhal nasal discharge in jagziekte but not in Montana progressive pneumonia.

Invariably, death terminated the diseases in affected animals. All recognized cases and their contacts were slaughtered as a control measure. Cowdry and Marsh stated that the etiological agent was not known in jagziekte and that the disease had not been transmitted by animal inoculation. Repeated intratracheal inoculations, of a diphtheroid type of bacteria which was isolated from sheep affected with Montana progressive pneumonia, produced small lesions in the lungs of the same type as naturally occurring cases. The disease was reproduced in one sheep in this manner.

In both diseases the lesions were confined to the thoracic cavity. Luxuriant proliferation of respiratory epithelial cells of the alveoli and bronchioles was the most prominent lesion (Fig. 16). Macrophages and leucocytes were present in the interstitial tissue and the engorgement of the alveolar capillaries resulted in a chronic catarrhal pneumonia.

The cause of death in both diseases was considered to be asphyxiation. The alveolar epithelial proliferation made the gaseous exchange between the blood vascular system and the lumen of the alveolus impossible.

Marsh (20) noted that Montana progressive pneumonia in sheep was first reported at Fort Benton, Montana, in 1915. The condition was popularly known as "lungers," "heavers" or "blowers."

Mitchell (22) in describing jagziekte stated that the cardiac lobe was the first portion of the lung to be affected, later the main lobe, and less frequently the anterior lobe. He believed the incubation period to be from three to five days.

Dungal (7) in doing experimental work in Iceland with jagziekte,

which he believed had been imported with sheep from Germany, made the following observations:

The infection was obtained in healthy lambs by exposing them to exhaled air from sick sheep. This was done by allowing the sick animals to breathe through a solution of glycerine and saline. When this solution was then injected intratracheally, the infection was reproduced.

Transmission of the disease by the use of filtered material was made easier when injections of "bacillary cultures" causing pneumonia in sheep were used in conjunction. This was more especially true if the sheep had been fed snails infected with lungworms. He did not believe, however, that the lungworm was a virus vector.

Dungal concluded that jagziekte was caused by a pneumotropic virus which was strictly limited to the lungs and bronchi and excreted with expired air.

He described intracellular corpuscles which he believed might be virus corpuscles.

Epizootic Adenomatosis in the Icelandic Ovine

Dungal, Gislason and Taylor (8) stated that the crowding of sheep during winter months seemed to be a factor in the spread of this disease and thus it was believed to be infectious. Evidence indicated the disease was not capable of transmission until symptoms were present. It appeared during the spring months from April to June. About one year after the infection was introduced, large losses occurred and very few sick animals recovered. The incubation period was usually from 6 to 8 months. The

disease had a chronic course and the animal might have been affected several weeks prior to clinical manifestations. Affected animals coughed. Rales could be heard early in the course of the disease in ventral portion of the lung and could be heard from a short distance when more lung became involved. No temperature rise was reported. Bronchial secretions which poured from the nostrils when the animals lowered their heads was of diagnostic significance. In some animals a discharge of 500 cc. volume in 24 hours was noted. The course of the disease was from 2 to 3 months.

The lungs were greatly enlarged and the widespread "greyish patches" were characteristic. They were not distinct and did not protrude above the surface as worm nodules do. The pleura was slightly thickened. There was no visible change in lymph nodes of the lung or mediastinum. Other organs were not affected.

Microscopically, adenomatous areas appeared in the lungs. Giant cells were seen which were believed to be formed by a more rapid nuclear than cytoplasmic division of the alveolar cells. The alveolar epithelial proliferation was pronounced. Desquamation of the epithelium was very extensive and the lumina of the bronchi were frequently filled with desquamated epithelium.

The Gottorp strain of Icelandic sheep was very susceptible and the Adalbol strain appeared to be quite resistant, indicating a hereditary influence.

Both contact experiments and inoculation of emulsified lesions into the lungs were capable of transmitting the disease in susceptible animals.

Animals fed on hay from pastures where the disease was present did not develop the condition. The condition was not transmitted when Seitz

filtrates prepared from the pulmonary lesions were inoculated intrapulmonarily into clinically healthy sheep.

Material injected intraperitoneally, intrapulmonarily, and intravenously into white mice and rabbits did not produce the disease. Epizootic adenomatosis was considered by Dungal to be indistinguishable from jagziekte.

Maedi

Maedi was reported as a chronic progressive disease in the ovine in Iceland (29).

The primary gross lesions were confined to the lungs. Microscopic lesions included proliferation of the mesenchymal tissue, thickening of alveolar septa, macrophages in the alveoli, hypertrophy of the smooth muscle in the alveolar ducts and lymphoid accumulations more conspicuous than usual in ovine lung around the bronchi and bronchioles (Fig. 17). Sigurdsson et al. (29) states, "the cause of the disease is not known, but it is believed that microscopically visible organisms have been ruled out as a possible cause."

Transmission experiments with maedi (30) indicated the disease could be transmitted by contact and the incubation period was about two years.

Sigurdsson et al. (29) believed that maedi was a distinctly different disease from infectious adenomatosis or jagziekte both anatomically and clinically. However, proof of the differences was lacking.

Pulmonary Emphysema in the Bovine

Schofield first made reference to pulmonary emphysema in the bovine in the Annual Report of the Ontaria Veterinary College in 1924, as an acute alveolar emphysema in calves. In 1948 Schofield (27) again wrote about acute pulmonary emphysema in cattle. He stated the disease had been reported in France, England and Holland. Barker, in a personal communication to Schofield, said he believed the disease in England "to be a form of hypersensitivity to some agent in the pasture." Seekles in Holland, according to Schofield, believed pulmonary emphysema to be an enterotoxemia associated with Clostridium welchii. He reasoned that the Clostridium welchii toxin damaged the capillary bed in the lungs giving rise to the edema and emphysema. The occasional cases of pulmonary emphysema in which tympany, constipation or diarrhea and jaundice occurred were explained as manifestations of an enterotoxemia.

Schofield mentions the following factors which may have been of etiological significance: Most of the cases he observed were in animals pastured on succulent feed. During years of heavy rainfall, when the plants grew rapidly, the disease was more prevalent. The inclusion of hay or straw in the diet with rape seemed to reduce the incidence of the disease. Due to the repeated occurrence of the disease on certain farms he was of the opinion that soil constituents may have influenced the chemical composition of the plants. Specific bacteria or their toxins, such as Clostridium welchii, may cause edema and emphysema of the lungs. The majority of the cases in Canada occurred in phosphorus deficient areas.

Mackey (19) reported an acute pulmonary emphysema in cattle of the

western range areas.

The condition occurred primarily in the fall and the mortality rate approached 50 per cent.

A short time after the cattle were brought back to the valleys from the mountain summer ranges and thus subjected to a change of feed, the acute respiratory trouble appeared. The disturbance struck at random affecting a particular herd one year or several years in succession. It often skipped a year and then appeared in the same herd again. He reported no higher than two per cent morbidity in any one herd. The vast majority of the cattle became ill in the first week and especially on the seventh day. Both males and females were affected. The most common ages of cattle affected were between three and eight years. The most striking symptom shown was the "very audible expiratory grunt" with the head extended and tongue protruding. The pulse was rapid and weak and the temperature varied between normal and 104° F. The bowel evacuations were usually normal but rumen and intestinal stasis occurred in the more severe cases.

The condition produced death in as little as six hours after the animals were turned into the new feed.

The majority of the deaths occurred in two days and some lingered on a week or more. The costal impressions were still on the lungs when the thorax was opened.

He believed "the animals are sensitized to some substance or combination of substances, possibly protein in nature, which is common to many of the lush green plants."

By using antihistamines in combination with adrenalin intramuscularly, Mackey reported forty recoveries out of forty-two treated. "Along with

treatment, confinement and continued feeding on hay that has been stacked at least one month are essential," Mackey reports. He recommended feeding only hay for two or three days when the cattle first came from the mountain ranges, then allowing them only an hour on the green feed the next day, and gradually increasing this time so that in about a week they may be left entirely on green feed. He warned that early detection is a prime requisite to successful treatment.

Although he reported success in treating these animals it is interesting to note that he advised rest and a change of the ration.

Goodman (11) observed pulmonary emphysema in pastures where the water was highly alkaline, thus having a relatively high pH. He cited one case in which the pH of the water was 8.1 and ten head of cattle died of cow asthma. In another pasture the pH of the water was 7.6 and no trouble occurred. Cattle in both pastures were of same origin and the forage in both pastures was about the same. Goodman states that if Clostridium welchii is a factor, the high pH of the water may influence the growth of this organism or if allergy is a factor, the high pH of the water may influence the allergic reaction.

In the three reports cited here concerning pulmonary emphysema in the bovine, no discussion of the histological alterations of the lungs was presented.

Tissue blocks of bovine lung, with protocols from animals diagnosed as pulmonary emphysema or bovine asthma in Colorado, were courteously furnished by Collier and Flint (2).

Histological studies of these tissues which were stained with eosin and Mayer's hematoxylin presented a typical picture of pulmonary adenoma-

tosis as seen in Iowa. Pulmonary emphysema was evident as was the hyperplasia and hypertrophy of the alveolar and bronchiolar epithelium (Fig. 18). A passive hyperemia was present.

The clinical manifestations, gross and microscopic lesions in bovine asthma so closely parallel pulmonary adenomatosis that it seems probable the diseases are one and the same.

Jagziekte-like Disease of the Equine

Theiler (32) reported a jagziekte-like disease of the equine caused by the ingestion of Crotalaria dura plants. The main lesions were the proliferation of the pulmonary epithelium and the resultant pulmonary emphysema.

The incubation period was from 16 to 80 days. The course of the disease was from 6 to 29 days. In one experiment a minimum of 46 pounds of hay containing Crotalaria dura produced the disease.

It is interesting to note mention was made of a subcutaneous emphysema of cervical region as well as pulmonary emphysema. This lesion occurs in pulmonary adenomatosis and bovine asthma as well. A desquamation of epithelial cells into the lumina of the bronchioles was prominent. The bronchiolar epithelium proliferated markedly and was considered pathognomonic. Edema and fibrosis of the lungs also occurred. Liver cirrhosis and bile duct proliferation was noted.

Steyn (31) produced jagziekte in horses by feeding Crotalaria dura which had been stored for five years.

"Silo-filler's Disease" in Man

"Silo-filler's disease" (18) has been reported as a respiratory disease of man which includes any bronchial or pulmonary condition produced by the inhalation of oxides of nitrogen derived from fresh silage. The lung lesions varied with the amount of nitrogen dioxide which was inhaled.

Clinically, severe dyspnea occurred immediately or within a few hours after exposure by inhalation. Often the two to three week period following the severe initial symptoms was characterized by weakness and mild respiratory distress. Then the more severe symptoms recurred which were accompanied by a fever and chills.

Rales were manifested and roentgenography revealed discrete nodular consolidation throughout the lung.

Treatment consisted of bed rest and oxygen administration. The acute and severe cases terminated in death.

The pathologic alteration was termed a bronchiolitis fibrosa obliterans. The nomenclature indicated the origin of the nodular involvement. The alveolar epithelium as well as the bronchiolar epithelium had undergone hypertrophy and hyperplasia. The fibrosis was pronounced in the bronchioles of man but was not in the bovine. This difference in the lesions may have been due to a species difference in tissue response to the irritant as pointed out by Monlux (25). Delaney et al. (6), in discussing a fatal case of "silo-filler's disease" wrote that the concentration of nitrogen dioxide was 151 parts per million in the silo as compared to the maximum of 25 parts per million allowable in factories. He also reported deaths in the area over a period of ten years in chickens, pigs and cattle when exposed to

such forage. No pathologic description of these animals was available.

Each of these respiratory conditions has much in common clinically and pathologically. Montana progressive pneumonia, jagziekte, epizootic adenomatosis and maedi are all diseases of sheep and all have been considered to be viral in origin. Actual virus isolations have been lacking, however. Jagziekte disease in the equine, pulmonary adenomatosis in Texas and Iowa cattle, and bovine pulmonary emphysema have been considered to be nutritional in origin. "Silo-filler's disease" in man has been caused by the inhalation of nitrogen dioxide gas.

Cowdry and Marsh (4) in comparing jagziekte and Montana progressive pneumonia believed that a dietary factor may have been involved and to illustrate their point they mentioned Theiler's (32) study of jagziekte in the equine. They commented that the respiratory epithelium of the sheep's lung must be unusually prone to undergo proliferative changes because bacterial infections, parasitic infections, and a variety of experimental agents produce such an alteration. Cowdry and Marsh commented further about the etiology of jagziekte and said, "Jagziekte may be caused by a virus but we do not believe that the entire disease complex is caused by such a virus."

The limited etiological studies with oxides of nitrogen were undertaken as a result of the similarity of lesions in "silo-filler's disease" in man caused by nitrogen dioxide and pulmonary adenomatosis. The results indicated that the etiological agents in these two diseases were similar if not identical (28) and (Figs. 19, 20).

In view of the lack of proof concerning definite viral agents in the sheep diseases and in view of the nutritional character of the equine and

bovine diseases, and the proven non-infectious nature of the human disease, all eight of which are pathologically similar, the possibility of a common precursor, if not a common etiologic agent, seems real. Such a precursor or etiologic agent may be food plants and their seeds, high in nitrate content, which release toxic gases during their digestion (21).

Food plant nitrates are known to be increased in immature plants, such as in fast growing lush pastures, in plants grown in drought areas and in plants grown on soils fertilized heavily with nitrates. The possibility that rumen fermentation of such food plants may give off oxides of nitrogen during the conversion of nitrates to nitrite and thereby initiate the disease seems plausible but as yet unproven. The failure of the rumen bacteria to adjust to the rations may produce toxic agents due to incomplete digestion which thereby stimulate septal cell proliferation.

Goodman (11) touched on the subject of nitrates and their possible relation to pulmonary emphysema, if that disease was caused by a bacterial toxin. He cited an article in Journal of the American Medical Association (June 11, 1949, p. 564) entitled, Cyanosis in Infants Due to High Nitrate of Well Water Due to Low Acidity of Gastric Content. The following sentence was among those quoted. "Low acidity permits growth of several organisms capable of reducing nitrate to nitrite in the upper gastrointestinal tract." This statement may have bearing on the pathogenesis of pulmonary adenomatosis if this condition is produced by the absorption of nitrogen dioxide gas when it is given off in the conversion of nitrates to nitrites. The pH of the individual animal's rumen and its resultant bacterial flora may determine the animal's fate.

Although pulmonary adenomatosis in cattle was first reported by

Monlux et al. (23), the syndrome was observed by veterinarians and stockmen in Texas for at least twenty years prior to that time. Acute cases of a similar severe respiratory distress which usually terminated in death had occurred in the Iowa State College cattle herds for at least twenty-five years prior to the report of pulmonary adenomatosis in Iowa (3). Case histories and bacteriological and pathological findings suggest that the condition may have been pulmonary adenomatosis. These observations lead one to believe pulmonary adenomatosis is not a new disease, but one which is only recently recognized. No response to antibiotics, when they were used as a pneumonia therapeutic agent, probably forced the disease to be recognized.

Only a few of the cases of pulmonary adenomatosis observed in Iowa had a subcutaneous emphysema. Monlux et al. (23) found it to be a more prominent lesion in Texas. This has been a common lesion in bovine pulmonary emphysema of the western mountain ranges. It was due to

> over-distention of the alveoli and rupture of the alveolar walls which allowed air to escape into the interstitial tissue of the lung. When the air entered the interstitial tissue it migrated to the hilus of the lung and then escaped into the mediastinum. From there it passed through the anterior thoracic inlet and appeared under the skin of the neck and shoulder (23).

Hartroft (14) states that histologically, in uncomplicated pulmonary emphysema, rupture of the alveolar walls is seldom seen. If rupture does occur it is usually at the alveolar bases abutting the pleura or vascular sheaths. He lists the microscopic diagnostic criteria of pulmonary emphysema as follows: A marked decrease in the average alveolar depth was seen as was a corresponding increase in the average alveolar diameter. The alveolar bases were flattened. That pulmonary adenomatosis is com-

plicated by tissue alterations other than pulmonary emphysema is evident as shown by the proliferation of the septal cells. The same statement can be made in the case of bovine asthma.

Geever et al. (10), in discussing the alveolar lining under various pathological conditions in man and animals, did not find evidence of a continuous "alveolar epithelium" in normal adult lungs. Only occasional scattered septal cells were observed. Under various spontaneous pathologic conditions epithelial-like lining cells were found, and such a lining layer of cells probably prevented a gaseous exchange. He indicated the origin of the epithelium-like cells was probably from the mesenchyme and he believed a high per cent of the mononuclear phagocytes in the lung originated from septal cells.

Bell (1) observed that epithelization of the alveoli was often seen in chronic passive congestion and intestitial pneumonia, apparently as a result of the thickening of the interalveolar septa. He stated that the alveolar walls were not normally covered by a continuous layer of epithelium but in certain diseases a continuous epithelial layer was formed.

Liebow et al. (15) stated that muscle hypertrophy and hyperplasia was common in chronic pulmonary disease. It was especially common in pulmonary emphysema and may have been derived from the alveoli and bronchi, blood vessels and lymphatics. He stated that the bronchioles leading to an emphysematous region may possess great collars of muscle which narrow the lumina, perhaps producing or contributing an obstructive factor to the development of emphysema.

In pulmonary adenomatosis it is readily apparent that the reaction of alveolar septal cells described by Bell (1), the muscular hypertrophy and

hyperplasia described by Liebow et al. (16), and the pulmonary emphysema described by Hartroft (14) are all occurring simultaneously and contribute fuel to each other's flame.

The most acute pulmonary adenomatosis cases, in which the animals died in less than twelve hours, often did not show a pronounced septal cell proliferation. The primary change in the alveolus was the deposition of an eosin staining protein rich plasma which pavemented the alveolar walls. This material had a heavy, viscid, homogeneous appearance. The clinical manifestations in these acute cases were the same as in cases in which the cellular proliferation was pronounced. The functional respiratory area was reduced to a minimum and the animals died of asphyxiation due to the interference with the gaseous exchange. A special staining technique for the detection of fibrin in these cases gave a negative reaction.

The focal coagulation necrosis of the cardiac muscle could be explained as the result of exhaustion and anoxia.

The general passive hyperemia observed in all organs of the body was due to the pulmonary embarrassment. The centro-lobular necrosis in the livers was a direct result of the passive hyperemia and anoxia.

Although the lungs were diffusely involved, the typical adenomatous reaction was often in multiple foci. For that reason, in making a diagnosis of pulmonary adenomatosis, it was necessary to obtain multiple lung samples for histological study.

The treatment of pulmonary adenomatosis consisted in rest and in changing the ration regardless of its content. This procedure was advised routinely and spectacular recoveries were commonplace. Complete rest was a necessity as the least exertion may cause severe respiratory distress

and prove to be fatal. Although many medicaments have been employed as therapy, none of them have been beneficial.

The rapid and complete recoveries which usually followed ration changes added evidence to the belief that pulmonary adenomatosis was nutritional in origin. Frequently recovery occurred when the ration remained qualitatively the same but was from a different source. This fact suggests that the varying chemical composition of the food plants may be a factor.

The entire answer to the question of the pathogenesis of pulmonary adenomatosis may revolve around the alterable chemical constituents of food plants and the appropriate bacterial flora necessary for their digestion.

SUMMARY AND CONCLUSIONS

1. A clinical and pathologic description is presented of an acute non-infectious respiratory disease of the bovine characterized by sudden onset and short duration, varying degrees of pulmonary emphysema and edema and by the hypertrophy and hyperplasia of the respiratory epithelium. It is called pulmonary adenomatosis.
2. This disease has been reported in Iowa with increasing frequency for the last five years. It has been reported in four midwestern states and it is reasonable to believe it occurs throughout the midwest.
3. Pulmonary adenomatosis attacks the bovine regardless of age, breed, or sex.
4. The course of the disease ranges from six hours to five days in those cases terminated by death. Death typically occurs on the third day after onset of dyspnea.
5. The morbidity rate averaged 5.36 per cent in affected herds and the mortality rate in affected animals averaged over 90 per cent in cases not experiencing complete rest and a change of ration.
6. The data and materials used in this study were derived from forty-one herds. Detailed necropsies were performed on ten animals.
7. Histopathologic studies were conducted on most of the important organs of ten cadavers and represent approximately 300 tissue sections. Ethyl eosin and Mayer's hematoxylin stains were routinely used. Weigert's fibrin stain and Gomori's methenamine-silver nitrate stain was used on selected cases.

8. The incidence of the disease was greatest in late summer and fall.
9. The disease is characterized microscopically by pulmonary edema and emphysema, hypertrophy and hyperplasia of the respiratory epithelium and an acute general, passive, hyperemia of all organs of the body.
10. Routine bacteriological studies of the tissues including blood did not reveal the presence of bacteria.
11. Transmission of the disease to other animals was not successful.
12. Limited etiological studies were conducted. It was shown that pulmonary adenomatosis could be produced by the inhalation of nitrogen dioxide gas.
13. Histories, symptoms, gross and microscopic lesions of pulmonary adenomatosis were compared with jagziekte in sheep, epizootic adenomatosis in Icelandic sheep, a jagziekte-like disease in the horse, pulmonary emphysema in the bovine and "silo-filler's disease" in man.
14. In light of the clinical and pathologic similarities of these diseases, it seems possible that all may have a common precursor or even a common etiologic agent.

LITERATURE CITED

1. Bell, E. Hyperplasia of the pulmonary alveolar epithelium in disease. Am. J. Path. 19:901-911. 1943.

2. Collier, J. R. and J. C. Flint. Fort Collins, Colorado. Tissues and protocols of pulmonary emphysema cases. Private communication. 1957.

3. Covault, C. H. Ames, Iowa. Information on atypical pneumonia in Iowa cattle. Private communication. 1957.

4. Cowdry, E. V. and H. Marsh. Pathology of South African jagziekte and Montana progressive pneumonia of sheep. J. Exptl. Med. 45:571-585. 1927.

5. Cross, K. Iowa City, Iowa. Information on "silo-filler's disease." Private communication. 1956.

6. Delaney, L. T., H. W. Schmidt and C. F. Stroehel. Proc. Staff Meet. Mayo Clin. 31:189-198. 1956.

7. Dungal, N. Experiments with jagziekte. Am. J. Path. 22:737-759. 1946.

8. Dungal, N., Gislason, G. and E. L. Taylor. Epizootic adenomatosis in the lungs of sheep - comparisons with jagziekte, verminous pneumonia and progressive pneumonia. J. Comp. Path. and Therap. 51:46-48. 1938.

9. Eber, A. Multiple Adenombildung in den Lungen der Schafe. Zeitschrift f. Thiermed. 3:161-172. 1899.

10. Geever, E. F., K. T. Neubuerger and C. L. Davis. The pulmonary alveolar lining under various pathological conditions in man and animals. Am. J. Path. 19:913-937. 1943.

11. Goodman, A. A. Bovine asthma. North Am. Vet. 37:850-852. 1956.

12. Gridley, M. F. Laboratory manual of special staining technics. Armed Forces Institute of Pathology. Washington, D. C. 1953.

13. Grocott, R. G. A stain for fungi in tissue sections and smears. Tech. Bul. Reg. Med. Technol. 25:171-175. 1955.

14. Hartroft, W. The microscopic diagnosis of pulmonary emphysema. Am. J. Path. 21:889-903. 1945.

15. Liebow, A. A., W. E. Loring and W. L. Felton. The muscle tissue of the lung in chronic pulmonary disease. Scientific Proc., Am. Ass'n. Path. and Bact. 49th Ann. Meeting. (Abstract) Am. J. Path. 28:541. 1952.

16. Liebow, A. A., W. E. Loring and W. L. Felton. The musculature of the lungs in chronic pulmonary disease. Am. J. Path. 29:885-912. 1953.

17. Lillie, R. D. Histopathologic technic. Philadelphia, The Blakiston Co. 1948.

18. Lowry, T. and L. M. Schuman. "Silo-filler's disease" - a syndrome caused by nitrogen dioxide. J. Am. M. A. 162:153-160. 1956.

19. Mackey, D. R. Acute pulmonary emphysema in cattle. Southwestern Vet. 5:342-344. 1952.

20. Marsh, H. Progressive pneumonia in sheep. J.A.V.M A. 62:458-473. 1923.

21. Missouri Agricultural Experiment Station. Forage poisoning in Missouri due to excessive amounts of nitrates. Missouri Agr. Exp. Sta. Bul. 652. 1955.

22. Mitchell, D. Investigations into jagziekte or chronic catarrhal pneumonia of sheep. Third and Fourth Rpt. Dir. Vet. Serv. South Africa. Capetown, South Africa. 585-614. 1915.

23. Monlux, W., J. Fitte, G. Kendrick and H. Dubuisson. Progressive pulmonary adenomatosis in cattle. Southwestern Vet. 6:267-269. 1953.

24. Monlux, W., P. Bennett and B. Kingrey. Pulmonary adenomatosis in Iowa cattle. Iowa Vet. 26, No. 6:11-13. Nov.-Dec. 1955.

25. Monlux, W. Ames, Iowa. Information on the pulmonary response of different species. Private communication. 1956.

26. Parrot, M. J. Ganglions bronchiques et lesions pulmonaires chez les enfants. Compt. rend. Soc. Biol. 28:308-309. 1876.

27. Schofield, F. W. Acute pulmonary emphysema of cattle. J.A.V.M.A. 112:254-259. 1948.

28. Seaton, V. A. Pulmonary adenomatosis in cattle produced by nitrogen dioxide poisoning. North Am. Vet. 38:109-111. 1957.

29. Sigurdsson, B., H. Grimsson and P. Palsson. Maedi, a chronic progressive infection of sheep's lungs. J. Inf. Dis. 90:233-241. 1952.

30. Sigurdsson, B., P. Palsson and A. Tryggvadottir. Transmission experiments with maedi. J. Inf. Dis. 93:166-175. 1953.

31. Steyn, D. G. Recent investigations into the toxicity of known and unknown poisonous plants in the Union of South Africa. Seventeenth Rpt. Dir. Vet. Serv. and Anim. Indust. Capetown, South Africa. 707-727. 1931.

32. Theiler, A. Jagziekte in horses (Crotalariosis equorum). Seventh and Eighth Rpts. Dir. Vet. Serv. South Africa. Capetown, South Africa. 57-104.

APPENDIX: CASE HISTORY FORMS

Path. Accession No. _____ Clinical Diagnosis _____

Vet. Diag. Lab. No. _____ Date _____

Owner

Veterinarian

No. of animals affected _____ No. of animals in herd _____

Sex _____ Age _____ Breed _____

How long has the animal(s) been sick?

Was the onset of symptoms simultaneous in all affected animals?

If not what was the time interval?

Symptoms

Temperature range

General condition

Heart rate

Auscultation

Temperament

Discharges?

Conjunctivitis?

Dermatitis?

Subcutaneous emphysema?

Constipation or diarrhea?

Respiratory movements and other observations

Treatment, if any:

Response

Has this animal(s) been sick previously?____ When____ Diagnosis_____

Has this same respiratory condition ever occurred on this farm previously?___

When?_____

Origin of affected animal: Home raised_____ Purchased_____

Type of feed or pasture

How long has the animal been on this feed or pasture?_____

Has any change in feeding routine occurred recently?

Have the affected animal(s) been subjected to any sudden change of weather or environment: When and in what manner? New additions to the herd?

Did any of the affected animals experience a recurrent attack when returned to the original feed or pasture?

Post mortem lesions.

FIGURES

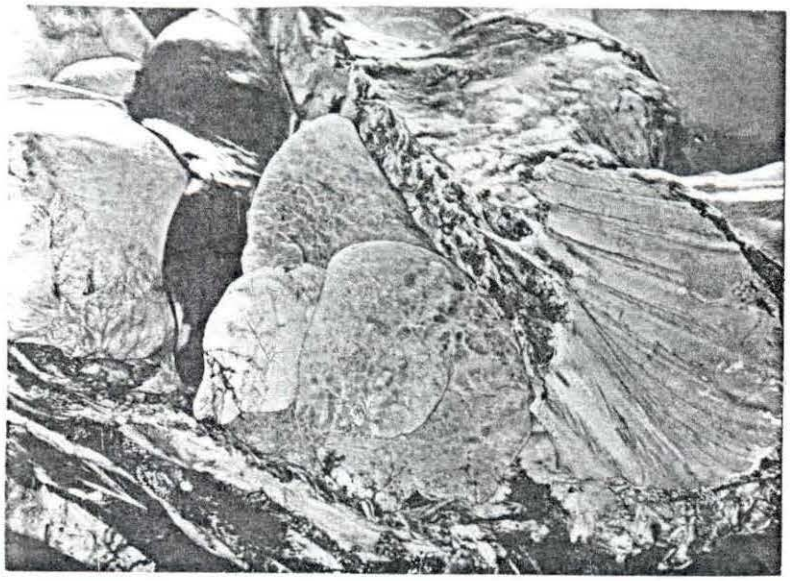

Fig. 1. Large, firm, heavy lungs fill the thoracic cavity.

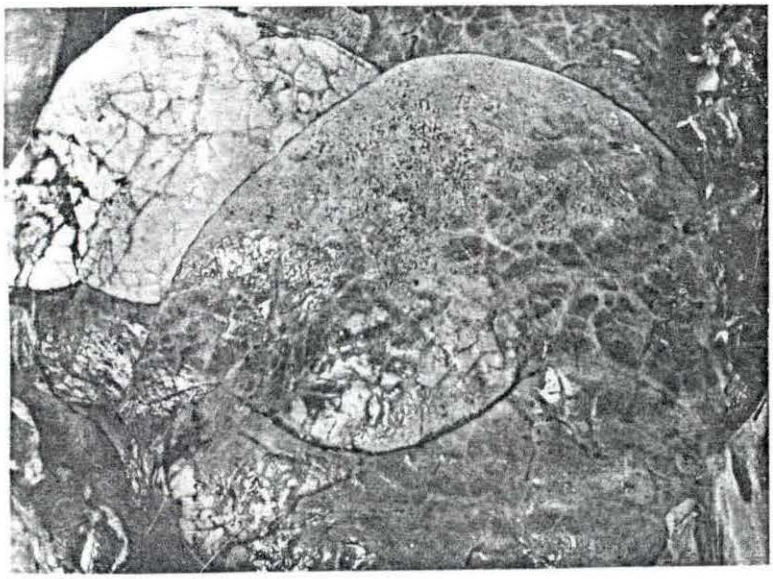

Fig. 2. Pulmonary edema and emphysema.

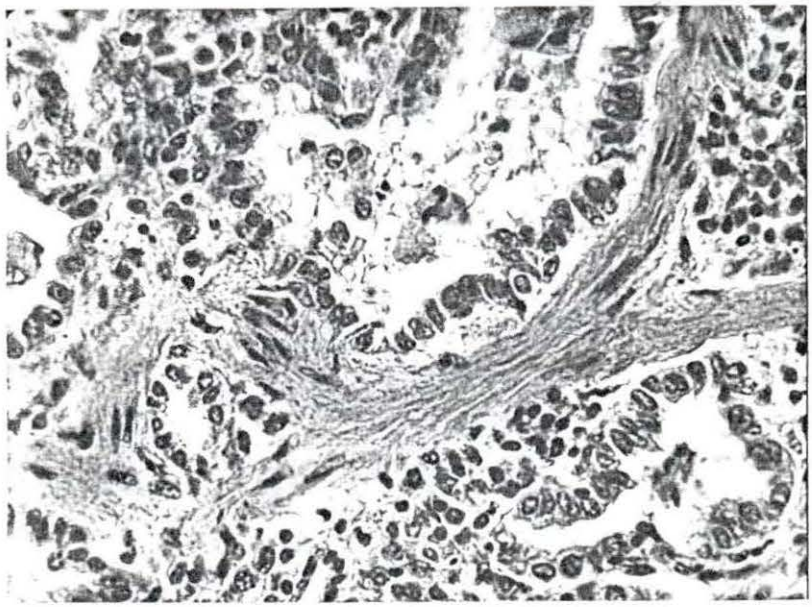

Fig. 3. Hypertrophy and hyperplasia of the pulmonary epithelium and muscle.
X410.

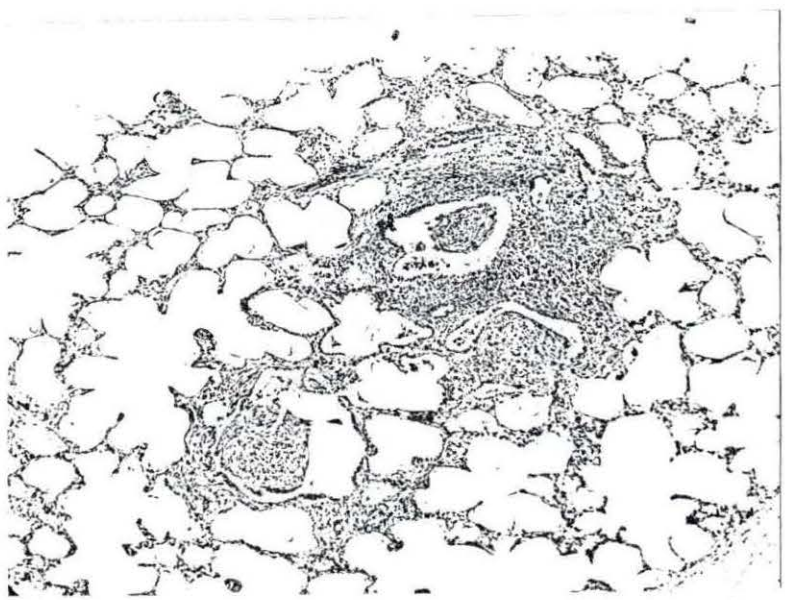

Fig. 4. Focal adenomatosis.
X100.

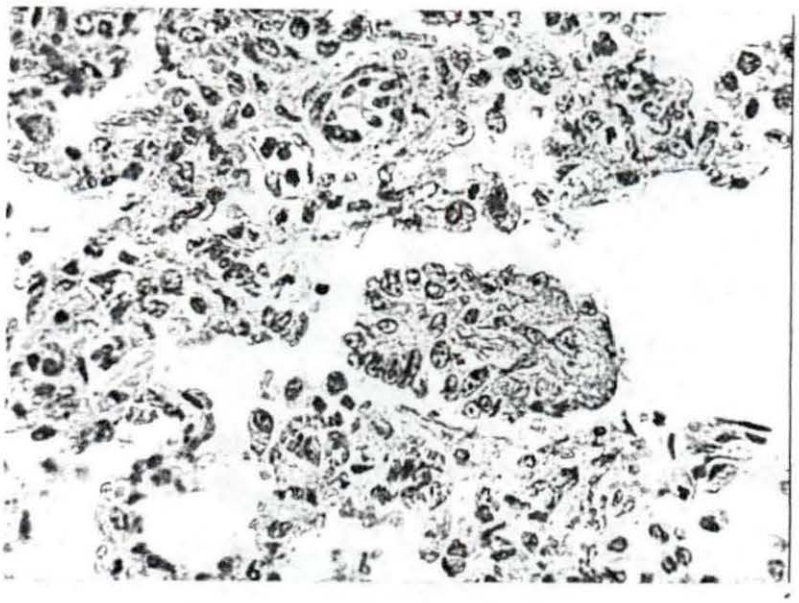

Fig. 5. The pulmonary epithelium can assume a giant cell appearance due to rapid proliferation.
X410.

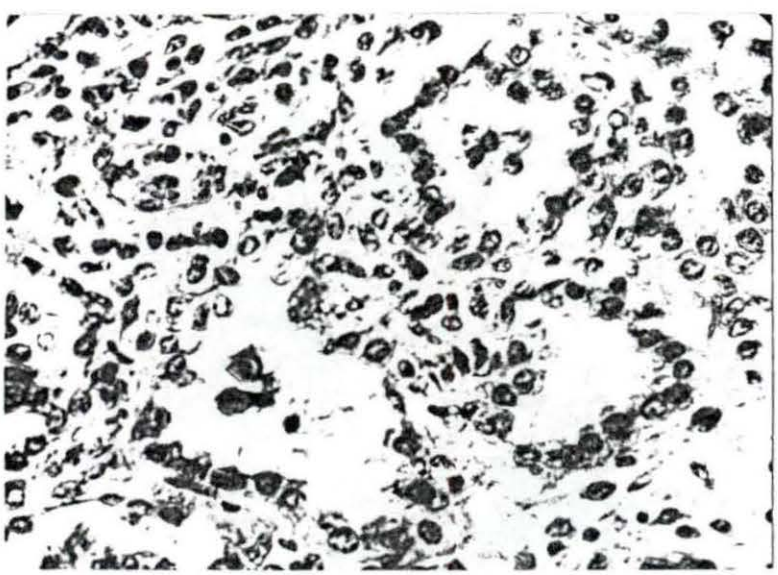

Fig. 6. Proliferation of the septal cells simulates a glandular architecture.
X410.

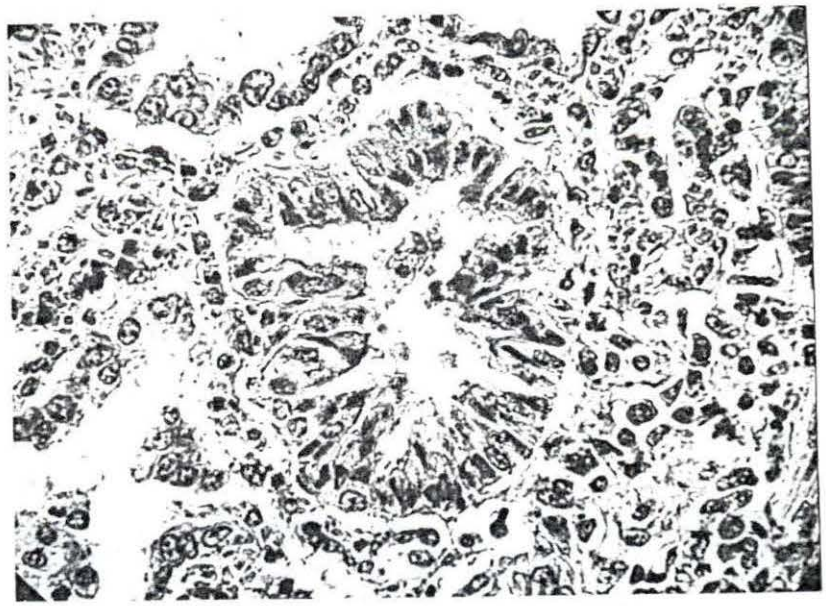

Fig. 7. Proliferating pulmonary epithelium forms layers of cells.
X410.

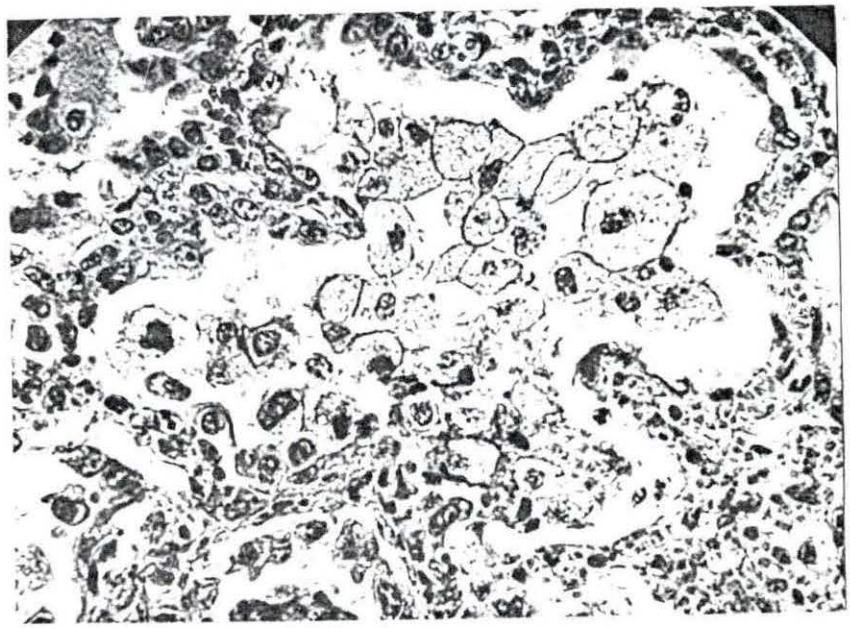

Fig. 8. Alveoli are filled with new layers of septal cells and their desquamated predecessors.
X410.

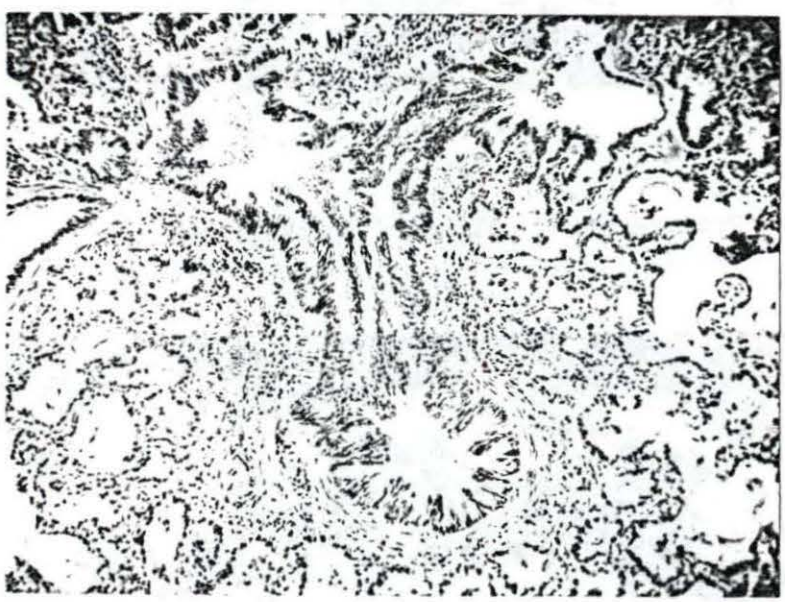

Fig. 9. Hyperplasia and hypertrophy of the bronchiolar epithelium.

X100.

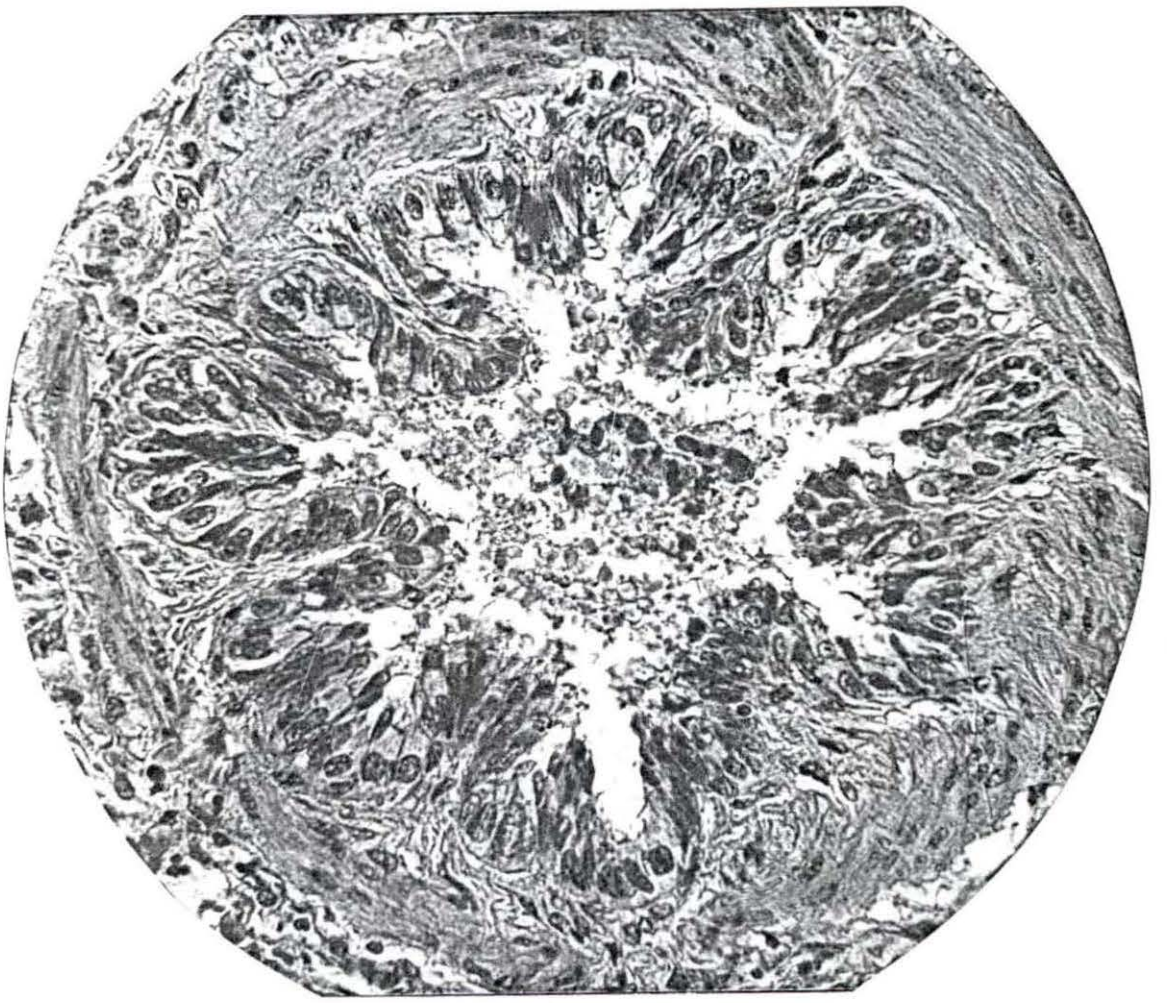

Fig. 10. Desquamated alveolar and bronchiolar epithelium nearly fills the bronchiole.
X410.

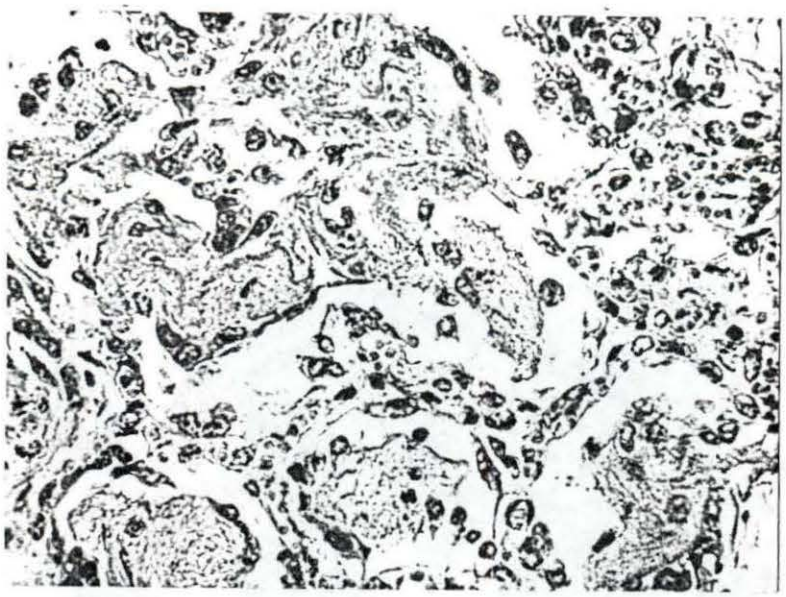

Fig. 11. In acute cases, the alveolar walls are pavemented with a protein substance.
X410.

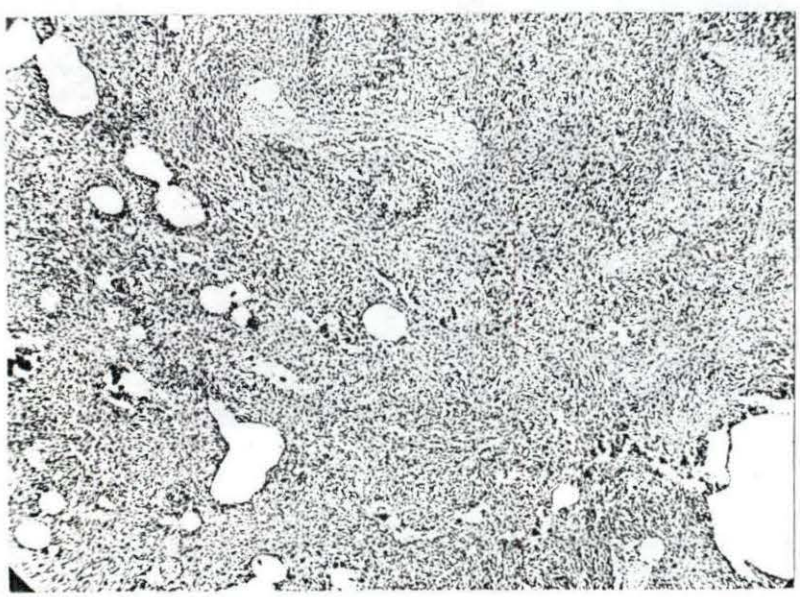

Fig. 12. Hyperplasia of the lymph node.
X100.

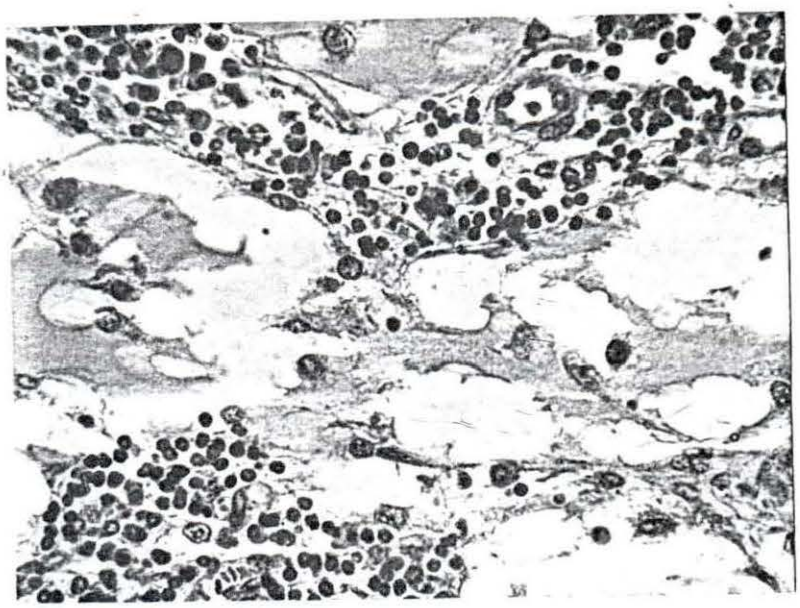

Fig. 13. Emphysema and edema of the lymph node. X410.

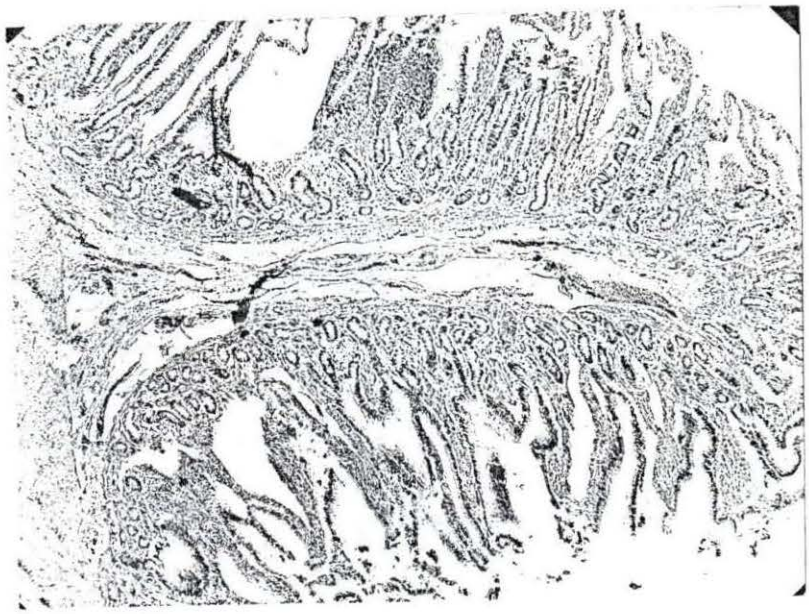

Fig. 14. Passive hyperemia of the small intestine. X34.

Fig. 15. Passive hyperemia and centro-lobular necrosis of the liver.
X100.

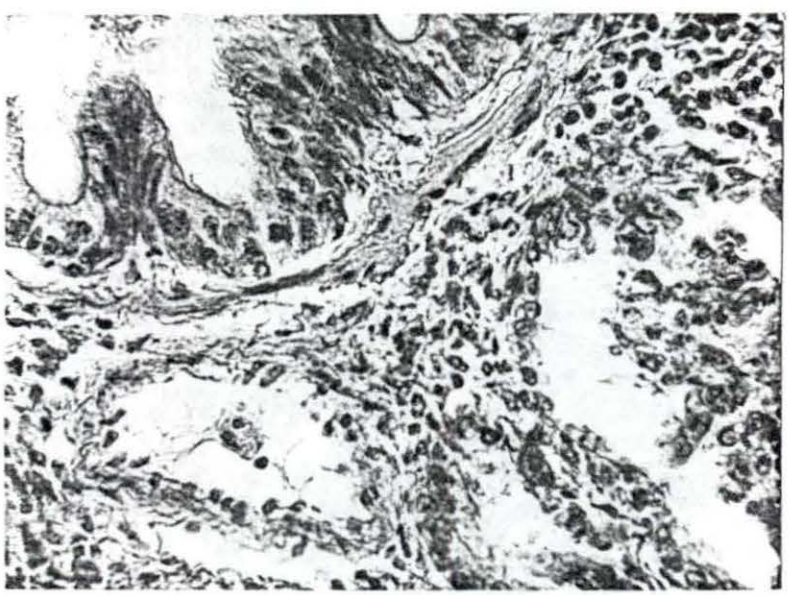

Fig. 16. Montana progressive pneumonia in the ovine.
X410.

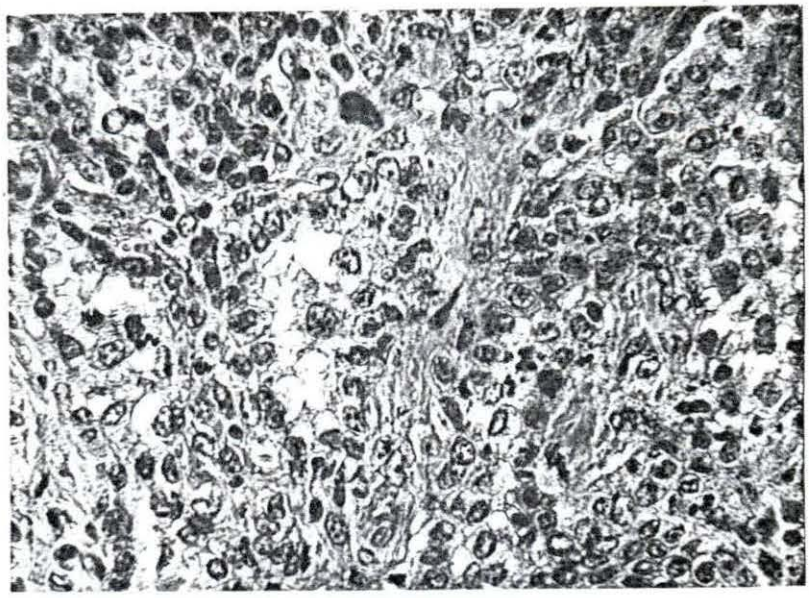

Fig. 17. Maedi in the ovine. (From 1954 seminar of the American College of Veterinary Pathologists.) X410.

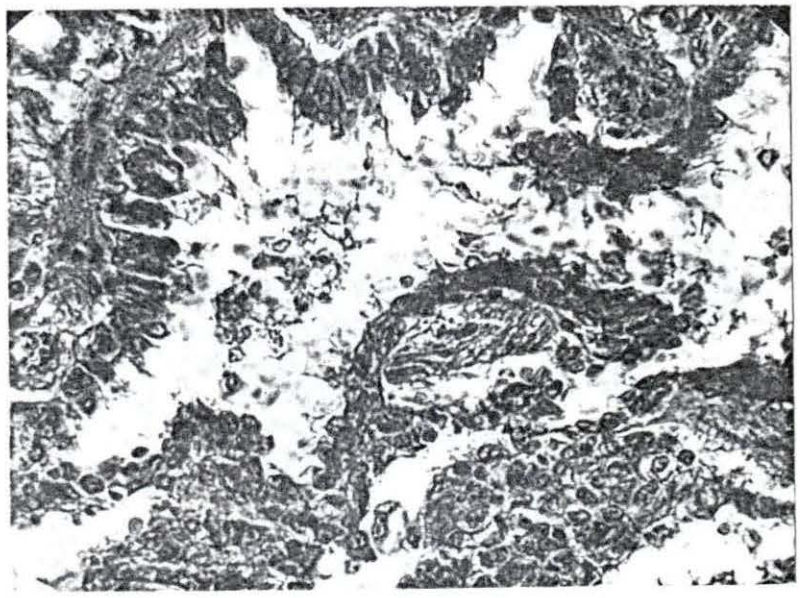

Fig. 18. Pulmonary emphysema in the bovine. X410.

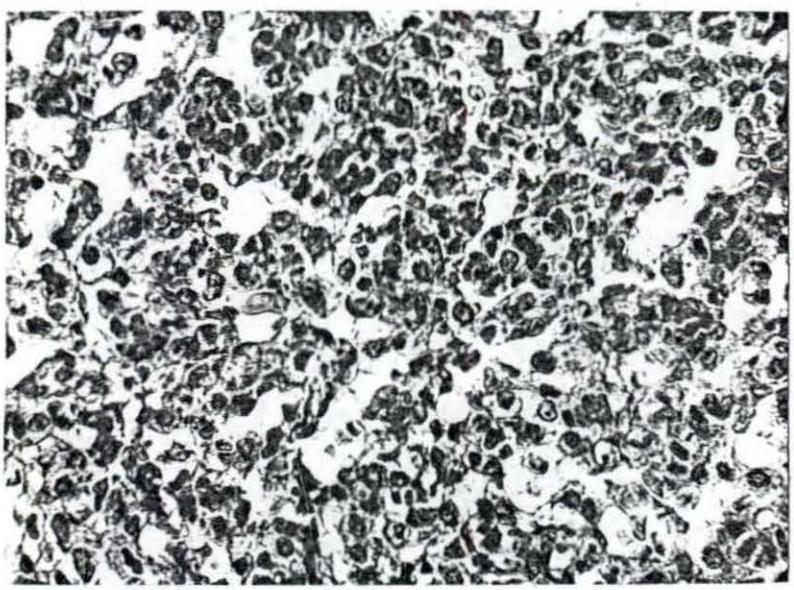

Fig. 19. Pulmonary adenomatosis experimentally produced in a guinea pig.

X410.

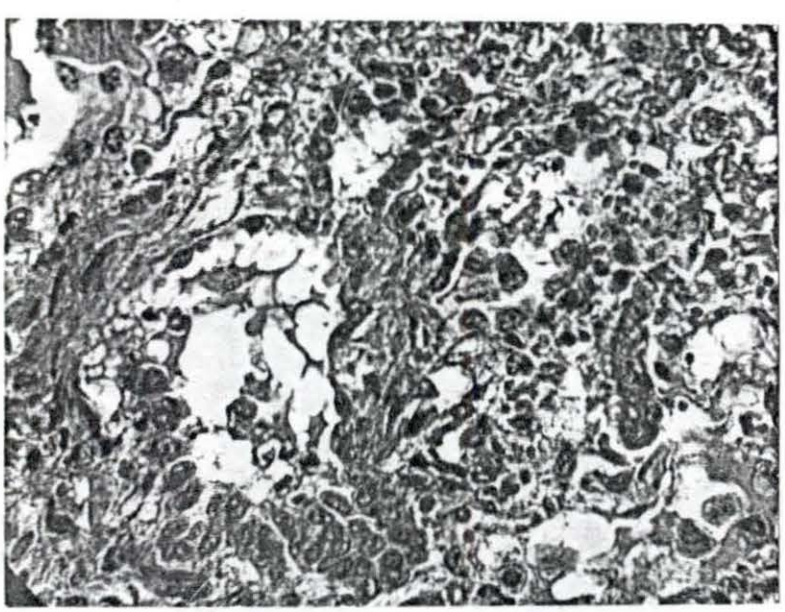

Fig. 20. Pulmonary adenomatosis experimentally produced in a bovine.

X410.

ACKNOWLEDGMENTS

The writer wishes to express his profound appreciation to Dr. W. S. Monlux, Department of Veterinary Pathology, for his invaluable guidance, patient counsel and stimulating critique throughout this investigation.

The helpfulness and interest of Dr. E. A. Benbrook, Head, Department of Veterinary Pathology, was deeply appreciated.

The writer gratefully acknowledges the following members of the veterinary staff for their assistance:

Dr. P. C. Bennett, Supervisor, Iowa Veterinary Medical Diagnostic Laboratory, for his interest and aid in obtaining specimens for study.

Dr. B. W. Kingrey, Head, Department of Veterinary Medicine and Surgery, for the use of clinical equipment and facilities during the etiologic studies.

Mr. Donald T. Mason for his suggestions and technical advice in the preparation of tissues for study.

Many thanks are due to Dr. Hadleigh Marsh, State Veterinarian, Helena, Montana, for histological specimens of Montana progressive pneumonia in the ovine.