

THESIS

Guinea pigs - Diseases

Streptococcus lympho-
dermitis,

Bacteriology

STREPTOCOCCIC LYMPHADENITIS

IN THE GUINEA PIG

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THESIS

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THESIS

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INTRODUCTION

From time to time during the past eighteen months several guinea pigs have been found in our colony with abscesses in the lymph glands. In the fall of 1930 this condition became of considerable importance as it appeared in our stock pigs with a tendency, in many cases to run an acute course. Many of the pigs showing enlarged glands and many of those heretofore apparently healthy suddenly became sick and died. New projects involving the use of guinea pigs could not be started as the stock pigs were badly affected and new cases were appearing rapidly. It was due to this condition that an investigation of this problem was undertaken.

There are no data available upon which an accurate estimate of the economic importance of this disease can be based. However, it occurs frequently in guinea pig colonies and, once established, is a very stubborn condition to eradicate.

There appears thus far to be no effective prophylactic nor curative treatment. Furthermore, no diagnostic procedure has been recommended that has a high degree of efficiency in severe epizootics. Megrail and Hoyt (14) found that the serum of guinea pigs which had abscesses possessed no agglutinins for the strains of streptococci isolated from their abscesses. Several have made frequent manual examinations for swellings of the lymph glands and subsequent isolation of all affected animals, together with the exercise of hygienic methods of handling. Here again one meets with difficulties. Due to the insidious onset and chronic course

usually manifested, the disease may be present for a long period of time in a latent form in some hidden part of the body and the organism be eliminated from the body openings such as the eyes, nasal passages, vagina, etc. from time to time. It may even produce internal abscessation which escapes the most careful examination. As a chronic case may at any time develop septicaemia and discharge numerous bacteria in the body excretions, an animal thus affected may be a severe menace to all guinea pigs with which he comes in contact.

One of the important requirements of the biological sciences is the maintenance of good health in laboratory animals. Diseased animals are a severe handicap to any scientist who has to use them for experimental work. Their use leads to incorrect interpretation of pathological lesions, confuses clinical symptoms, and the presence of their etiological organism may make it impossible to obtain cultures of the organism used in the experiment. This is especially true with animals spontaneously infected with streptococcus. For example, it is sometimes difficult, especially on gross examination, to differentiate between streptococcus lesions and those due to Brucella abortus.

REVIEW OF LITERATURE

Not a great deal of literature on Streptococcus diseases in the guinea pig is available. That covering its pathologic aspects is especially meager. Most authors have dealt mainly with the bacteriological phases, only mentioning the more conspicuous gross pathological lesions.

Among the earlier reports Malassey and Vignal (2) in 1883 and 1884 described an infection which they named "Tuberculose Zoogleique". The lesions are large, mass-like structures containing large numbers of an organism which was undoubtedly streptococcus. This was not, however, a spontaneous epidemic. The disease was produced by injection of material from a subcutaneous abscess in a child dying of tuberculous meningitis. No tubercle bacilli were found in the pus from this abscess, but after several animal passages the coccoid organisms disappeared and the tubercle bacillus was found. Also the animals survived longer after inoculation. In 1885 Eberth (1) described gross and microscopic lesions in the lungs, liver, abdominal lymph glands, and spleen, a condition which he named pseudotuberculosis. He also found chain formations of cocci. Chantemesse (3) in 1887 and Dor (4) in 1888 also reported infections which were probably the same as those of Malassey and Vignal. Dor's infection in guinea pigs, however, was experimental. He obtained the material from an abscess in a rabbit.

Epizootics have apparently taken different forms as reported by various twentieth century writers. In 1901 Weber (5) reported an epizootic affecting chiefly the lungs.

Wagner (6) in 1904 found the uterus involved, mainly causing abortion of fetuses and puerperal endometritis. Teacher and Burton (8), in 1914, reported an epizootic which caused nearly all of their breeding sows to abort or give birth to immature young. The placentas showed degeneration and extensive necrosis with large numbers of streptococci in the uterus and on the placenta. Boxmeyer (7) in 1907 reported an extensive epizootic of lymphadenitis due to a gram positive staining hemolytic streptococcus in which over 3000 guinea pigs were affected. Studies were made on over 100 of these in which he found 90 % to have affected lymph glands, and occasionally the liver, uterus, and lungs were involved. A few cases developed septicaemia and pyemia. In pigs three to four weeks of age the infected cervical glands appeared as palpable, shot-like nodules about the size of small peas beneath the skin. These, on sectioning, were found to be edematous and congested. As the pigs grew older, the glands increased in size and developed areas of softening which fused to form abscesses. The abscesses enlarged rapidly, occasionally reaching the size of a hen's egg. Endothelial cells and fibroblasts formed large groups of mononuclear cells between the lymph follicles which involved them as they increased in size. In more advanced cases these foci softened in their centers, increased in size, and fused together to produce abscesses. Infection was found to take place early in the life of the animal largely through abrasions in the throat from eating contaminated rough foods. Experimental infection was produced in this manner. The organism was found to be pathogenic for guinea pigs, rabbits,

and mice. Adult guinea pigs were much less susceptible than immature animals.

In 1916 an article was published by Holman (10) on "Spontaneous infection in guinea pigs", in which streptococcus infections were found in 94 guinea pigs. Streptococcus pyogenes was isolated from 49 cases of pneumonia, ten cases of acute endometritis, and occasionally from various other parts of the body. Only one cervical abscess was found.

Hardinbergh (11) in 1926 reported an epizootic in which 65 guinea pigs out of a colony of 750 were affected. In 58 guinea pigs a total of 89 abscesses was found. The submaxillary lymph nodes in 45 cases were involved, the cervical in 26, the precrural in fourteen, and the parotid and inguinal each in two. Pure cultures of hemolytic streptococcus were found in 51 of these cases. Subcutaneous inoculation killed two out of three guinea pigs and produced a local abscess in the third. Three guinea pigs were fed cultures of hemolytic streptococcus. Two of these remained well, and the third developed pneumonia, and streptococcus was obtained from the lungs. Inoculation via the conjunctiva did not develop any disease. Spontaneous infection ran a chronic course (only two cases died) while the artificial infection usually ran an acute fatal course. (The organism was pathogenic for white mice, white rats, and rabbits.)

In 1928 Parsons and Hyde (12) examined 189 cases of streptococcic infection in a colony of complement deficient guinea pigs. A combination of lymphadenitis, pneumonia, and puerperal types was found. From these, 77 strains of streptococcus were studied. According to growth on blood agar,

twelve were A, 49 were B, and fifteen were Y types. All of these strains produced capsules.

Experimental intraperitoneal inoculation produced subcutaneous abscesses at the point of injection in one half of the cases and chronic lymphadenitis in a few cases. Acute types were produced experimentally only in new born guinea pigs.

Another epizootic was reported in 1928 by Megrail and Hoyt (14) in which 35 animals with abscesses mostly in the cervical region were examined. Every animal but one showed the presence of both streptococcus and staphylococcus organisms. This one gave a pure culture of streptococcus. The organism showed a definite tissue localization, only one case showing any involvement of internal organs. After a series of experiments, they concluded that the disease was due to both B and Y types of streptococcus and that the staphylococcus was merely a secondary invader. Experimental intradermic inoculation of animals gave the highest percentage of infection. Most cases developed local abscesses at the point of inoculation and in the regional lymph glands. A few cases ran an acute course, resulting in septicaemia and pyemia. The serum of pigs with abscesses did not agglutinate streptococci isolated from their abscesses. The organism was found to be pathogenic for white mice, white rats, and rabbits. An epizootic was described by Cunningham (13) in 1929 which involved the cervical lymph glands principally. The organism was an incapsulated streptococcus similar to that found by Parsons and Hyde.

ETIOLOGY AND CULTURAL CHARACTERISTICS

The material used in this investigation, except for the experimental animals, had its origin in a lot of 65 guinea pigs which were intended to be used for another project. From time to time infected pigs from the stock colony were added, bringing the total number of animals kept under observation up to 80. Many other guinea pigs in the stock colony developed abscesses in the lymph glands, but due to the amount of routine necessary for a detailed study it was not possible to utilize all of the available material.

Out of the 65 original guinea pigs only nine remained well, gave negative cultures, and showed no pathological lesions attributable to streptococcus infection.

Because of limited housing conditions, it was necessary to keep these animals for three months in a basement room of one of the campus buildings. During the early fall it was difficult to maintain an even temperature in this room, which resulted in the room becoming overheated a few times. However, this condition was promptly corrected, and no further trouble of that kind developed. The high morbidity of the infection in this group of animals may possibly be due to the animals' becoming overheated a few times.

B. streptococcus was isolated, in most cases in pure cultures, from all cases examined. All strains were gram positive, aerobic, and non capsulated and produced acid on all culture media used. No hydrogen sulphide or other gases could be detected. Nitrates were reduced to ammonia. Three strains reduced nitrates to nitrites. The size of the cocci

varied considerably with different strains and on different culture media, averaging about .7 microns. The length of the chains varied from 2 to 30 or more elements, usually growing singly and in chains of two to six. Acid was produced in litmus milk, but there was no coagulation of the casein nor reduction of litmus. On nutrient agar, the growth was visible after 18 to 24 hours as minute, round, smooth, finely granular, semi-translucent, discrete, raised colonies. They showed a marked tendency to remain discrete for several days even when sown thickly. Nutrient broth remained clear with a fine granular sediment at the bottom and small flakes adhering to the sides of the tube. On blood agar, all types produced a wide zone of hemolysis which was noticeable after six to eighteen hours. Twenty five strains were tested on the sugars according to Holman's (39) classification. Mannite, raffinose, and inulin were not fermented, saccharose only was fermented by five, lactose and saccharose by two, and salicin and saccharose by one.

PATHOGENICITY

Pus containing hemolytic streptococcus from the lymph glands of an infected guinea pig was found to be pathogenic for mice and rabbits. Two mice injected subcutaneously developed large, local, subcutaneous, inflammatory swellings and died of septicaemia in 72 hours. One rabbit, inoculated subcutaneously, developed a local inflammatory swelling and died of septicaemia in twelve days.

ACUTE LYMPHADENITIS

The period of incubation in acute cases varies from one to ten days. The course is rapid, terminating in death in from eight to 48 hours after the first noticeable symptoms. Indeed, in the majority of cases, the animal may appear well and be found dead on the following day without giving one a chance to observe clinical symptoms.

The clinical symptoms of acute lymphadenitis occurring as a primary condition or developing secondarily in a case of chronic lymphadenitis are those of septicaemia. The onset is sudden. In cases which we have had an opportunity to observe the animal, the general symptoms of an acute febrile affection such as debility, weakness, and anorexia are presented. Rather marked loss of weight is noticeable even in animals which have been sick but a short time. In case of respiratory complications there may be a purulent nasal discharge which adheres to the nostrils, usually respiratory sounds are heard, coughing and sneezing are common, and in case of pneumonia or pleuritis a marked dyspnea is noticed. There may be conjunctivitis involving either one or both eyes with reddened mucous membranes and a mucous or mucopurulent discharge which adheres to the hair below the eyes. Upon handling the animal does not make the usual vigorous effort to escape and will often lie limp in the hand. The temperature as taken per rectum bears no relation to the condition of the animal or stage of the disease. It fluctuates considerably from day to day, anywhere from 37° to 40° with an average of 39°. This temperature range is found

to be the same in normal animals as in sick animals.

Anatomical changes - The acute forms assume the role of a septicaemia. Hyperemia and inflammatory edema with numerous streptococci in the superficial lymph glands are constant symptoms with a slight increase in their size, which is due mainly to edematous swelling as there is usually no hyperplasia of the cells. There may or may not be exudation of leucocytes. Parenchymatous organs manifest changes usually associated with septicaemia and pyemia. Streptococcus bronchopneumonia is the most frequent general manifestation. Next in importance are fibrinous, sero-fibrinous, or fibrinopurulent pleuritis and peritonitis. Other organs occasionally affected are in order of their frequency: liver, heart, uterus, spleen, small intestine, bone marrow, thyroid, and adrenal glands. The lesions in these organs are usually focal in character, suggestive of pyemic origin. Often in acute cases there is little or no exudation of blood cells into the affected part. In cases of septicaemia developing in an animal with chronic lymphadenitis we find a very active exudation of leucocytes. Degenerative changes including cloudy swelling, hydropic and fatty degeneration are frequently seen in the liver, kidneys, and heart muscle.

CHRONIC LYMPHADENITIS

The period of incubation has not been established. Apparently it varies considerably.

Abscesses may develop in a few weeks and rupture or may

remain visible to the eye for several months.

The only clinical symptom that can be observed in chronic cases is swelling of the superficial lymph glands. In the early stages this can be detected by palpation only as firm, shot-like nodules in the submaxillary, cervical, sublingual, prescapular, postscapular, and prefemoral regions. These occur single or multiple and vary in size from two to five mm. in the early cases up to as much as 40 mm. in those showing advanced abscessation. As the nodules enlarge in size, an area of softening and fluctuation appears over which the skin becomes adherent. Eventually the abscess ruptures at this point and discharges a large quantity of thick, creamy white, homogeneous, finely granular pus which on stained smear shows large numbers of streptococci and necrotic debris. The abscess continues to drain for several days after which the wound closes and complete healing takes place. Another abscess may develop in the same region or in other glands. No cases have been observed in this epizootic in which an animal has recovered completely from the infection even after one or several abscesses have ruptured and healed.

Out of 82 cases observed, 65 involved the cervical glands, 42 the submaxillary, 14 the prefemoral, 20 the sublingual, 6 the prescapular, 2 the postscapular, and 3 the internal iliac lymph gland.

Anatomical changes - Scattered throughout the cortex of the gland and arising independently of the germinal centers are foci in which the normal lymphoid cells are entirely replaced by large mononucleated cells with pale staining cytoplasm and large reticular nuclei. These cells have a

very marked phagocytic activity for streptococci which are often found scattered throughout the central portion of the lesions. For convenience these will be called macrophages. As the lesions increase in size, they become confluent and develop areas of necrosis in their centers. At this time polymorphonuclear leucocytes invade the lesions, the bacteria multiply, and the suppurative process develops rapidly. At the same time there is great fibroblastic and vascular endothelial cell hyperplasia at the margin of the lesion showing a tendency to incapsulate the developing abscess. Soon the primary lesion is entirely obliterated and reduced to pus. The necrotic process attacks the inner layers of the fibrous tissue capsule, and at the same time more layers of fibrous tissue are laid down at the periphery. Thus the abscess increases in size until the overlying skin becomes involved. Due to inadequate circulation no further incapsulation can take place at this point, and the suppurative process erodes its way to the surface with subsequent rupture of the abscess.

TECHNICAL METHODS

All living animals were killed by a blow on the head. Sections from the heart, liver, spleen, kidneys, lungs, lymph glands, and any other organs or tissues showing evidence of disease were removed with sterile instruments and smeared over beef liver agar plates containing 5 % defibrinated cow's blood. These were incubated for 48 hours at 37° and then 48 hours at room temperature. In every case a markedly hemolytic streptococcus was obtained often in pure culture

and in a few cases a non-hemolytic dyplococcus was obtained from the lung.

Subsequent inoculations were made on nutrient agar slants containing 5 % defibrinated cow's blood.

Histological technique - The tissues were fixed in Zenker's fluid, imbedded in paraffin, and stained by the following method:

1. Stain to a deep blue color in Harris's hematoxylin and differentiate until the section shows a pale pink color in 95 % alcohol containing about ten drops of HCl to each 50 cc.
2. Neutralize acidity in weak aqueous NH_4OH solution.
3. Wash in water.
4. Stain lightly in 1 % eosin.
5. Mix 3 cc. of 5 % aqueous solution of NaHCO_3 with 6 cc. of 1 % aqueous solution of Gentian violet. Pour onto slides immediately and allow to stain for two minutes.
6. Pour off excess stain and cover with Lugol's solution, (one third U. S. P. strength) one minute.
7. Rinse off excess iodine and stains under tap.
8. Decolorize slightly by dropping a mixture of one part ether and three parts acetone on the slide until the excess of stain begins to come out of the section. This should be watched very closely so as not to decolorize too much, thereby removing the hematoxylin stain. Two or three seconds time is usually long enough.
9. Wash in water immediately.
10. Dehydrate by dipping the section four or five times in 95 % and then absolute alcohol.

11. Clear in xylol.

12. Mount in xylol Canada balsam.

From 8 to 10 inclusive the slides should be handled individually since this is the most critical part of the staining technique, and these steps must be accomplished rapidly or a part of the nuclear stain will be lost. One should not attempt to remove all of the excess stain by washing in acetone-ether. This is not necessary. The acetone-ether quickly dissolves all of the precipitated gentian violet except that which is contained in Gram positive bacteria. It is then readily removed by the water, alcohol, and xylol baths. This method is very simple, and, if directions are followed, one should be able to obtain very good histological sections with the bacteria well stained in situ.

EXPERIMENT I

Feeding Experiment

Guinea pigs 101, 102, and 103, weighing 750, 620, and 740 grams respectively, were prepared by feeding each 1 cc of bile to render the mucous membranes more permeable. Two hours later each animal received orally with a medicine dropper 1 cc. of a 48 hour liver infusion broth culture of hemolytic streptococcus isolated from a case of lymphadenitis.

Guinea pig 101 was found dead with streptococcus septicaemia on the 117th day after exposure. The principal anatomical lesions found were unilateral bronchopneumonia with serofibrinous pleuritis. A pure culture of hemolytic strep-

tococcus was isolated from the lung, pleural fluid, and cervical lymph glands. All other organs cultured were negative. The long incubation period and the acuteness of the pathological conditions found, together with the total absence of any long standing lesions, makes it doubtful that infection could have been due to inoculation and suggests that it might be due to natural exposure.

Guinea pig 102 died seventeen days after exposure with acute bronchopneumonia, acute lymphadenitis, acute myocarditis, and nephrosis. Pure cultures of hemolytic streptococcus were isolated from the lungs, heart, and cervical lymph glands.

Guinea pig 103 remained well 208 days and showed no clinical evidence of infection at any time.

Protocols

Guinea pig 101.

Sex - female.

Weight - 750 grams.

History - On the 117th day after exposure the animal was found dead.

Autopsy findings:

The general condition is fair. The animal has lost 60 grams in weight and shows a slight serous nasal discharge.

Thoracic cavity - Contains about 10 cc. of serosanguinous fluid. The dorsal aspect of the right lung with the adjacent parietal pleura and the apical portion of the pericardium with the adjacent parietal pleura are covered with a heavy layer of fibrinous exudate. All of the right apical, cardiac, and about one half of the right diaphragmatic lobes are consoli-

dated and show a mottling of red and grey hepatization. The entire left lung shows variable amounts of edema and congestion. The bronchial mucous membrane is somewhat hyperemic. The lumina of the bronchi contain a considerable amount of frothy sanguinous watery fluid. The bronchial lymph glands are somewhat enlarged and congested.

Peritoneal cavity - Contains no excess of fluid. The surfaces are smooth.

Heart - Apparently normal.

Liver - Marked cloudy swelling and slight fatty changes.

Kidneys - Marked cloudy swelling.

Uterus - Slightly hyperemic.

Cervical lymph glands - Slightly enlarged.

All other organs - Apparently normal.

Histological examination:

Lungs - There is great thickening of the pleura with fibroblastic proliferation involving the subpleural lung tissue to a small extent. The pleural surface is covered with a dense layer of fibrinous exudate heavily infiltrated with polymorphonuclear leucocytes. The subpleural zones are greatly congested and consolidated with fibrinous exudate in the alveoli. The bronchial and vascular walls are somewhat thickened and edematous and contain a small number of leucocytes. The mucous membrane of the bronchi is in most cases almost completely eroded and contains a few leucocytes and streptococci. The alveoli in the lung tissue surrounding the bronchi contain an exudate mainly leucocytic but with some fibrin. This region also contains dense chains of streptococci. Few foci show a hemorrhagic exudate in the

alveoli and in a few places mainly laked blood. Throughout the lung variable amounts of edema are found.

Bronchial lymph glands - Swollen, congested, and edematous.

Heart - Apparently normal.

Liver - Extensive passive congestion and edema with considerable atrophy of the liver cords especially noticed in the central part of the lobe. Occasionally a focus of necrosis is found.

Kidney - The cortex and medulla are congested and contain a few scattered small intertubular hemorrhages. The tubular epithelium shows marked cloudy swelling. Many glomeruli present degenerative changes as evidenced by hydropic appearance of some of the endothelial cells of the capillary tuft with the presence of erythrocytes in the subcapsular space of Bowman's capsule. A few glomeruli show slight evidence of proliferative changes but not enough to classify as acute diffuse proliferative glomerulonephritis. There is also a considerable amount of finely granular pink staining homogeneous material in the glomerular subcapsular spaces and tubular lumina.

Cervical lymph glands - Moderately swollen, moderately congested, and show diffuse inflammatory edema with some fibrin, numerous macrophages, and polymorphonuclear leucocytes in the exudate. There are a few streptococci in the gland almost completely phagocytosed by the macrophages. Occasionally a polymorphonuclear leucocyte is found with bacteria in its cytoplasm. The capsule and marginal sinuses are very edematous.

All other organs - Apparently normal.

Anatomical diagnosis: Streptococcus septicaemia with bronchopneumonia, serofibrinous pleuritis, acute lymphadenitis, and acute diffuse degenerative glomerulonephritis.

Guinea pig 102.

Sex - female.

Weight at time of exposure - 620 grams.

History - On the twelfth day after exposure the animal showed a general lassitude and a greatly reduced reflex excitability. Respiration 100. Died on the seventeenth day.

Autopsy findings:

The animal is slightly emaciated, loss in weight 135 grams.

Pleura - Somewhat dry and dull in appearance.

Lungs - Both apical, one half of right cardiac, and one third of right diaphragmatic lobes are consolidated, showing a mottling of red and grey hepatization. The left diaphragmatic lobe is fluctuating, edematous, and congested. The cut surface presents numerous greyish-white translucent glistening foci around the bronchi. A considerable quantity of sero-sanguinous, frothy fluid oozes from the cut surface when the organ is compressed.

Bronchial glands - Enlarged, edematous, and congested.

Bronchi and trachea - Contain a copious amount of turbid fluid.

Heart - A few small greyish spots on the myocardium,

Larynx - Shows a marked congestion.

Peritoneal cavity - Contains no excess of fluid. The surfaces are smooth.

Liver - Normal in size, greyish brown, showing some congestion and a few petechial hemorrhages on the surface of the liver. The interlobular spaces appear swollen, translucent, glistening. The cut surface is flat or slightly raised and shows no hemorrhages.

Spleen - Apparently normal.

Kidney - Apparently normal.

Stomach - Slightly hyperemic.

Small intestine - Slightly hyperemic.

Uterus - Pregnant, contains two fetuses each 1 1/2 cm. in length. The placenta and the adjacent uterine wall are speckled with pin point hemorrhages.

Cervical glands - Enlarged about 100 %. Edematous and congested.

Histological examination:

Pleura - Infiltrated with leucocytes. It contains a thin deposit of fibrin on the surface.

Lung - Right apical, right cardiac, and right diaphragmatic lobes show considerable red hepatization with fibrinous exudate, edema, a few erythrocytes, and large tangled chains of streptococci in the alveoli, and marked congestion of the capillaries. In areas surrounding the small bronchioles the exudate is made up of leucocytes and macrophages with a slight thickening of the alveolar wall. Other areas more remote from the bronchi show considerable congestion and edema, but no increased cellular material of the alveolar wall.

Bronchi - The epithelium is greatly desquamated and shows some evidence of albuminous degeneration. The lumina

are partly filled with desquamated cells and a few leucocytes.

Bronchial lymph glands - are increased about 100 % in size, very congested, and edematous. A few small foci in which numerous macrophages are found are seen in the marginal sinus. The capsule is congested and shows slight evidence of fibroblastic hyperplasia.

Heart - There is cloudy swelling of the muscle cells of the myocardium with some edema between the muscle bundles.

Liver - There is well marked cloudy swelling throughout with moderate fatty changes in the central portion of the lobules. Two small focal hemorrhages 1 mm. in diameter are found near Glisson's capsule.

Spleen - Apparently normal.

Kidneys - There is marked cloudy swelling of the convoluted tubules with necrosis of occasional tubular cells. Many of the tubules are dilated and filled with a fine granular material taking a pale eosin stain suggestive of albumin. The glomeruli are swollen and congested but show no evidence of severe degenerative changes.

Stomach - Apparently normal.

Small intestine - Apparently normal.

Colon - A mild mucoid degeneration of the mucosa.

Uterus - The fetus is apparently normal. There is considerable hemorrhage involving the fetal and maternal placenta.

Cervical lymph glands - Middle cervical glands are swollen, somewhat edematous, and congested. A severe inflammatory reaction is found involving a portion of the marginal sinus and following the septa down into the cortical portions of the gland. Some necrosis and suppuration with

an exudate made up chiefly of polymorphonuclear leucocytes involves the marginal sinus and adjacent lymph tissue. A considerable number of macrophages and a slight fibroblastic hyperplasia is found in the zone surrounding the necrosis. The lymph sinuses are impacted by thrombi composed of lymphocytes and fibrin.

Anatomical diagnosis: Acute progressive bronchopneumonia with acute lymphadenitis and nephrosis.

EXPERIMENT II

Subcutaneous inoculation

Two guinea pigs, 201 and 202, weighing 265 and 400 grams respectively were injected subcutaneously over the ventral wall of the abdomen with 1 cc. of a physiological NaCl solution containing approximately 30 % of pus taken from a case of chronic lymphadenitis.

Guinea pig 201 developed a local swelling which disappeared in a short time. At the end of 40 days an abscess developed in front of the shoulders from which a pure culture of hemolytic streptococcus was isolated. All other organs cultured were negative.

Guinea pig 202 died of septicaemia in fourteen days. Pure cultures of hemolytic streptococcus were isolated from the peritoneal cavity, liver, spleen, kidney, adrenal gland, lung, heart blood, and precrural lymph glands.

Protocols

Guinea pig 201.

Sex - male.

Weight at time of exposure - 265 grams.

History - Animal was examined daily, and a local swelling was noticed in 24 hours, which continued for seven days. No further clinical symptoms were noticed for 40 days when an abscess was observed in front of the left shoulder. The animal was killed on the 53rd day.

Autopsy findings:

An abscess 1 cm. in diameter is found in the subscapular region and one .5 cm. in diameter involving the prescapular lymph gland.

Pleura - Apparently normal.

Lungs - The right cephalic and dorsal one half of the right cardiac lobes are moderately congested.

Trachea and larynx - Apparently normal.

Heart - Apparently normal.

Peritoneal cavity - Contains no excess of fluid. The serous membranes are smooth.

Liver - Light greyish brown color, some mottling with congestion. There is slight cloudy swelling.

Spleen - Apparently normal.

Kidneys - The capsule strips easily, and the cortex has a dull greyish brown, slightly parboiled appearance suggestive of cloudy swelling. The cut surface of the cortex shows some mottling of hyperemia.

Stomach - Apparently normal.

Small intestine - Apparently normal.

Colon - Apparently normal.

Testes - Apparently normal.

Cervical glands - Apparently normal.

All other organs - Apparently normal.

Histological examination:

Pleura - Apparently normal.

Lungs - There are a few areas of congestion. One focus 4 mm. in diameter of atelectasis and fibrous thickening of the alveolar walls.

Bronchial glands - Apparently normal.

Heart - Very extensive hydropic degeneration of the parenchyma.

Spleen - Moderately congested.

Kidney - There is well marked tubular cloudy swelling with well marked congestion in the cortex and medulla.

Bladder - Apparently normal.

Stomach - Apparently normal.

Small intestine - Apparently normal.

Colon - Apparently normal.

Testicles - Apparently normal.

Cervical lymph glands - Apparently normal.

The abscesses were collapsed after culturing and were not in good condition for histological study.

Anatomical diagnosis: Chronic streptococcus lymphadenitis with abscessation.

Guinea pig 202.

Sex - female.

Weight at time of exposure - 400 grams.

History - The animal developed a firm, hot, painful swelling at the point of inoculation three days after exposing, which rapidly became necrotic and caused a complete perforation of the epidermis on the seventh day. The left precrural lymph

gland was found, by palpation, to be somewhat enlarged and firm on the fifth day. This condition persisted until death. After thirteen days the animal refused to move when disturbed and would lie completely relaxed in the hand. It was found dead the following morning, fourteen days after inoculation.

Autopsy findings:

A scab covering a perforating area of necrosis 5 mm. in diameter is found on the skin of the abdomen about 5 mm. to the left of the median line and about one cm. in front of the flank.

Pleura - Apparently normal.

Lungs - There are a few scattered foci of congestion from 1 to 10 mm. in diameter and a few petechial hemorrhages on the surface of the lung just beneath the pleura.

Trachea - Contains some mucus.

Heart - Apparently normal.

Peritoneum - Peritoneal cavity contains about 3 cc. of slightly turbid, flocculent serous fluid. Most of the loops of the small intestine are adherent to each other, and some parts are adherent to the liver and spleen by a thick layer of fibrin.

Liver - Shows some hypostatic congestion. A few slightly raised translucent, glistening white areas are found on the surface. The cut surface is convex, glistening, and appears somewhat translucent.

Spleen - Slightly enlarged.

Kidney - Capsule strips easily, light chocolate color. The cut surface of the cortex is slightly raised and has a somewhat parboiled appearance suggestive of cloudy swelling.

Adrenal glands - The left adrenal shows a well marked congestion and is enlarged about 50 % in size.

Stomach - Peritoneal surface is somewhat roughened. Other than this the organ appears normal.

Small intestine - The peritoneal surface is dull, somewhat hyperemic, and covered in patches with fibrin. The mucosa appears normal.

Colon - Peritoneal inflammation same as above but much less fibrin. The mucosa is somewhat swollen, hyperemic, and covered with a layer of tenacious mucus.

Uterus - Shows a very marked congestion and edema of the mucosa.

Cervical lymph glands - Apparently normal.

Preauricular lymph glands - The right gland is apparently normal. The left is slightly enlarged but normal in consistency.

Histological examination:

Skin - In the region of inoculation the skin presents an ulcer with necrosis extending completely through the epidermis and derma. The necrotic and inflammatory process appears to involve the derma more extensively than the epidermis so as to undermine the latter. Long tangled chains of gram positive staining streptococci and numerous macrophages are found invading the necrotic tissue debris and involving the margin of healthy tissue. The macrophages show a very active phagocytic activity usually containing countless numbers of bacteria and often so many as to compress the nucleus against the cell wall.

Pleura - Apparently normal.

Lungs - There are a few foci of mild congestion.

Bronchi and trachea - The lumina of the trachea and of the large bronchi contain a large quantity of mucus in which are numerous chains of streptococci and many desquamated epithelial cells. The mucous membrane of the trachea appears normal but that of the bronchi is partly desquamated and somewhat thickened by lymphoid infiltration.

Heart - There is well marked cloudy swelling and moderate fatty changes in the myocardium.

Peritoneum - Described with the organs involved.

Liver - Moderate fatty changes in the tubular cells. There are numerous subcapsular foci one half to one mm. in diameter, of metastatic infection, with degeneration and necrosis of the liver cells but no hematogenous reaction. Some phagocytic activity is shown by Kupffer's cells. The peritoneum is covered with a heavy layer of fibrin containing many tangled chains of gram staining streptococci and numerous macrophages showing a marked phagocytic activity. There is some tendency toward organization of the exudate.

Spleen - Slightly congested. The peritoneum presents the same condition as described with the liver.

Kidney - Shows a well marked cloudy swelling with some congestion in the cortex and medulla. The capsule presents the same condition as the peritoneal covering of the liver.

Adrenal glands - Show an acute inflammatory process with congestion and edema. Large masses and long tangled chains of gram staining streptococci are found throughout the cortex and medulla. The cellular exudate is entirely monocytic and shows a well marked phagocytic activity.

Stomach - Apparently normal except for peritoneal involvement as above described.

Small intestine - Scattered throughout the small intestines are foci of infection. These show superficial necrosis of the epithelium, numerous streptococci in the stroma, and inflammatory edema of the submucosa. The lumen of the intestine near many of these foci shows an abnormally large number of streptococci and rod forms. The jejunum shows an extensive mucoid degeneration of the epithelium in addition to numerous foci of infection as described. In all cases there is a conspicuous absence of congestion of the capillaries of the stroma of the mucous membrane and submucosa with a marked dilatation of the lymph ducts of the latter. An inflammatory process as described above involves the serosa together with a very marked engorgement of the blood vessels.

Colon - The epithelium shows a marked desquamation and mucoid degeneration with edema of the mucosa and submucosa. Occasionally a few streptococci are found scattered throughout the submucosa.

Uterus - Moderately congested.

Preauricular lymph glands - The left shows an acute inflammatory reaction. The gland is swollen, edematous, and congested, and contains many streptococci, fibrin, and monocytes, with very little evidence of phagocytic activity on the part of the leucocytes and macrophages. The marginal sinuses are dilated and packed with streptococci. The capsule is of normal thickness.

Anatomical diagnosis: Streptococcus septicaemia with sero-fibrinous peritonitis, focal hepatitis, acute focal osteo-

myelitis, acute lymphadenitis, acute focal enteritis, and acute diffuse adrenalitis.

EXPERIMENT III

Conjunctival Inoculation

Two guinea pigs, 203 and 204, weighing 345 and 465 grams respectively were inoculated by instilling a drop of pus suspension in the right conjunctival sac. The pus suspension was of the same source as used in the subcutaneous inoculation experiment.

Guinea pig 203 developed conjunctivitis in the right eye in 72 hours and died of septicaemia in eight days. A pure culture of hemolytic streptococcus was isolated from the right eye, the cephalic and cervical lymph glands, liver, spleen, kidney, heart blood, and lung.

Guinea pig 204 developed conjunctivitis after an incubation period of six days. This disappeared after a few days. The animal remained well and was killed after 36 days. A pure culture of hemolytic streptococcus was isolated from the right eye, but no growth could be obtained from any other organ. Unfortunately no tissues could be saved for section from the conjunctiva as the frontal bones were so badly crushed that they could not be cut for fixation.

Protocols

Guinea pig 203.

Sex - male.

Weight at time of exposure - 345 grams.

History - Swelling of the conjunctiva with lacrymation was

detected 72 hours after inoculation. This continued until death. The animal was found dead on the eighth day. It had lost 50 grams in weight.

Autopsy findings:

Considerable gummy exudate adheres to the lids of the eyes and to the anterior nares.

Conjunctiva - Congested slightly and presents numerous greyish white, dull, opaque foci one fourth to one mm. in diameter.

Lacrymal gland - Somewhat enlarged and presents a few greyish white, dull, opaque foci.

Pleura - Apparently normal.

Lungs - Occasional petechial subpleural hemorrhages. There is very moderate congestion throughout.

Bronchial glands - Slightly enlarged.

Bronchi and trachea - Contain a small amount of flocculent fluid.

Heart - Apparently normal.

Peritoneal cavity - Contains no excess of fluid. The surfaces are smooth.

Liver - Dark reddish chocolate color. Normal size. The cut surface is slightly convex. Pin point areas of hemorrhage are found at the periphery of the lobules.

Spleen - Apparently normal.

Kidney - There is some congestion in the cortex.

Stomach - Contains about 15 cc. of water and mucus.

Small intestine - Apparently normal.

Colon - Apparently normal.

Testicles - Apparently normal.

Cervical lymph glands - Moderately congested but show no appreciable enlargement.

Histological examination:

Right conjunctiva - The mucous membrane is completely eroded. There is a marked thickening of the submucosa with congestion of the capillaries, engorgement of the small vessels, and infiltration with small round cells and macrophages. The latter show very well marked phagocytic activity for streptococci. The entire submucosa is moderately heavily invaded with streptococci growing mainly singly but often forming chains of two to twelve. Numerous small foci of early necrosis are found in which polymorphonuclear cells are plentiful in the exudate. In the margins of these foci and scattered throughout the submucosa are a few fibroblasts.

Left conjunctiva - Apparently normal.

Posterior nares - No evidence of inflammatory reaction of the mucous membrane but a large quantity of exudate containing a few streptococci are found adhering to the surface. This probably comes from the facial sinuses.

Pleura - Apparently normal.

Lung - Extensive congestion and numerous patches of red hepatization with congestion of the alveolar walls. There is some fibrin, a few erythrocytes, and a few streptococci in the alveoli. There are some patches showing well marked edema.

Bronchi - Moderate amount of desquamation of the mucous membrane. The walls of the smaller bronchi are edematous and slightly infiltrated with small round cells.

Bronchial lymph glands - The marginal sinuses are dilated,

edematous, and show slight hyperplasia of the endothelial cells.

Heart - Slight congestion in the myocardium. The blood shows evidence of leucocytosis.

Liver - Well marked, extensive congestion and hydropic changes are seen.

Spleen - Apparently normal.

Kidney - Congestion of the capillaries of the cortex and medulla with tubular cloudy swelling.

Stomach - Apparently normal.

Small intestine - Apparently normal.

Colon - Apparently normal.

Testicles - Considerable pyknosis of the spermatocytes and desquamation of the spermatids. A few live spermatozoa are found in the tubules of the epididymis.

Cervical lymph glands - Swollen, congested, and infiltrated by inflammatory edema, polymorphonuclear leucocytes, and finely granular material involving most of the glands. This condition involves a large part of the peripheral sinuses and to a great extent the capsule. The marginal sinuses also contain a variable number of proliferating endothelial cells. A diffuse infection with *Streptococcus* is found throughout the gland, growing singly and also forming chains of from two to twenty. Very little evidence of phagocytosis can be found.

Anatomical diagnosis: Acute conjunctivitis with acute lymphadenitis and early bronchopneumonia.

Guinea pig 204

Sex - female.

Weight at time of exposure - 465 grams.

History - Lacrymation with swelling of the conjunctiva was noticed after 24 hours. This gradually subsided after six days. The animal at no time appeared to be sick. It was killed on the 36th day. The gain in weight was 140 grams.

Autopsy findings:

The animal is in good condition.

Conjunctiva - Apparently normal. No tissues can be saved for section as the skull is too badly crushed in killing the animal.

Nasal passages - Apparently normal.

Pleura - Apparently normal.

Lungs - Apparently normal.

Bronchi - Some thickening of the bronchial walls is found.

Trachea - Apparently normal.

Heart - Apparently normal.

Peritoneal cavity - Contains no excess of fluid. The surfaces are smooth.

Liver - Chocolate brown color. Apparently normal.

Spleen - Apparently normal.

Kidneys - Apparently normal.

Stomach - Apparently normal.

Small intestine - Apparently normal.

Colon - Apparently normal.

Uterus - Apparently normal.

Ovaries - Apparently normal.

Cervical lymph glands - Apparently normal.

Histological examination:

Pleura - Normal.

Lungs - There are a few scattered foci surrounding the bronchi showing marked thickening of the alveolar wall due to fibrosis and, to a lesser extent, endothelial proliferation with a few monocytes in the alveoli.

Bronchi - Moderate amount of desquamation of the mucosa. The exudate in the lumen is made up chiefly of desquamated cells with an occasional leucocyte. The bronchial wall is somewhat thickened by fibrosis. This condition extends out into the lung tissue for a distance of from .5 mm. to 2 mm. as above described.

Bronchial glands - Apparently normal.

Heart - The myocardium presents a well marked cloudy swelling with some evidence of fatty changes.

Liver - Very hydropic. Some cells have degenerated so badly that the nuclei have become shrunken.

Spleen - Apparently normal.

Kidney - There is a very extensive well marked tubular cloudy swelling.

Stomach - Apparently normal.

Small intestine - Apparently normal.

Colon - Apparently normal.

Uterus - Apparently normal.

Cervical lymph glands - Apparently normal.

EXPERIMENT IV

Inoculation via nasal passages

Two guinea pigs, 205 and 206, weighing 470 and 220 grams respectively were exposed by instilling one drop of normal salt solution pus suspension into the right nostril. This was accomplished by holding the animal in one hand with the nostrils in a vertical position and using a medicine dropper to make the instillation.

Both animals died of septicaemia in eight days.

A pure culture of hemolytic streptococcus was obtained from the liver, spleen, heart blood, and cervical lymph glands of both pigs. The organism was obtained also in culture from the lungs of guinea pig 205.

Protocols

Guinea pig 205.

Sex - male.

Weight at time of exposure - 470 grams.

History - No clinical symptoms were observed until the eighth day when a slight nasal discharge developed and the animal showed signs of general malaise. The animal died eight days after exposure. The loss of weight was twenty grams.

Autopsy findings:

The condition of the animal is good. There is a small amount of dried nasal discharge adherent to the nostrils.

Pleura - Apparently normal.

Lungs - A well marked patchy congestion with numerous scattered petechial hemorrhages is observed. The accessory lobe is completely atelectatic.

Bronchi and trachea - Filled with a frothy serous exudate.

Bronchial lymph glands - Apparently normal.

Heart - Apparently normal.

Peritoneal cavity - Contains no excess of fluid. The surfaces are smooth.

Liver - Medium chocolate brown color. It appears normal except for a greyish white dull opaque focus one cm. in diameter on the left lobe of the liver.

Spleen - Apparently normal.

Kidney - Marked congestion.

Stomach - Apparently normal.

Small intestine - Apparently normal.

Colon - Apparently normal.

Testicle - Apparently normal.

Cervical lymph glands - Moderately congested, pliable and firm in consistency, and moderately enlarged averaging 5 mm. in diameter.

Nasal passages - Mucous membrane of nasal cavity and turbinate bones is very congested, somewhat thickened, and covered with a thin layer of mucus.

Facial sinuses - Frontal, palatine, and maxillary show a well marked congestion of the mucosa and contain a large amount of thin, white, opaque, granular fluid.

Histological examination:

Pleura - Apparently normal.

Lung - Well marked and extensively congested. Patchy areas of red hepatization in which the alveoli are loaded with streptococci, fibrin, and a few erythrocytes are found

throughout both right and left lungs. Numerous patches of edema are also found scattered throughout the lung. The condition is essentially what is usually described as acute patchy bronchopneumonia with variable recognizable stages from congestion and edema to red hepatization.

Bronchi and trachea - The bronchi are partly filled with debris consisting mainly of desquamated cells. The bronchial mucous membrane is almost completely eroded. The bronchial wall appears to be thickened and moderately infiltrated by mononuclear cells.

Bronchial lymph glands - Congested and edematous.

Heart - Shows a slight cloudy swelling.

Liver - Moderate congestion. A slight amount of fatty degeneration is found in the central portion of the lobules. There is a necrotic focus one cm. in diameter just beneath Glisson's capsule. This is loaded with streptococci growing singly and in long chains. Numerous leucocytes are found infiltrating the periphery of the lesion but show no phagocytic activity for the bacteria. A zone surrounding the lesions contains numerous fibroblasts, macrophages, and polymorphonuclear leucocytes, but no evidence of phagocytosis is recognizable. The surface of the liver at this point contains a large deposit of fibrin and polymorphonuclear leucocytes.

Spleen - Apparently normal.

Kidney - Moderate cloudy swelling of the tubular epithelium. Slight congestion of the capillaries of the medulla.

Stomach - Apparently normal.

Small intestine - Apparently normal.

Colon - Apparently normal.

Testicle - Apparently normal.

Cervical lymph glands - Both middle cervical lymph glands are enlarged about 7 mm. in diameter due mainly to hyperplasia of the lymphoid cells. A few foci of early infection, apparently of pyemic origin, are found near the periphery of the gland containing numerous streptococci. The lymphoid cells in these foci are entirely replaced by large mononuclear cells which have great phagocytic power for streptococci. An occasional polymorphonuclear leucocyte showing very little phagocytic activity for bacteria of this species is found scattered throughout these lesions. At the peripheral zone of these lesions numerous fibroblasts and a few vascular endothelial cells can be found trying to incapsulate the developing lesion. The marginal sinuses are partly filled in some places with proliferating endothelial cells. The capsule is thickened slightly by fibroblastic hyperplasia.

Nasal cavity - A large quantity of pus is found on the surface containing many degenerated leucocytes and a large number of chains of streptococci. The mucosa is congested, edematous, and in many places shows desquamation of the superficial epithelial cells. The edema of the connective tissue stroma is of an inflammatory nature containing some fibrin and an occasional leucocyte..

Facial sinuses - Present the same condition as that described for the nasal cavity.

Anatomical diagnosis: Acute mucopurulent rhinitis and sinusitis with septicaemia.

Guinea pig 206.

Sex - male.

Weight at time of exposure - 220 grams.

History - On the third day the animal developed a copious nasal discharge and made slight rattling noises from the throat when breathing. After eight days the animal was found dead. The loss in weight was ten grams.

Autopsy findings:

The animal is in fair condition.

Pleural cavity - Contains no excess of fluid. The pleural surfaces are smooth.

Lungs - Moderate congestion.

Bronchi - Some of the bronchi show some thickening of the alveolar walls involving the lung tissue in a narrow surrounding zone.

Bronchial lymph glands - Apparently normal.

Heart - Apparently normal.

Liver - Moderately congested.

Spleen - Apparently normal.

Kidney - Apparently normal.

Stomach - Apparently normal.

Small intestine - Apparently normal.

Colon - Apparently normal.

Testicles - Apparently normal.

Subaxillary and retropharyngeal lymph glands - Slightly enlarged and congested.

Nasal passages and facial sinuses - All contain a copious quantity of thin, white, creamy pus. The mucous membranes are hyperemic and appear slightly thickened.

Histological examination:

Pleura - Apparently normal.

Lungs - Moderate to slightly congested, with small foci of atelectasis. Several small foci of consolidation surrounding the bronchi with lymphocytic infiltration of the alveolar walls and an exudate in the alveoli made up of leucocytes and lymphocytes. No evidence of streptococci can be found in the sections.

Bronchi - A rather marked desquamation of the epithelium of the bronchi is dominant throughout the lung in some places completely plugging the lumen. A lymphoid infiltration involves the wall of the small bronchi, peribronchial tissues, and in some places the surrounding lung tissues to a variable extent.

Bronchial lymph glands - Apparently normal.

Heart - Apparently normal.

Liver - Very hydropic and moderately congested.

Spleen - Apparently normal.

Kidney - Well marked tubular cloudy swelling and a moderate congestion in the cortex and medulla. The subcapsular spaces and tubules contain numerous shadow cells which are possibly desquamated and degenerated cells from the glomerular epithelium.

Stomach - Apparently normal.

Small intestines - Apparently normal.

Colon - Apparently normal.

Testicles - Apparently normal.

Submaxillary and retropharyngeal lymph glands - The glands are swollen, congested, and edematous. There are a

few scattered foci of infection, some of them involving the marginal sinuses and others located in the deeper structures of the glands. The cellular content of these foci is made up mainly of polymorphonuclear leucocytes showing a marked phagocytic activity for streptococci and a few mononuclear cells showing very active phagocytosis. The marginal zones of these foci contain numerous proliferating fibroblasts. There is a slight dilatation of the marginal sinuses and a slight proliferation of the endothelial lining. The capsules are thickened moderately by edema, infiltration with lymphocytes, and proliferation of fibroblasts.

Nasal passages - The surface of the mucous membrane is covered with a large amount of exudate made up mainly of polymorphonuclear leucocytes and numerous streptococci growing singly and in short chains of from two to six. There is slight desquamation of the superficial epithelial cells of the mucosa with some edema and congestion in the connective tissue stroma.

Anatomical diagnosis: Acute rhinitis with acute lymphadenitis.

EXPERIMENT V

Skin Inoculation

Two guinea pigs, 207 and 208, were prepared by clipping the hair over a small region on the left lateral wall of the abdomen and scraping the skin with the blade of a scalpel over an area about 5 cm. in diameter until it appeared slightly hemorrhagic. Next a drop of the pus suspension of

of the same source as used in the other experiments was lightly massaged into the denuded area.

Guinea pig 207 died of streptococcic septicaemia in eight days. A pure culture of hemolytic streptococcus was recovered from peritoneal fluid, liver, spleen, kidney, uterus, pleural fluid, heart blood, lungs, cervical lymph glands, and the subcutaneous tissues at the point of inoculation.

Guinea pig 208 was killed by a blow after 53 days. A pure culture of hemolytic streptococcus was isolated from abscesses in the precrural and cervical regions. No cultures could be obtained from any other organ.

Another guinea pig, 301, weighing 310 grams was prepared as above and inoculated with a freshly isolated eighteen hour nutrient agar culture of hemolytic streptococcus taken from guinea pig 207. A drop of physiological NaCl suspension of this culture was massaged into the abraded area of skin. The animal showed no clinical symptoms of acute lymphadenitis and was killed after 43 days. Abscesses from which pure cultures of hemolytic streptococcus were isolated were found involving the precrural, cervical, and submaxillary lymph glands. Cultures from all other organs were negative. The results of this experiment might suggest that the resistance of the individual animal has a greater influence on the course of the streptococcic infection than either the virulence of the organism or age of the animal. Guinea pig 207 died of a fulminating type of infection while streptococci from this case produced chronic lymphadenitis when subsequently inoculated in a similar manner into another animal

of about the same age and the same sex.

Protocols

Guinea pig 207.

Sex - female.

Weight at time of exposure - 240 grams.

History - After five days a circumscribed, firm, hot, painful swelling developed at the point of inoculation. This rapidly became necrotic and a scab developed over the surface which remained until death. The inflammatory swelling spread out peripherally involving mammary glands and the left precrural lymph gland, which became enlarged and hard. The animal was found dead eight days after exposure.

Autopsy findings:

The hair coat is dull and rough. The loss in weight is 65 grams. A necrotic area, 5 mm. in diameter, covered with a thick scab is found on the skin over the abdominal wall 5 mm. to the left of the median line and 1 cm. in front of the pubis.

Pleura - The thoracic cavity contains about 5 cc. of serosanguinous fluid containing a brick dust-like sediment. The pleural surfaces are dull and rough, but no great amount of fibrin deposit can be found.

Lungs - The right apical, about three fourths of the right cardiac, and a small area on the ventral border of the right diaphragmatic, and all of the left apical lobes are consolidated and show a variation in color from a dark red to a dull grey. These areas cut with increased resistance and have a dull nodular cut surface from which no creamy fluid can be expressed. Extensive congestion and some edema

are found in regions not showing consolidation. The lung is about 25 % air containing.

Bronchi - On section the walls appear somewhat thickened. The lumen contains a small quantity of serosanguinous frothy fluid.

Bronchial lymph glands - Enlarged and somewhat edematous.

Heart - A small amount of serosanguinous fluid is found in the pericardial sac. The epicardium shows a few patchial hemorrhages on the auricular walls and around the base of the pulmonary arteries and aorta.

Peritoneal cavity - Contains about 10 cc. of serosanguinous brownish fluid containing a large quantity of fine brick dust sediment.

Liver - Dark red in color. It is about normal in size. There are about twelve white translucent glistening areas and a few dull opaque greyish white areas from 1 to 3 mm. in diameter on the surface of the liver just beneath Glisson's capsule and extending to a depth of about 1 mm. in the liver tissue. The cut surface is convex and bleeds slightly. A few dull opaque greyish white foci averaging about 1 mm. in diameter are found scattered throughout the organ.

Spleen - Slightly congested.

Kidneys - Capsule strips easily leaving a smooth glistening surface of a chocolate brown color. The cut surface is convex and shows slight congestion in the capillaries of the medulla.

Stomach - Apparently normal.

Small intestine - Apparently normal except for a moderate congestion of the serous coat.

Colon - Apparently normal.

Uterus - Apparently normal.

Preauricular lymph glands - The right gland is apparently normal. The left is slightly enlarged and firm in consistency.

Histological examination:

Pleura - Markedly thickened and covered with a thin layer of fibrin, rich in mononuclear cells and containing a few chains of streptococci.

Lungs - About three fourths of the right cardiac and a small area on the ventral border of the right diaphragmatic lobes are completely consolidated. Fibrin, a few erythrocytes, desquamated epithelial cells, and long tangled chains of streptococci are found in the alveoli. This condition is associated with a general pulmonary hyperemia accompanied by edema. The edema is confined to those areas in which there is congestion but no hepatization. The edematous material is finely granular, acidophilic, and almost hyaline in character. Scattered throughout the consolidated regions are patchy areas one fourth to one half mm. in diameter, surrounding the terminal bronchioles and smaller bronchi. The exudate is chiefly leucocytic in character with a few desquamated epithelial cells and macrophages. Numerous streptococci are found in these areas, a few of which are phagocytosed by the leucocytes and macrophages.

Bronchi - The bronchi are the seat of an acute catarrhal inflammation with a distinctly purulent exudate in the lumen. There is a well marked and extensive desquamation of the epithelium of the bronchi and bronchioles with exudation

of polymorphonuclear leucocytes into the walls. Many streptococci are present in the exudate, and occasionally a few may be found in the bronchial walls.

Bronchial lymph glands - Very hyperemic and edematous. Several foci of liquefaction necrosis averaging 250 u. in diameter involve the germinal centers. There is no cellular exudation involved in these foci, but the lymphocytes and endothelial cells are apparently very active.

Heart - Occasionally a small hemorrhage of about 1 mm. in diameter involves the connective tissue stroma of the auricular epicardium. The epicardium is very hyperemic and shows a rather marked thickening due to edema. The myocardium shows distinct degenerative changes evidenced by cloudy swelling and fatty degeneration of the muscle cells.

Liver - Moderately congested and presents a slight fatty degeneration in the central portion of the lobules. One focus of early necrosis 1 mm. in diameter is found containing numerous streptococci growing singly and in chains of two to twelve. There is a slight exudation of polymorphonuclear leucocytes and a few macrophages at the margin of this lesion. Not much phagocytosis of bacteria is seen by either of these cells. Glisson's capsule is swollen slightly and covered with a thin layer of fibrin containing numerous erythrocytes.

Spleen - The organ is engorged with blood and edematous. The architecture is very indistinct due to a wide spread and scattered necrosis of the lymphoid cells. Numerous bacteria are found scattered throughout the spleen pulp and in the lymph sinuses. The capsule is thickened slightly. Numerous

large masses of streptococci are found on its surface. No where throughout the whole organ is there any evidence of leucocyte exudation.

Kidney - Presents a well marked tubular cloudy swelling with necrosis of the epithelium. There is a finely granular, acidophilic, albuminous material in the tubules, also in the subcapsular spaces of the glomeruli. The capillaries of the medulla and cortex are moderately congested. The glomerular loops are engorged with blood. Many of the glomeruli show degenerative changes with escape of erythrocytes into the subcapsular spaces.

Stomach - Apparently normal except for a moderate congestion and thickening of the serosa with numerous erythrocytes and large masses of bacteria on the surface.

Small intestine - Apparently normal. The serosa shows the same condition as that of the stomach.

Colon - Apparently normal. The serosa shows the same condition as that of the stomach.

Uterus - Apparently normal. Serosa greatly thickened, edematous and congested. Numerous streptococci are found on the surface together with a few erythrocytes and a small amount of fibrin.

Skin at region of inoculation - Presents an area of necrosis in which large masses of streptococci are found. The lesion involves the stratum lucidum, stratum germinativum, of the epidermis and the pars papillaris and pars reticularis of the derma. The subcutaneous tissues are greatly thickened due to engorgement of the blood vessels, edema, and numerous variable sized hemorrhages. Dense

masses and tangled chains of streptococci are found scattered throughout the subcutaneous tissues in many places so numerous as to obscure the other structures. The veins and arteries show enormous thickening of their walls due to acute inflammatory processes. Many of the veins present thrombi on their internal layers. No where throughout the entire inflamed area is there any evidence of leucocytic or monocytic exudation.

Preauricular lymph glands - Left gland is apparently normal. The right gland is increased to about 1 cm. in length by 5 mm. in width. It is very edemic and heavily loaded with streptococci throughout. The structure is so indistinct as to be unrecognizable due to the great pressure of the fluid contained causing a spreading apart of the cellular structures. There is no evidence of leucocytic exudation in any part of the gland.

Cervical lymph glands - Present the same condition as the preauriculars.

Anatomical diagnosis: Streptococcus septicaemia.

Guinea pig 208.

Sex - male.

Weight at time of exposure - 245 grams.

History - Seven days after exposure a slight thickening of the skin with a superficial area of necrosis 5 mm. in diameter was found at the point of inoculation. This was entirely healed after fourteen days, and at that time the left preauricular lymph gland became palpable as a hard shot-like body about the size of a small pea. This slowly

developed into an abscess which became .5 cm. in size at the time the animal was killed. On the 28th day the middle cervical lymph glands became slightly enlarged and more firm than normal. They gradually increased in size until they became 1 cm. in diameter. The animal was killed on the 53rd day following exposure.

Autopsy findings:

The animal is in fair condition. It has gained 175 grams since exposure. The hair coat is smooth. There is a group of circumscribed swellings in the cervical region and one in front of the right shoulder joint.

Pleura - There is no excess of fluid in the pleural cavity. The surfaces are smooth.

Lungs - A few very small irregular areas of congestion are found. The cut surface is regular except for a few raised thickened areas surrounding the bronchi that cut with increased resistance.

Bronchi - The lumen contains a small amount of purulent fluid. The walls are thickened and stand out as raised branching areas on cut surface.

Bronchial lymph glands - Appear slightly enlarged and edematous.

Heart - Apparently normal.

Peritoneal cavity - Contains no excess of fluid. The surfaces are smooth.

Liver - It is light greyish brown color.

Spleen - Apparently normal.

Kidneys - The capsule is tense and strips with ease leaving a smooth surface of a light greyish brown color.

The organ cuts without increased resistance and bleeds slightly. The cut surface is raised slightly and shows a fairly well marked hyperemia in the cortex and medulla.

Stomach - Apparently normal.

Small intestine - Apparently normal.

Colon - Apparently normal.

Testicles - Apparently normal.

Precrural lymph glands - The left gland is .5 cm. in size, firm in consistency, and cuts with increased resistance.

Cervical and cephalic lymph glands - Both middle cervical and submaxillary lymph glands average 1 cm. in diameter and are converted into abscesses with a thick dense fibrous wall which cuts with increased resistance allowing a thick granular greyish white pus to ooze out.

Histological examination:

Pleura - Apparently normal.

Lungs - There are no lesions that are attributed to streptococcus infection.

Bronchi - There is a mild catarrhal degeneration with some desquamation of epithelium in some bronchi. The alveoli contain some granular debris and a few desquamated cells.

Bronchial glands - Apparently normal.

Heart - Apparently normal.

Liver - Shows a well marked and extensive hydropic degeneration of the liver cords.

Spleen - A hyalin necrosis involves a part of the periphery of the Malpighian corpuscles.

Kidney - Very marked cloudy swelling of the tubules with some fine granular albuminous material in their lumina.

There is a moderate hyperemia of the capillaries in the cortex and medulla.

Stomach - Apparently normal.

Small intestine - Apparently normal.

Colon - Apparently normal.

Preauricular lymph gland - The left gland presents an advanced chronic inflammatory condition. The capsule is thickened about ten times by fibroblastic hyperplasia which envelops the marginal sinuses completely obliterating them. There is a well marked increase in connective tissue framework throughout the gland with numerous endothelial cells and macrophages completely replacing the lymphoid cells. Numerous foci of infection containing many streptococci and a collection of leucocytes are found throughout the cortical portion of the gland. These show a tendency to necrosis in their centers. Those in the more central portion of the gland are entirely necrotic and converge to form a suppurating mass about two mm. in diameter.

Cervical and submaxillary lymph glands - Show a condition similar to that of the preauricular gland described above only apparently more rapid in abscess formation. The capsule is thickened about fifteen times, completely obliterating the marginal sinuses. Just beneath the capsule are a number of individual abscesses, completely encapsulated, measuring from .5 mm. to 1 mm. in diameter. Towards the center of the gland these converge to form large abscesses averaging about 5 mm. in diameter.

Anatomical diagnosis: Chronic streptococcus lymphadenitis.

Guinea pig 301.

Sex - female.

Weight at time of exposure - 310 grams.

History - A slight thickening of the skin was noticed 48 hours after inoculation. This healed promptly, and no other clinical symptoms could be observed until the fifteenth day when a slight enlargement became palpable in the left pre-crural and submaxillary lymph glands. These gradually increased in size and averaged about 1 cm. in diameter at the time the animal was killed 43 days after inoculation.

Autopsy findings:

Condition good. A group of circumscribed swellings like marbles are found in the cervical and submaxillary regions and in the left flank.

Pleura - The cavity contains no excess of fluid. The surfaces are smooth.

Lungs - A few small slightly congested areas are found. The anterior borders of both diaphragmatic, all of the left cephalic, and about one half of the right cardiac lobes show partial atelectasis. The accessory lobe is completely atelectatic.

Bronchi and trachea - Apparently normal.

Bronchial glands - Apparently normal.

Heart - Apparently normal.

Abdominal cavity - Contains no excess of fluid. The surfaces are smooth.

Liver - Medium chocolate brown in color. Apparently normal.

Spleen - Apparently normal.

Kidneys - The cut surface is raised slightly, dull, pale, pinkish red color, suggestive of cloudy swelling.

Stomach - Apparently normal.

Small intestine - Apparently normal.

Colon - Apparently normal.

Uterus - Right horn is 2 mm. in diameter and non pregnant. The left horn is 3 mm. in diameter and apparently in a state of early pregnancy.

Ovaries - Present no unusual condition.

Preaural lymph glands - The right gland is apparently normal. The left gland is 6 mm. in diameter, presents a thick tough capsule which cuts with increased resistance allowing a small quantity of thick granular greyish white pus to escape.

Middle cervical lymph glands - Average 12 cm. in diameter and are abscessed the same as the preaurals.

Submaxillary and sublingual glands - Average 9 mm. in diameter and are all abscessed.

Histological examination:

Pleura - Apparently normal.

Lungs - Apparently normal except for a few small areas of consolidation from .1 to .5 mm. in diameter located around the bronchioles and larger bronchi. These are characterized as a low grade inflammatory process, apparently of long standing, with marked thickening of the alveolar walls due to fibroblastic and endothelial proliferation. The exudate in the alveoli is scanty in amount and made up of macrophages with a few eosinophiles and occasionally a few polymorphonuclear leucocytes.

Bronchi - Show a mild catarrhal inflammation with some desquamation of the epithelium and a little leucocytic exudation. The bronchial walls are thickened slightly.

Bronchial lymph glands - Apparently normal.

Heart - Apparently normal.

Liver - Moderate cloudy swelling of the epithelium.

Spleen - Apparently normal.

Kidney - Well marked tubular cloudy swelling.

Stomach - Apparently normal.

Small intestine - Apparently normal.

Colon - Apparently normal.

Uterus - The left horn is pregnant. (Fetus is not found in section.) The fetal membranes and all coats of the uterine wall are apparently normal. The mucous membrane is 1.5 mm. thick. The mucous membrane of the right horn is .4 mm. thick and shows no evidence of injury.

Lymph glands - They are described collectively as all the glands recorded above in the autopsy protocol show the same condition. They are entirely converted into abscesses and bear no resemblance to lymph glands. The capsules are greatly thickened, one of them 1/4 mm. thick. The subcapsular areas show considerable fibroblastic hyperplasia, numerous endothelial cells, leucocytes, and streptococci. Towards the center the mass becomes necrotic.

Anatomical diagnosis: Chronic suppurative streptococcus lymphadenitis.

DISCUSSION

Both acute lymphadenitis with septicaemia and the

chronic form with abscessation of the lymph glands were seen in this guinea pig epizootic. Out of 82 infected guinea pigs examined, 23 died of acute lymphadenitis with septicaemia. These animals were apparently normal until a few hours before death. Most of them were found dead without any clinical symptoms being noticed. Upon histological examination no evidence of chronic disease process attributable to streptococcus could be found. There was also a great tendency for chronic cases suddenly to become acute, resulting in septicaemia and death of the animal. Fifty two guinea pigs were examined which developed chronic lymphadenitis. Eighteen of these animals died of septicaemia.

The most frequent point of localization was in the cervical lymph glands. Sixty five guinea pigs showed involvement of these glands. Next in frequency are the submaxillary glands with 42 animals involved. Others are as follows: prefemoral in fourteen animals, sublingual in twenty, pre-scapular in six, posterior scapular abscesses in two, the internal iliac in three, and the spleen in one case.

Among the septicaemic cases bronchopneumonia was the most frequent complication. Forty four cases of pneumonia were found, and hemolytic streptococci were found in each. Twenty seven cases were complicated with streptococcus pleuritis, nine with focal infection in the liver, eight with focal infection in the heart, seven with streptococcus peritonitis, and four each with focal infection involving the spleen, intestine, and uterus.

Due to the insidious nature of the disease at the onset and the apparent contagiousness, together with a lack of

efficient diagnostic methods, the control of this infection, once it has become established in a flock of guinea pigs, is difficult. Diseased pigs can be readily located by palpation of the superficial lymph glands when the disease has become far enough advanced to produce an appreciable increase in the size of these organs. However, this method alone does not serve to locate the cases at the beginning of infection. Indeed, some of the cases of acute lymphadenitis with septicaemia showed no enlargement of the lymph glands palpable through the skin even though they showed, upon histological examination, some swelling with inflammatory edema and were teeming with streptococci.

With these facts in mind then, it would appear that either a more efficient method of diagnosis is necessary, some method of immunization, or a more effective method of sanitation. I am not in a position to offer any suggestions for improving the diagnosis or for immunization. Herbert and Meyer (15) were unable to produce local immunization in guinea pigs against streptococcus infection by means of a Besredka filtrate. Single or multiple doses of heat killed vaccines gave no protection against subsequent inoculations, and no local non specific resistance could be induced by injecting sterile broth or salt solution intradermally.

Where one is able to maintain a small colony of guinea pigs, it would appear that the spread of infection could be best prevented by separating the animals into individual cages, thereby eliminating the possibility of a carrier coming in contact with unaffected animals and using precautions in handling the feed, feed dishes, and litter of these

animals.

SUMMARY

1. Clinical, bacteriological, and pathological aspects of a guinea pig epizootic are described.
2. B. type of hemolytic streptococcus is found to be the etiological factor, affecting principally the peripheral lymph glands.
3. Both acute septicaemic forms and chronic forms with abscesses in the lymph glands are found in spontaneous and artificially infected guinea pigs.
4. Cases of chronic lymphadenitis frequently terminate in septicaemia.
5. The gland lesions in acute lymphadenitis consist of inflammatory edema with numerous streptococci with or without leucocytic exudation.
6. The gland lesions in chronic lymphadenitis begin as focal lesions containing numerous macrophages, usually a few streptococci, and occasionally a few leucocytes and develop into abscesses through central necrosis and peripheral extension of the lesion.
7. Pyemic focal streptococcus lesions occur in liver, heart, uterus, spleen, small intestine, bone marrow, thyroid glands, and adrenal glands.
8. A simple method of demonstrating gram positive bacteria in tissue sections, which at the same time produces sections stained excellently for histological study, is described.

9. A method of eradication is recommended consisting of maintaining a small colony of guinea pigs and isolating each animal in an individual cage.

KEY TO TABLE II

Lymph glands

Early focal lesions	+
Acute lymphadenitis	++
Chronic lymphadenitis	+++

Lungs

Congestion	+
Hemorrhage	++
Pneumonia	+++

Streptococci in section

Few, completely phagocytosed	+
Moderate number, completely phagocytosed	++
Numerous, partly phagocytosed	+++
Numerous, no phagocytosis	++++

Streptococci in culture

Light growth	+
Moderate growth	++
Heavy growth	+++

Table III
DISTRIBUTION OF LESIONS IN LYMPH GLANDS

Guinea pig No.	Sub-maxillary	Cervical	Sublingual	Prescapular	Post-scapular	Prefemoral	Internal Illiac
1		+++					
2	+						
3		++					
4	++	+				+++	
5	+++	+++					
7		+++					
8			+++				
10	+++	++	++				
11	+++						
12		++		+++			
13	+++	+++					
14	+++	+++	+	+++			
15	+++	+			+++		
17	++	+					
18	++	+++	+++		+++		
19						+++	
20		++				+++	
21	+++					+++	
23		+					
24		+++					
25	++	+++	+++				
26		+					
27	+	+		+		+	
28		++					
29		+++					
30		+++	+			+++	
31	+						
35		++					
36	++	+++					
37	+++	+++					
38	++						
39		+++					+++
40		+++		+++			
41		+	+	+++			
42	+	+					
43		++					
44		++					
45		+++		+++		+++	
46	+	++					
47	++						
48		+++					
49	+	+++				+++	
50		+++				+++	
51	+++	++				+++	
52	+++	+++	++				
53		++					+++
54	++	+++					
56		++					
57	+++	++	+++		+++		
58	+++	++	+++				
60		+					
61	++	++	+				
62			+++				
66	+++	++					
67		+++					
68	++						
69	+++	++					
70	++	++	+	++		+++	
71	+	+					
72		++					
73	++	++	+			+++	+++
74		+++					
75	++	+++					
76		+++	+				
77		+++					
78	+++	++	++			+++	
79	+++	+++	++				
80	+++	++	+				
101		+					
102		+					
201				+++	+++		
202						+	
203	+						
205		+					
206	+	+					
207	+	+				+	
208	++	++	++			+++	
301	++	+++	+			+++	

Key: Early focal lesions +
Acute lymphadenitis ++
Chronic lymphadenitis with abscessation. +++

DESCRIPTION OF PLATES

Plate I

Fig. 1. Guinea pig 24, showing enlarged cervical lymph gland.

Plate II

Fig. 2. Section from submaxillary lymph gland of guinea pig 72.

a. Early focus of infection containing numerous macrophages, few fibroblasts, and an occasional polymorphonuclear leucocyte. A few scattered streptococci can be seen in this lesion at higher magnification.

b. Marginal sinus. Magnification approx. 200x.

Fig. 3. Bronchial lymph gland from guinea pig 207.

a. Focus of liquefaction necrosis showing no evidence of cellular reaction.

b. Marginal sinus.

c. Septum.

Magnification approx. 200x.

Plate III

Fig. 4. Lymph gland from guinea pig 7, showing edema, degeneration of the lymphocytes, and clumps of streptococci in the lymph sinuses (a).

Magnification approx. 200x.

Fig. 5. Lymph gland from guinea pig 207. Acute lymphadenitis showing edema and chains of streptococci.

Magnification approx. 400x.

Plate IV

- Fig. 6. Lymph gland from guinea pig 37. Streptococci in the marginal sinus, showing phagocytosis by macrophages. Magnification approx. 400x.
- Fig. 7. Lymph gland from guinea pig 39 showing early abscessation at (a) with great thickening of the capsule. The great thickening of the capsule is indicated by the distance between the two arrows. Magnification approx. 200x.

Plate V

- Fig. 8. Lymph gland from same guinea pig as figure 7, showing an advanced abscess at (a) just prior to rupturing. The almost complete erosion of the capsule at (b). Compare with the thickness of capsule in the earlier abscess shown in figure 7.
- c. Blood vessel.
- d. Areolar tissue.
- Magnification approx. 200x.
- Fig. 9. Section from lung of guinea pig 74 showing early acute bronchopneumonia with fibrinous exudate and leucocytes in the alveoli.
- a. Bronchus showing slight desquamation of epithelium and peribronchial round cell infiltration.
- Magnification approx. 200x.

Plate VI

Fig. 10. Lung from guinea pig 69 showing acute broncho-pneumonia.

- a. Sagittal section of a bronchus.
- b. Bronchial exudate made up of desquamated epithelial cells and polymorphonuclear leucocytes. The bronchial epithelium shows marked desquamation at (c).
- d. Slight hyperemia of the alveolar capillaries with slight swelling of the alveolar epithelium. The exudate in the alveoli is made up of leucocytes, macrophages, and desquamated epithelial cells. Streptococci are visible in these alveoli at higher magnification.
- e. Area in which there is considerable leucocytic exudate distending the alveoli and compressing their walls.

Magnification approx. 200x.

Fig. 11. Lung from guinea pig 27 showing bronchopneumonia.

- a. Bronchus showing desquamation of epithelium with exudate in the lumen made up chiefly of desquamated cells and mucus.
- b. Marked swelling of the epithelial lining of the alveoli with an exudate made up of leucocytes, macrophages, and desquamated epithelial cells. A few alveoli in this region show atelectasis.

Magnification approx. 200x.

Plate VII

Fig. 12. Lung from guinea pig 43.

- a. A focus of early necrosis. The alveoli surrounding this focus show pneumonia and contain leucocytes, desquamated epithelial cells and edema.

Magnification approx. 200x.

Fig. 13. Lung from guinea pig 44. Pneumonia with a fistulous tract opening on the pleural surface.

Magnification approx. 200x.

Plate VIII

Fig. 14. Liver from guinea pig 202. Focus of necrosis with no evidence of cellular reaction. Numerous pyknotic liver cells are seen throughout the central part of the lesion. The arrow points to a group of streptococci barely visible at this magnification.

- a. Liver cells showing fatty degeneration.

Magnification approx. 200x.

Fig. 15. Same lesion as figure 14 magnified approx. 400x.

- a. Streptococci growing singly and in chains of two to six elements, some phagocytosed by Kupffer cells.
- b. Fat globules in liver cells.

Plate IX

Fig. 16. Liver from guinea pig 202. Focus of infection showing chains of streptococci.

Magnification approx. 400x.

Fig. 17. Spleen from guinea pig 33. Acute spleenitis showing edema and phagocytosis of streptococci by splenocytes.

Magnification approx. 400x.

Plate X

Fig. 18. Mammary gland from virgin guinea pig 207, showing acute interstitial mastitis. The alveoli are distended with mucoid material. The interlobular tissues are very edematous. The lower half of the picture shows early necrosis. With higher magnification numerous streptococci can be found in this region.

Magnification approx. 200x.

Fig. 19. Uterus from guinea pig 45. Pyemic focus in the muscular coat.

a. Polymorphonuclear leucocytes.

b. Macrophages.

Magnification approx. 200x.

Plate I



Fig. 1.

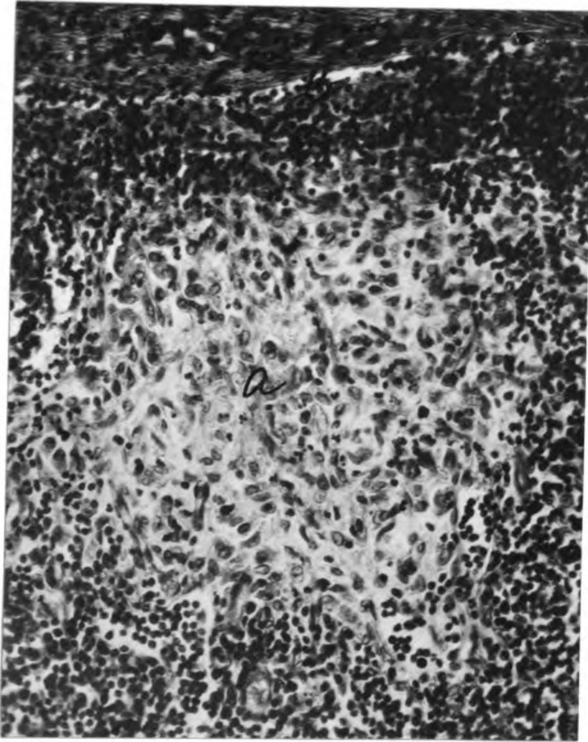


Fig. 2.

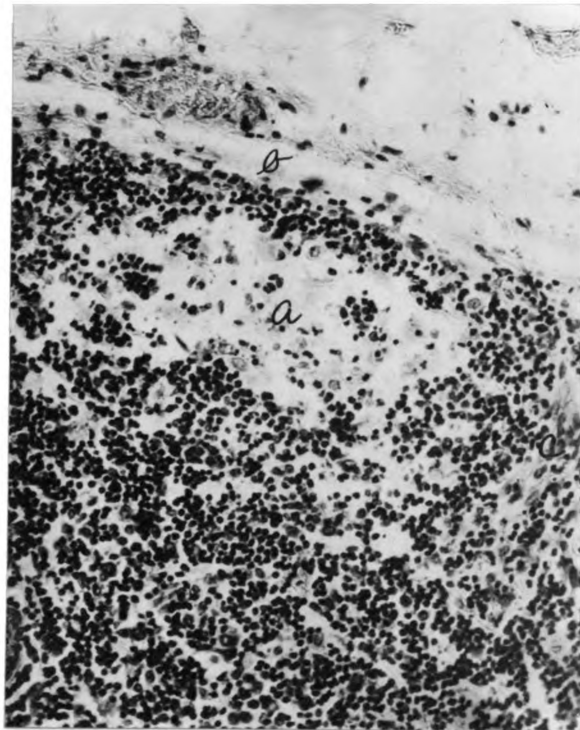


Fig. 3.

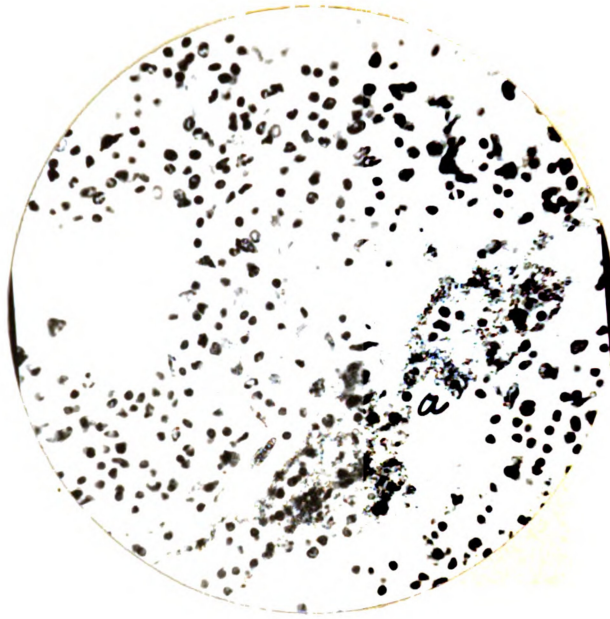


Fig 4.

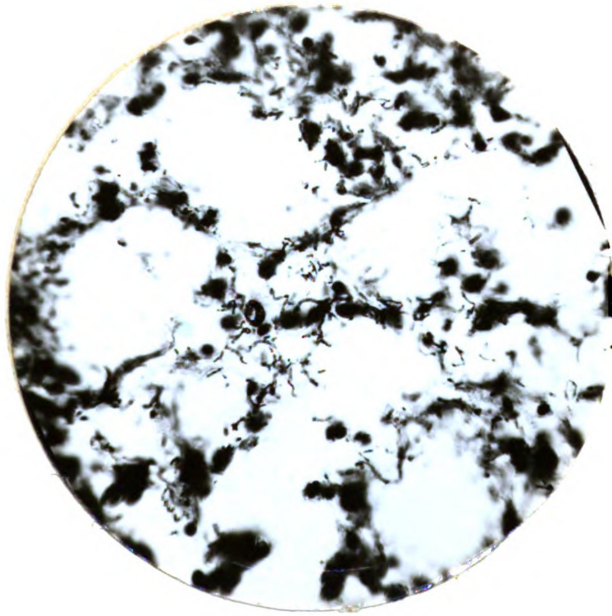
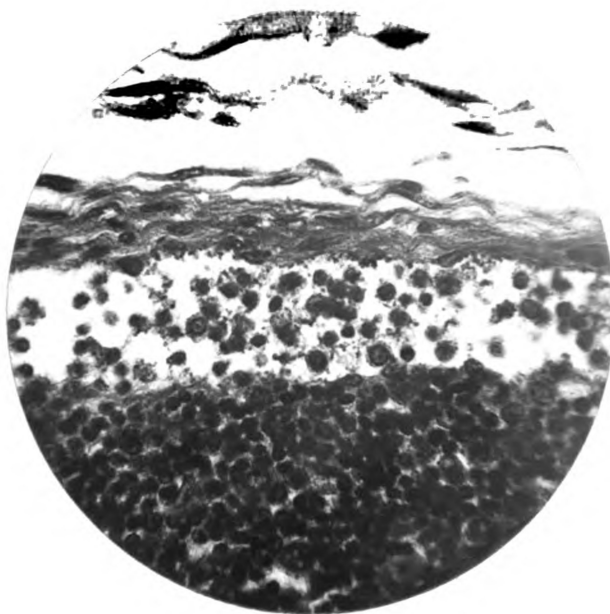
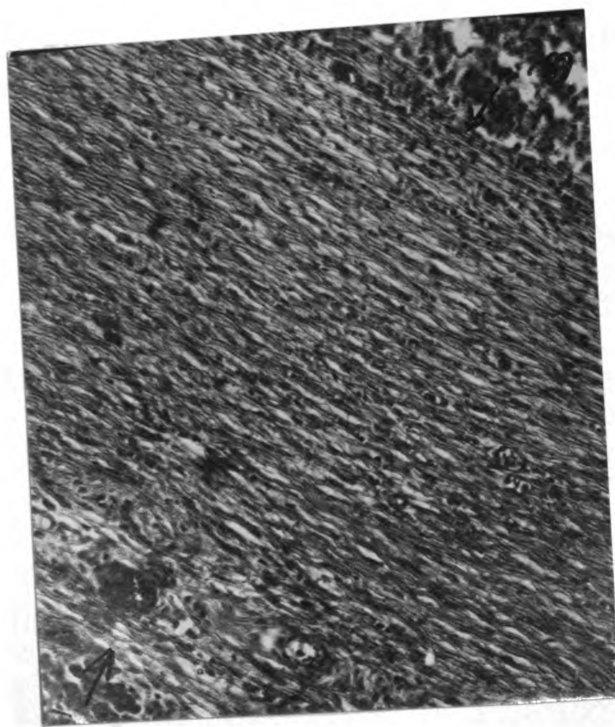


Fig 5

Plate IV*Fig. 6.**Fig. 7.*

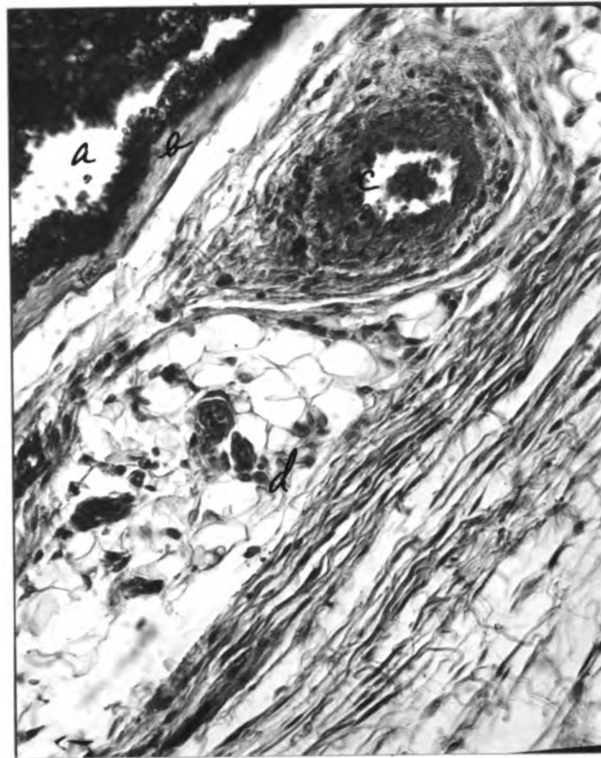


Fig. 8.

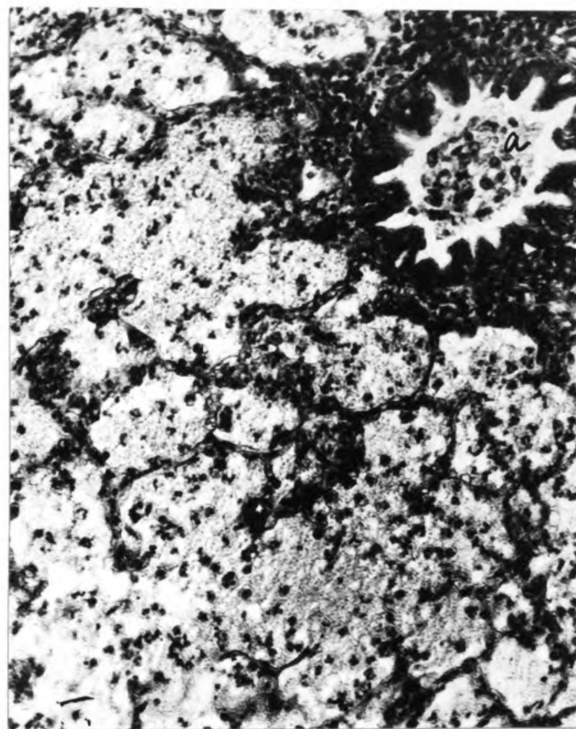


Fig. 9.

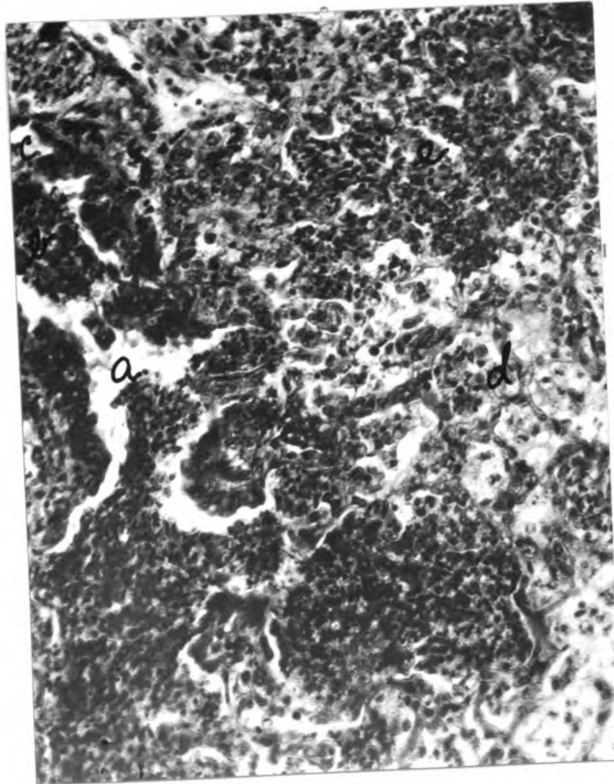


Fig. 10.

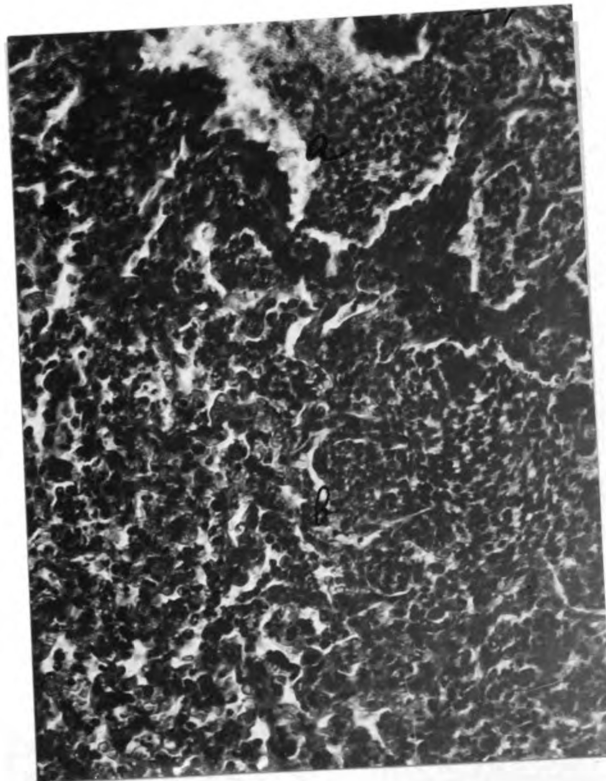


Fig. 11.

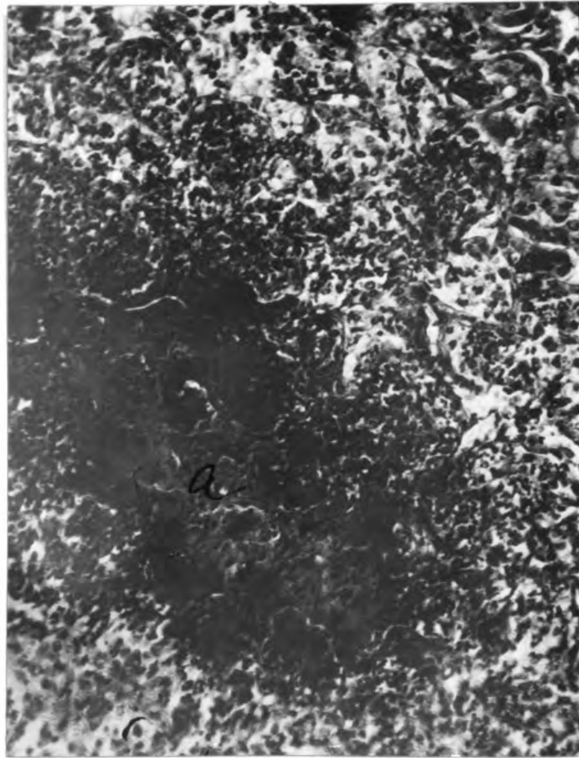


Fig. 12.

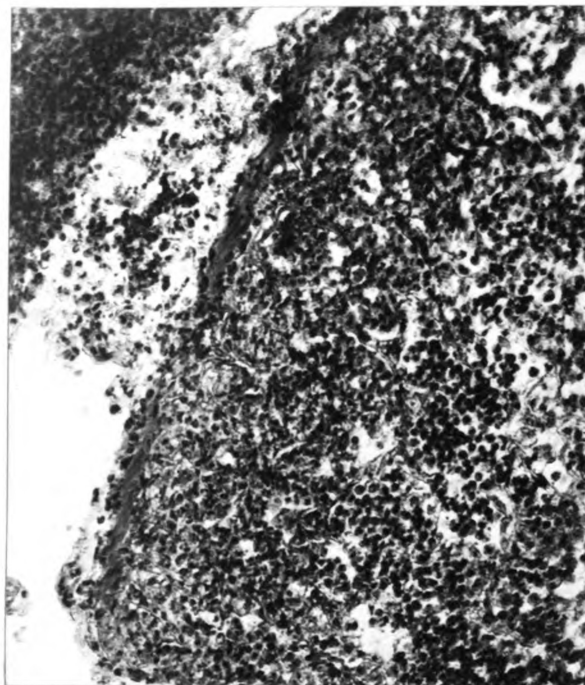


Fig. 13.

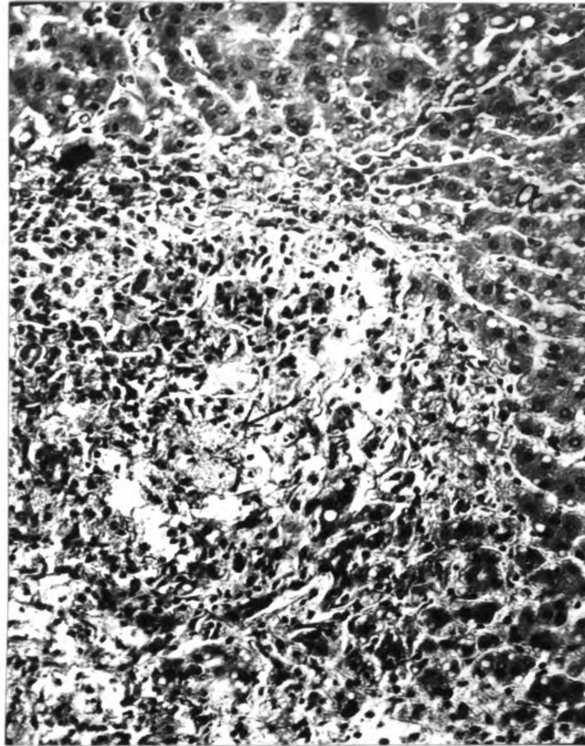


Fig. 14

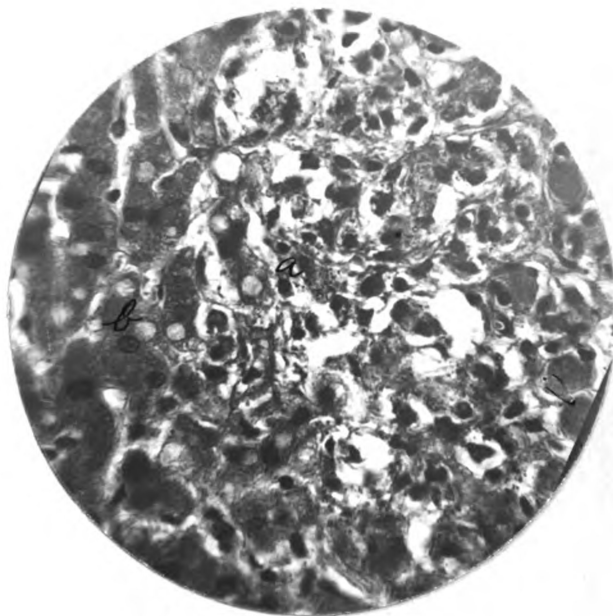


Fig. 15.



Fig. 16.

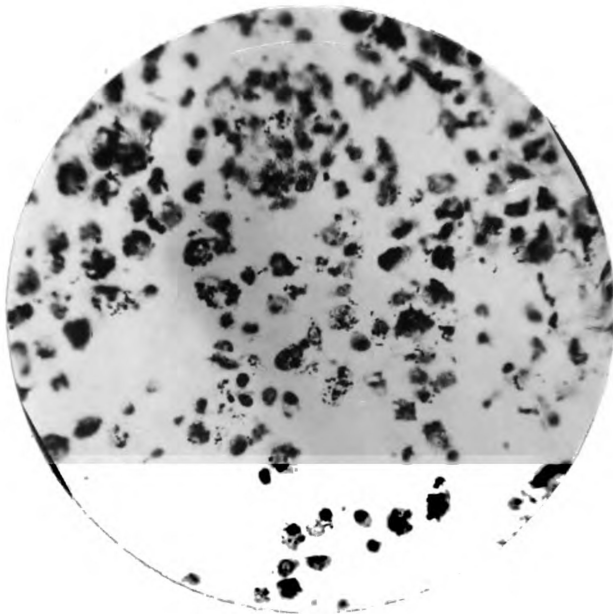


Fig. 17.

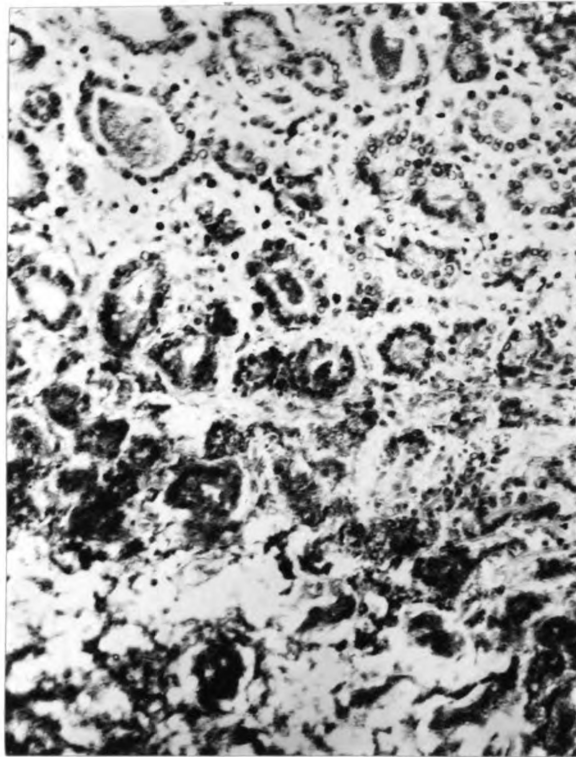


Fig. 18.

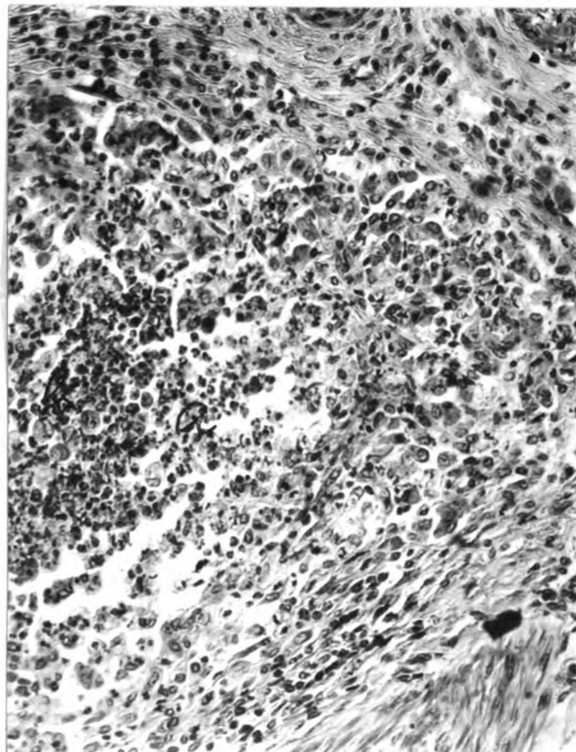


Fig. 19.

ACKNOWLEDGMENT

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