THE ETIOLOGY OF RAT-BITE FEVER.

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PLATES 8 TO 14.

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Rat-bite fever, or Sodoku, has long been recognized in Japan as a definite febrile disease, following the bite of a rat.

Miyake (1) in 1899 was the first to describe the disease in detail as a definite clinical entity and reported eleven cases of his own with references to others in the Japanese literature. For many years reports of sporadic cases have appeared in America, the first being recorded as early as 1840 by Wilcox (2). In 1909 Horder (3) reported three cases from England, and since that time instances of the disease have been recorded with increasing frequency in the British literature. The incidence of rat-bite fever in continental Europe seems to have been less frequent. Cases have been recorded in France by Millot-Carpentier (4), De Micas (5), and Curtillet and Lombart (6); in Spain by Peña y Maya (7); in Italy by Frugoni (8); and in Germany by Schottmüller (9).

The clinical characteristics of rat-bite fever have been well presented in papers by Miyake (1), Horder (3), Ogata (10), Atkinson (11), Gouget (12), Proescher (13), and Frugoni (8). A comprehensive description of the disease with report of a new case and summary of 53 cases collected from the literature has recently been published by Crohn (14). To the cases collected by him may be added the following, making a total of 81 cases: in America, Farquhar (15)[1] 6; in the British Isles, Atkinson (11) 6; Nixon (16) 1; Dick and Rutherford (17) 1; in France, Curtillet and Lombart (6) 1; in Spain, Peña y Maya (7) 1; in India, Dalal (18) 1; in Japan, Ogata (19, 20) 9; and in Germany, Schottmüller (9) 1.

None of these cases with the exception of that reported by Schottmüller (9), which will be discussed below, has added anything new to our knowledge of rat-bite fever, so that it does not seem of value to review them in detail.

In view of the recent publication by Crohn (14) the clinical features of rat-bite fever will be given only in brief and the more detailed discussion will be devoted to the etiology and pathology of the disease.

Rat-bite fever is a paroxysmal febrile disease of the relapsing type following the bite of a rat. The wound heals readily, but after a variable incubation period of a few days to a month the wound becomes inflamed and painful. Lymphangitis and adenitis set in and are quickly followed by symptoms of systemic infection

[1] Farquhar's report is too brief to make the diagnosis certain in his cases.

ushered in by a chill and rapid rise in temperature. There is extreme prostration, severe generalized muscular pain, headache, weakness, and loss of appetite. Stupor, delirium, and even coma may supervene. There is muscular tenderness and rigidity and the tendon reflexes are frequently exaggerated. A characteristic exanthem of bluish red, erythematous, sharply marginated macules appears, varying in size from 1 to 10 cm. in diameter and of general distribution. After 5 to 9 days the temperature falls by crisis accompanied by a drenching sweat and all symptoms subside. The disease then assumes the relapsing type with paroxysms occurring at fairly regular intervals, usually about once a week. The course may vary from one to three months or even longer. Gradually the relapses become less frequent and less severe and the disease often terminates with an abortive paroxysm. The more important complications are nephritis, severe anemia, and emaciation. About 10 per cent of the cases terminate fatally, usually during the first febrile period, occasionally later from nephritis or exhaustion.

That rat-bite fever is an infectious disease dependent upon the introduction of a specific organism or virus at the site of the bite seems highly probable. There has been no definite evidence presented to show that the rat inflicting the bite was in any way diseased or other than a normal rat. In view of this negative evidence it does not seem improbable that the etiological agent is simply a saprophyte in the mouth of the rat. Individual susceptibility seems to play a definite part in the contraction of the disease, as instances are recorded in which the second of two people bitten by the same rat has been the only one to develop rat-bite fever (Miyake (1)). Nixon (16) has reported a case similar to rat-bite fever following the bite of a ferret, and Schottmüller (9) a case incident on the bite of a South African squirrel. That the etiological factor in such cases is closely related to that occurring in rat-bite fever is possible.

The relapsing type of the fever has suggested that the disease may be of protozoan or spirochetal origin, but there are no facts to substantiate this supposition.

Most of the cases reported during the last decade have been carefully studied bacteriologically without yielding definite results until the recent case of Schotmüller (9) reported in 1914. Ogata (10, 19) in a series of eight cases has described parasitic organisms in the blood, excised lymph nodes, and smears from the local lesions. He considered the organism to be a sporozoon and has observed various stages in its development,—sporozoites, merozoites, etc. Guinea pigs and rabbits inoculated with material from his cases died in 18 to 21 days. The same organism was observed in the blood and smears from lymph nodes, liver, and spleen of the experimental animals. In a subsequent communication Ogata (20) has reported on his findings in three additional cases. The same organisms were described in the blood and lymph nodes, and in addition mycelial threads were observed. The organism was cultivated at room temperature on gelatin and agar slants from blood obtained from the finger tips of his patients. Animal experimentations yielded the same results as in the former cases. It is to be noted, however, that he has changed the classification of his organism and con-

siders it to be an aspergillus, basing his conclusions on the cultural characteristics and appearances in smears prepared from experimental animals. Ogata's work has not been confirmed by other observers.

Middleton (21) in his case noted rod-like organisms in fresh blood smears, and one colony of a non-capsulated diplococcus appeared in an anaerobic gelatin blood culture. The organism was considered a contaminant and was not studied further.

Proescher (13) in 1911 reported finding numerous bacilli in sections from the excised wound in his case. The organisms stained bluish with Giemsa solution in tissue fixed in bichloride and alcohol, but could not be found in sections hardened in formalin. They were straight or slightly curved, from 0.5 to 1.5 microns long, and showed irregular or bipolar staining. A guinea pig inoculated subcutaneously with a portion of the excised wound after a three weeks' incubation period developed enlarged lymph nodes followed by inflammatory skin lesions. Sections of the enlarged lymph nodes showed a great number of the same bacilli that were found at the site of the bite of the patient. The organism could not be cultivated.

Schottmüller (9) has recently reported a case of rat-bite fever from which he obtained an organism in pure growth in eight consecutive blood cultures taken during a period of two months. Colonies appeared well developed in agar plates on the second or third day. The organism was cultivated on blood agar, Loeffler's blood serum, milk agar, and in human blood serum, but failed to grow on other media. The colonies on solid media were discrete, colorless, and pin-head size. In human blood serum growth appeared as a whitish floccular sediment. Microscopical examination showed long, fine, twisted threads, some homogeneous, some fragmented, some branching. They often showed spindle- or ball-shaped swellings, and coccus-like forms developed. The organism was non-motile, stained with the ordinary stains, and was tinged bluish with Gram's method. Growth occurred only at incubator temperature. The organism was not pathogenic for rabbits or guinea pigs. Schottmüller considered the organism to be a streptothrix and has called it *Streptothrix muris ratti.*

From a case in its clinical manifestations closely resembling rat-bite fever following the bite of a South African squirrel he isolated a similar organism which he has designated *Streptothrix taraxeri cepapi.* Inoculation of a monkey proved the organism to be pathogenic for that animal.

Of the pathological anatomy of rat-bite fever but little is known. Only one autopsy by Miura (22) is published. Macroscopically there was increase of the cerebrospinal fluid and injection of the pial vessels of the brain and cord. No further pathological changes were recorded and no mention was made of microscopic examination. Histological study of the excised wound in Proescher's (13) case showed a mixed inflammatory and proliferative lesion. The corium was infiltrated with numerous endothelial cells, lymphocytes, and polynuclear leukocytes. Young connective tissue elements were noted, and the whole lesion was surrounded by a wall of dense, hyaline connective tissue. Examination of excised lymph nodes recorded in a few instances has shown only hyperplasia.

Further pathological changes can only be surmised from knowledge of the clinical features of the disease. The inflammatory process at the site of the wound, the lymphangitis, and adenitis are rarely if ever suppurative in character in the absence of secondary infection. Superficial or deep ulceration, vesicle formation, and gangrene may occur at the site of the bite. The extensive and often severe systemic symptoms presumably may be the result of a profound toxemia from the elaboration of a toxin at the site of the wound, or may be due to a general invasion of the body by the etiological agent. Whichever occurs, the effects are especially shown in the severe muscular pain, wide-spread exanthem, and profound disturbance of the nervous system.

There is meager evidence in the literature pointing to cardiac complications. In Millot-Carpentier's (4) case a systolic murmur was discovered at the base of the heart and over the carotid arteries late in the course of the disease, but there is no definite statement as to the patient's previous cardiac condition. Reece's (23) patient, who had previously been well, six months after recovery was unable to walk rapidly without becoming breathless, and causing violent palpitation of the heart. There is, however, no mention of a physical examination.

The respiratory system except for an occasional mild bronchitis seems to be equally exempt. Gastro-intestinal symptoms are rarely of importance. The liver and spleen are almost never enlarged. The rather frequent occurrence of nephritis as a severe and often fatal complication indicates that the kidneys may be severely damaged.

The following case of rat-bite fever, which terminated fatally and came to autopsy, has proved of considerable interest from the standpoint of etiology and pathology.

The patient entered the Peter Bent Brigham Hospital, May 15, 1915, in the service of Dr. Henry A. Christian, to whom I am indebted for the privilege of reporting the case. I wish here also to express my thanks for many courtesies from the pathological department of the hospital.

E. S. A. A white woman, age 67 years, born in New York, dry goods merchant. The patient was referred to the medical service of the Peter Bent Brigham Hospital on May 15, 1915, by Dr. William P. Bolles, of Roxbury, Mass., with the following history.

Complaint.—Rat-bite.

Family History.—Unimportant. Habits good.

Past History.—Measles in childhood. Malaria 20 years ago. She has had fibroids of the uterus for many years. Otherwise she has been very well. She has had no symptoms of respiratory, cardiac, gastro-intestinal, hepatic, or renal disease.

Present Illness.—Two weeks ago, while taking a rat out of a trap, the patient

was bitten on the tip of the right index finger. The wound was not severe and she paid no further attention to it than to wash it in hydrogen peroxide. Two days later the finger became reddened and red streaks appeared running up the forearm. The arm and right axilla became painful. The patient consulted a physician who opened and dressed the wound and prescribed phenacetine. After four days the inflammation and pain had entirely subsided and she resumed her ordinary course of life, feeling perfectly well until 10 hours before admission to the hospital. At that time she had a severe chill which lasted about thirty minutes, suffered severe pain in the legs, arms, and sides, felt very feverish, and was completely prostrated. She was nauseated, but did not vomit. No other symptoms were noted and her condition was unchanged at the time of admission.

Physical Examination.—The patient is a well developed and well-nourished woman, very drowsy, dull, and apathetic, evidently suffering from severe pain throughout the body, especially in the legs. There is no cough or dyspnea. Temperature 101.4° F.; pulse 108.

Skin is pale and dry; no exanthem. Eyes, ears, nose, mouth, and throat are negative. Neck is readily flexed. Thyroid not felt.

The right axillary lymph nodes are enlarged, not tender, non-fluctuant. No other nodes are palpable. Lungs are negative.

The heart's action is regular. Apex impulse is not felt. There are no thrills. Left border of dulness is 11 cm. to the left of the midsternal line in the 5th intercostal space; right border is 3 cm. to the right of the midsternal line in the 4th interspace; upper border is at the 3d rib. Heart sounds are muffled. At the apex a soft systolic murmur is heard, not widely transmitted. There is no diastolic murmur. A2 is slightly accentuated, P2 normal.

Pulses are equal, regular, synchronous, of small volume and moderated tension.

Blood pressure: systolic 140; diastolic 86.

In the right lower quadrant of the abdomen there is a large rounded firm tumor (fibroid). Otherwise abdominal examination is negative.

Liver and spleen are not palpable.

On the tip of the right index finger is a small linear scar. There is no inflammation about the scar and no evidence of lymphangitis. There is muscular tenderness in both arms and legs.

Reflexes are normal.

June 15. Blood: hemoglobin 92 per cent; red blood corpuscles 4,400,000; white blood corpuscles 22,100. Smear: neutrophils 74 per cent; small mononuclears 17 per cent; large mononuclears 8 per cent; eosinophils 1 per cent; basophils 0. The red blood corpuscles appear normal. No parasites.

Urine is amber, clear, acid; specific gravity 1.024; trace of albumin; sugar 0; acetone 0; diacetic acid 0; bile 0; sediment, many white blood corpuscles and finely granular casts. No blood.

Blood culture, see below.

Phenolsulphonephthalein test: 48 per cent excreted in 2 hours.

May 16. Pulse and temperature, see Text-fig. 1. Patient is apathetic and complains of severe muscular pains; has no appetite. A blotchy, bluish red, macular, and maculopapular exanthem has appeared on the arms, thorax, thighs, and knees. The macules vary from 2 to 6 mm. in diameter, are sharply marginated, slightly raised, fade on pressure, and are neither painful nor itchy.

May 17. Condition unchanged. Tendon reflexes of arms are exaggerated. Stained blood smears and fresh smears examined with dark-field illumination show no parasites or bacteria.

May 18. Exanthem has faded somewhat. General condition is unchanged. Stool is negative. Wassermann reaction is negative.

May 19. Blood culture, see below. Blood serum does not agglutinate *B. typhosus*. Urine contains a trace of albumin; sediment, few finely granular casts.

May 20. Patient appears very sick, is very apathetic. Exanthem has nearly disappeared. White blood corpuscles 19,300.

May 24. General condition is improved. White blood corpuscles 14,700.

May 25. Patient's temperature has fluctuated considerably during the past few days. She had a severe chill followed by a rise in temperature this evening.

May 27. Condition is steadily improving. Muscular pain and tenderness are slight. No exanthem is present.

May 28. Temperature normal. White blood corpuscles 17,400.

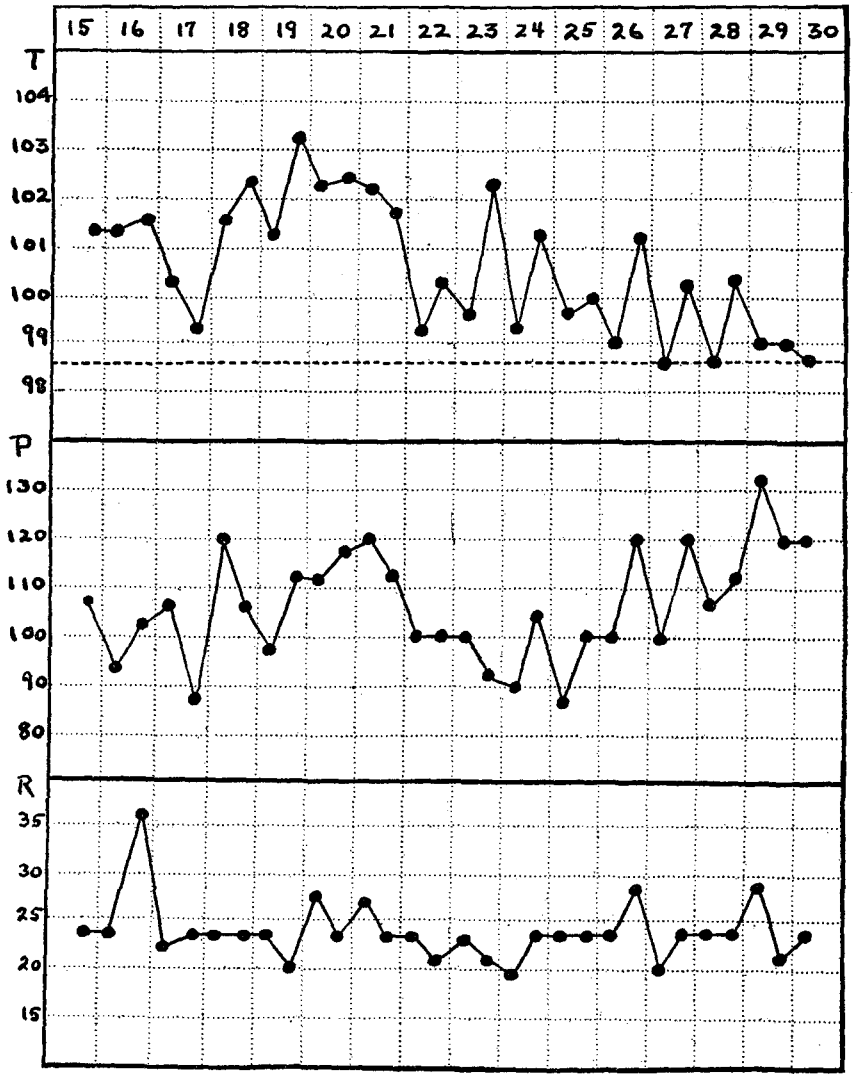
May 29. Patient was restless during the night. Pulse became rapid and weak. Patient appears very sick. Lungs are negative. The systolic murmur at the apex of the heart has become louder and harsher. A finely mottled, reddish, slightly indurated skin eruption 5 by 10 cm. has appeared on the outer aspect of the left knee.

May 30. Patient became gradually weaker and died at 7 a.m.

Autopsy Protocol.

The autopsy was done by Dr. James L. Stoddard 7 hours post mortem.

Fairly well nourished adult showing no pigmentation and no subcutaneous edema. Peritoneal cavity is free from fluid and signs of inflammation. There are several large uterine myomata. Pleural cavities contain a small amount of bloody fluid; no adhesions. Pericardial cavity contains about 5 cc. of clear yellow fluid; no adhesions. Heart (360 gm.) has a normal appearing musculature. Tricuspid, pulmonic, and aortic valves appear normal. On the posterior cusp of the mitral valve there is a large raised area made up of soft tissue, which was formed apparently under the endocardium. The area is 15 mm. in diameter and 7 mm. in height. In its center is a perfora-



TEXT-FIG. 1. Temperature chart of case of rat-bite fever (E. S. A.)

tion 4 mm. in diameter passing through the valve leaflet. The other cusps of the valve appear normal. Lungs show moderate congestion. Liver shows marked passive congestion. Spleen (200 gm.) shows a brownish red and pale mottling. On section it appears soft and edematous, the pulp scraping off easily. Two firm, pale, wedge-shaped areas are seen, with their bases at the surface of the spleen. Pancreas, gastro-intestinal tract, adrenals, and bladder appear normal. Kidneys are small (95 gm. each); surface is slightly granular; cortex 4 to 5 mm., pale gray, without distinct markings. Aorta shows marked sclerosis in the abdominal portion. Brain appears normal.

Microscopic Examination.—The myocardium shows areas of subacute myocarditis with complete disappearance of the muscle fibers, their place being taken by loose tissue filled with endothelial cells and leukocytes (Fig. 8). In the fibers elsewhere there is a high degree of fat vacuolation. Sections of the mitral valve through the vegetation (Fig. 11) show a central perforation surrounded by granulation tissue infiltrated with leukocytes. At the periphery there are masses of connective tissue, parts of which are hyalinized, parts thickly infiltrated with leukocytes, and parts necrotic. In the necrotic areas are masses of organisms appearing as long slender bacilli (Fig. 12). The muscle fibers adjacent to the lesion show all stages of necrosis.

The lung shows hemorrhage, edema, and passive congestion.

Sections of the liver show increased interlobular connective tissue, in many places thickly infiltrated with lymphocytes and polynuclear leukocytes (Fig. 9). In some places there is increased connective tissue extending within the lobules with slight infiltration with lymphocytes and polynuclear leukocytes. In these areas many of the liver cells are atrophic; elsewhere they appear normal.

The spleen shows marked hemorrhagic and necrotic areas. The adrenals show a perivascular exudate of lymphoid cells and moderate edema of the tissue throughout. The pancreas appears normal. Sections of the uterine tumor show an atrophic myoma.

The glomeruli of the kidneys are closely placed and large with considerable thickening of the capillary walls. There is an occasional completely sclerosed glomerulus. There is frequently an increased number of polynuclear cells in the capillaries. The interstitial tissue shows various stages from an acute to a healed process of uneven dis-

tribution. In many places there is an exudate chiefly of polynuclear cells extending in long streaks between the tubules (Fig. 10); in other places the exudate consists of lymphocytes and plasma cells, often situated about a glomerulus. In some places there is increased connective tissue. The tubular epithelium is granular, but shows little desquamation. The vessels show marked thickening of the intima and media with hyaline change. One section shows a small infarction.

Diagnosis.—Acute ulcerative endocarditis; subacute myocarditis; subacute interstitial hepatitis; subacute glomerular and interstitial nephritis; subacute perivascular exudate of adrenals; infarcts of spleen and kidney; congestion, hemorrhage, and edema of lungs; atrophic leiomyoma of uterus.

Bacteriological Data.—A blood culture was made on May 15, within 15 hours after the onset of systemic symptoms. 25 cc. of blood were drawn from the median basilic vein and distributed in dextrose agar and ascitic agar plates and deep tubes, plain and dextrose bouillon flasks and tubes, and Loeffler's blood serum slants. The cultures were incubated partly aerobically and partly anaerobically. On the third and fourth days after inoculation growth appeared in all the media, aerobic and anaerobic, except the dextrose agar plate and deep tube and the dextrose bouillon flask. These remained sterile. One colony appeared in the ascitic agar plate and three colonies in the ascitic agar deep tube. The colonies were grayish white, pin-head size, slightly irregular in outline. In bouillon the growth consisted of whitish flocculi which remained at the bottom of the tubes and flasks without clouding the media. In the Loeffler's blood serum slants the growth was most abundant, appearing as whitish flocculi in the blood and water of condensation at the bottom of the tubes.

A second blood culture was made on May 19. 20 cc. of blood were distributed in plain and ascitic bouillon, and Loeffler's blood serum tubes. No growth was observed in any of the media (seven days' incubation).

At autopsy, May 30, cultures of the heart's blood were made in 4 Loeffler's blood serum tubes and 3 bouillon flasks. After 48 hours' incubation all the blood serum tubes showed a moderate growth identical with that obtained in the first blood culture. One of the bouillon

flasks showed a staphylococcus which was considered a contaminant; the others remained sterile.

Cover-slip preparations from all the positive cultures showed a pure growth of a thin filamentous organism varying greatly in length. Many forms were homogeneous throughout their length, others fragmented giving the appearance of a chain of short bacilli. There were occasional forms containing deeply staining granules, and a few swollen spindle- and club-shaped forms. Here and there definitely branching forms were seen. These characteristics indicated that the organism was probably a streptothrix, a fact which further study has confirmed.

TABLE I.

Serum of patient E. S. A.	1:20	1:40	1:80	1:160	1:320	1:640	Salt solution.
2 hrs. at 37° C.	++	++	+	−	−	−	−
12 hrs. on ice	++	++	+	−	−	−	−
Normal human serum.	1:20	1:40	1:80	1:160	1:320	1:640	
2 hrs. at 37° C.	−	−	−	−	−	−	
12 hrs. on ice	−	−	−	−	−	−	

May 19. Numerous blood smears stained with Wright's stain and fresh dark-field preparations were carefully searched for parasites and organisms, but yielded negative results.

May 28. When the patient's temperature had fallen to normal, blood was drawn for agglutination tests with the organism isolated from the blood. 1 cc. of increasing dilutions of the patient's serum was mixed with 1 cc. of an 0.85 per cent salt solution suspension of the organism thoroughly shaken, in a series of small tubes and incubated for 2 hours at 37° C. in a water-bath. 0.85 per cent saline and the same dilutions of normal human serum were used as controls. Final readings were recorded after the tubes had stood in the ice-box for 12 hours. Positive agglutination occurred in dilutions of 1:20, 1:40, and 1:80. The controls were negative. The results are shown in Table I (Fig. 7).

Agglutination tests were repeated in a similar manner after the

organism had been growing in subculture for three weeks, partial agglutination occurring in dilutions as high as 1:320 (Table II) after one hour's incubation.

TABLE II.

Serum of patient E. S. A.	1:20	1:40	1:80	1:160	1:320	1:640	Salt solution.
1 hr. at 37° C.....	C	C	C	++	+	–	–
12 hrs. on ice.....	C	C	C	++	+	–	–

C indicates complete agglutination and sedimentation.

Description of Organism.

Morphology.—The organism is a slender, filamentous, branching organism, growing in interwoven masses not manifesting a definite radial arrangement at the periphery of the colonies. In young cultures the filaments vary greatly in length, are curved, waving, or straight, show many true branching forms and stain homogeneously (Fig. 1). After 18 to 24 hours' incubation fragmentation of the filaments appears and branching forms rapidly disappear. The filaments now appear as chains of bacilli varying in length (Fig. 3). Staining is no longer homogeneous and numerous granular or beaded forms appear (Fig. 5). Occasional filaments become spindle-shaped, while others show ball-shaped, oval, or terminal club-shaped swellings, and chains of coccus-like forms appear (Fig. 2). Older cultures show marked fragmentation and breaking up of the filaments into rods (Fig. 4). The rods vary considerably in length, are straight or slightly curved, and are frequently beaded, resembling in many respects the pleomorphic bacilli. The chains of coccus-like forms become more numerous, and remaining masses of filamentous forms stain very faintly.

Staining Reactions.—The organism stains readily with methylene blue, gentian violet, carbol-fuchsin, pyronin, and Bismarck brown. It is Gram-negative and is neither acid- nor alcohol-fast.

Capsule.—No capsule formation could be demonstrated. The club-shaped forms do not show the characteristic sheath of actinomyces as described by Wright (24).

Spores.—No true endospores could be demonstrated.

Motility.—The organism is non-motile.

Oxygen Requirements.—The organism is a facultative anaerobe. Growth under anaerobic conditions is somewhat less abundant than under aerobic conditions.

Thermal Death Point.—The organism is killed by exposure to 60° C. for 10 minutes. Cultures containing chains of coccus-like forms were used in determining the thermal death point.

Viability.—Cultures kept at 37° C. die out after 5 to 8 days. On ice cultures remain viable 7 to 14 days.

Temperature Requirements.—The optimum temperature for growth is 37° C. Scanty growth appears after 4 days at room temperature.

Reaction of Media.—The optimum reaction for growth is between the neutral point and 2.0+. Growth does not occur in media of greater alkalinity than 1.5− or of greater acidity than 3.0+.

Pigment Formation.—The organism is non-chromogenic.

Cultural Characteristics.

Gelatin.—No growth.

Loeffler's Blood Serum.—After 24 hours at 37° C. a moderately abundant growth of discrete, whitish, pin-point, circular, sharply marginated, elevated, smooth, glistening, moist, non-mucoid colonies appears (Fig. 6). There is a whitish, flocculent growth in the water of condensation. The medium is not liquefied. After 48 hours' incubation colonies may show slight coalescence if closely aggregated, but they do not tend to increase in size after the first 24 hours' incubation.

Human Blood Agar.—After 24 hours at 37° C. a very scanty growth similar to that on Loeffler's blood serum appears.

Ascitic Agar.—When first isolated, the organism failed to grow on this medium. Growth was finally obtained, however, after the organism had been subcultured on Loeffler's blood serum for 2½ months. Colonies show the same characteristics as on blood serum.

Ascitic Bouillon.—(Plain bouillon 4 parts, ascitic fluid 1 part.) After 18 to 24 hours at 37° C. a whitish flocculent growth appears at the bottom of the tube and to some extent along the sides (Fig. 6).

The medium remains clear and there is no surface pellicle. Growth ceases after 24 to 30 hours.

Plain and dextrose agar, plain and dextrose bouillon, ox bile, litmus serum water, potato, and litmus milk showed no growth after 7 days' incubation on repeated trials.

Fermentation.—No growth could be obtained in levulose, lactose, dextrose, mannite, maltose, saccharose, or dextrin litmus serum waters. A good growth was obtained in inulin, lactose, mannite, raffinose, saccharose, and salicin broths to which ascitic fluid had been added, 1:4, but there was no demonstrable change in reaction after 7 days' incubation.

Pathogenicity.—Guinea pigs, rabbits, and white rats were inoculated with blood from the patient, and with varying amounts of 24 hour cultures of the organism with the following results.

Four rabbits were inoculated, two intravenously and two intraperitoneally, May 19, 1915, each with 5 cc. of citrated blood from the patient. One rabbit died on May 26, 1915, of an intercurrent infection. The other three showed no evidence of disease. Autopsies, June 30, 1915, were negative.

Two white rats were inoculated intraperitoneally, May 19, 1915, each with 3 cc. of citrated blood from the patient. Neither showed any evidence of disease. Autopsies, June 22, 1915, were negative.

Six guinea pigs were inoculated, May 20, 1915, three subcutaneously, three intraperitoneally, with varying amounts of ascitic bouillon cultures. None of the animals showed any evidence of disease. Autopsies, June 22 and 29, 1915, were negative.

Two rabbits were inoculated intravenously, two intraperitoneally, and two subcutaneously, May 20, 1915, with varying dosages of 24 hour ascitic bouillon cultures. Five yielded entirely negative results during 6 weeks' observation and at autopsy. The protocol of the sixth experiment is given below.

Rabbit 6.—Weight 1,220 gm. Inoculated subcutaneously, May 20, 1915, with a salt solution suspension of the growth from 30 cc. of ascitic bouillon (24 hours' incubation).

May 25. Animal seems well. A firm nodule the size of a large pea has appeared beneath the skin at the site of inoculation.

June 1. Nodule is the size of a small marble, firm, non-fluctuant, apparently not tender.

June 30. The animal has shown no other evidence of disease than the subcutaneous tumor which has persisted. There has been a steady gain in weight. Animal killed.

Autopsy.—Weight 1,590 gm. In the subcutaneous tissue of the left flank at

the site of inoculation is a firm, slightly irregular, encapsulated tumor 1.2 cm. in diameter. On section it presents a yellowish white granular appearance with two small foci of caseation. The lymph nodes in the left axilla are enlarged, discrete, and firm. On section they present a yellowish white, homogeneous surface without suppuration or caseation. No other enlarged nodes were noted. Heart, lungs, liver, spleen, kidneys, adrenals, gastro-intestinal tract, brain, and spinal cord appear normal macroscopically.

Microscopic Examination.—The subcutaneous nodule shows a peripheral wall of dense fibrous tissue surrounding a reticulum of loose connective tissue in which are many large and small necrotic foci surrounded by fibroblasts, plasma, and endothelial cells. No giant cells are seen. No organisms are demonstrable. The lymph nodes show only hyperplasia. Sections of the lung, myocardium, liver, spleen, and kidneys appear normal.

Cultures made from the subcutaneous nodule and lymph nodes remained sterile.

Four white rats were injected with varying amounts of 24 hour ascitic bouillon cultures with the following results.

White Rat 1.—May 22, 1915. Intraperitoneal injection of a salt solution suspension of the growth from 75 cc. of ascitic bouillon (24 hours' incubation). The animal appeared sick for a few days following the injection, but by the end of a week had apparently entirely recovered. It remained well until June 28, 1915, when it was killed.

Autopsy.—There were numerous fibrous adhesions about the spleen, stomach, liver, and diaphragm. The mesenteric, axillary, and inguinal lymph nodes were enlarged. They appeared glistening on section and showed no areas of caseation. No other abnormalities were noted on gross examination.

Microscopic Examination.—The lymph nodes showed only hyperplasia. Sections of the spleen showed thickening of the capsule and general hyperplasia. Plasma cells and endothelial cells were numerous throughout and occasional giant cells were seen. There were no areas of caseation or necrosis. The lungs, myocardium, liver, and kidneys appeared normal.

Cultures from the spleen, heart's blood, and lymph nodes remained sterile.

White Rat 2.—May 22, 1915. Intraperitoneal injection with a salt solution suspension of the growth from a 30 cc. ascitic bouillon culture.

May 23, 1915. Animal found dead. Streptococcus septicemia.

White Rat 3.—May 22, 1915. Subcutaneous injection with a salt solution suspension of the growth from a 30 cc. ascitic bouillon culture. The animal remained well without local or general reaction until June 13, 1915, on which date a small area of induration appeared at the site of inoculation. The lesion gradually increased in size, and on June 16, 1915, broke down, discharging a small amount of seropurulent fluid. The animal appeared lively and showed no evidence of a general reaction. The cutaneous lesion which was 1 cm. in diameter became crusted over but showed no tendency to heal or to spread. No other lesions developed. The rat was killed on June 28, 1915.

Autopsy.—At the site of inoculation there was a well localized abscess 1 cm. in diameter which had discharged externally and was covered with a reddish brown crust. The lesion was situated in the subcutaneous tissue and thoroughly walled off by dense connective tissue. The center was filled with necrotic material and a purulent exudate. The axillary, inguinal, peritoneal, and thoracic lymph nodes were considerably enlarged. On section the nodes appeared glistening grayish white, and showed no areas of caseation. No other gross abnormalities were noted.

Microscopic Examination.—The lymph nodes showed only hyperplasia and the presence of numerous plasma cells and endothelial leukocytes. Sections of the abscess showed a mass of necrotic material infiltrated at the margin with fibroblasts and plasma cells and surrounded by dense connective tissue. No giant cells were seen. Sections of the spleen, kidney, liver, lung, and myocardium appeared normal.

Smears from the abscess showed numerous rod-shaped and coccus-like organisms and a few filamentous forms. Cultures from the abscess showed an abundant growth in pure culture of the organism with which the rat was inoculated. Cultures of the heart's blood and lymph nodes remained sterile.

White Rat 4.—July 1, 1915. Subcutaneous injection of a salt solution suspension of the streptothrix isolated from Rat 3. The growth from 50 cc. of a 24 hour ascitic bouillon culture was used. The animal remained well and showed no local or general reaction. It was killed Aug. 11, 1915. Autopsy showed one enlarged axillary lymph node which on microscopic examination showed moderate hyperplasia. There were no other abnormalities.

In summary, the organism is very slightly pathogenic for rabbits and white rats, producing in some cases a local inflammatory and proliferative reaction at the site of inoculation, and general lymph node hyperplasia. It is not pathogenic for guinea pigs. Passage through one rat did not increase its pathogenicity.

DISCUSSION.

The diagnosis of rat-bite fever in the case described above seems thoroughly justified by the clinical picture which the patient presented. The history of a rat-bite, latent incubation period, non-suppurative lymphangitis, high fever ushered in by a severe chill, severe generalized muscular pain, stuporous condition, and the bluish red macular exanthem were quite typical of the recognized symptom-complex of the disease.

The isolation of an organism in pure culture from the blood during life and at autopsy and the development of an agglutinin in the

patient's blood serum for that organism leaves little question as to its causative relationship to the disease in this case. The presence of a morphologically similar organism in the sections of the mitral vegetation in the absence of other demonstrable organisms is strong presumptive evidence that the same organism was the cause of the endocarditis.

Study of the organism has shown it to be a true branching, filamentous organism, showing fragmentation of the mycelial filaments, granule formation, and the development of chains of coccus-like forms. It is Gram-negative and not acid-fast. In ascitic bouillon it grows as a flocculent sediment without clouding the media, and on solid media it grows in discrete colonies. These characteristics place the organism in the group of filamentous fungi, the Hyphomycetes. The nomenclature of both species and genera in this group is still somewhat confused, different authors using several generic names,—Nocardia, Actinomyces, Streptothrix, Discomyces, Oospora. The weight of opinion and common usage, however, favor the adoption of the name Streptothrix for the genus, and it seems best to classify the organism described above as one of the Streptothrices.

Claypole (25), Foulerton (26), and Musgrave, Clegg, and Polk (27) have done much to clarify our knowledge of this group of organisms. The latter authors give the following generic characters for the Streptothrices: "Branching, filamentous organisms which develop into colonies made up of the organisms and 'transformation products.' The terminal hyphæ may or may not be radially placed on the surface of the colony and they may or may not develop 'clubs.' The group in general take Gram's stain and several members show acid-fast properties in a varying degree." Claypole states that the members of the group are alike in the following characteristics: "When grown in bouillon, the medium always remains clear. The growth on solid media is discrete. . . . . They are all gram positive, all have granule formation, either in mycelium or its products, as shown in chain sporulation, and, finally, branching organisms and thread-like forms are seen more or less frequently in all species."

The organism isolated in this case shows all the typical features of a streptothrix with the exception that it is Gram-negative, a variation which does not seem sufficiently important to exclude it from the genus.

The question of species is a more difficult one. The literature contains numerous more or less complete descriptions of organisms isolated from cases of streptothricosis. Musgrave, Clegg, and Polk (27) recognize six well established species: *S. actinomyces*, Boestrom (1890); *S. actinomyces*, Wolff and Israel (1891), Wright (1905); *S. nocardii; S. eppingeri; S. maduræ*, Vincent; *S. capræ*, Silberschmidt. The organism isolated in our case is definitely distinct from any of these, and differs from any streptothrix hitherto described with the exception of that isolated by Schottmüller in his case of rat-bite fever. Although Schottmüller does not give a complete description of his organism, it agrees in most particulars with the organism isolated in our case, the only difference being that Schottmüller's organism was "tinged bluish" with Gram's stain and it did not grow at room temperature. In spite of these slight differences it seems probable that the organisms are identical, and for that reason advisable to accept his name for the organism,—*Streptothrix muris ratti.*

Two features of interest in our case in addition to the relation of the organism to rat-bite fever are isolation of a streptothrix in pure culture from the blood during life, and the presence of an ulcerative endocarditis caused by a streptothrix. Cases of generalized streptothricosis resembling pyemia are not infrequently recorded in the literature, but the only other instance of a streptothrix septicemia in which the organism was isolated by blood culture is Schottmüller's case of rat-bite fever. Cases of streptothrix endocarditis are equally rare. Naunyn (28) in 1888 found in endocarditis vegetations of a case of chorea a branching organism which was identified as a cladothrix or leptothrix by Zopf. Pappenheimer and Satchwell (29) isolated a filamentous organism from the blood in a case of endocarditis and demonstrated the same organism in sections of the aortic vegetations. They considered their organism to be a cladothrix. No other instances of endocarditis caused by a filamentous microorganism are recorded in the available literature.

SUMMARY.

The similarity in the cases of rat-bite fever recorded in the literature establishes it as a definite clinical entity. The same symptomatology occurs in cases from Asia, Europe, and America. The greater fre-

quency of the disease in Japan than elsewhere is probably due to the housing conditions and habits of the people resulting in the more frequent occurrence of rat-bites. It does not seem necessary to consider that cases occurring in Europe and America are due to the bites of rats that have been imported from Japan.

The clinical picture and course of the disease indicate that it is infectious in origin. Until Schottmüller's case appeared in 1914, the etiology had been undiscovered. He isolated from his case in eight consecutive blood cultures a streptothrix which he has designated *Streptothrix muris ratti*. His work has been confirmed by the isolation of an identical streptothrix from the blood during life and at autopsy in the case here reported. Further confirmation of the etiological relationship of this organism to the infection in our patient is found in the production of powerful agglutinins for the organism in the blood serum of this case and in the demonstration of the organism in the vegetation on the mitral valve. It is not unreasonable to suppose that Proescher (13) observed the same organism in the sections of the excised wound in his case. Although it is fully realized that Koch's postulates have not been fulfilled in the absence of successful animal experimentation, nevertheless the accumulated evidence here presented leaves little reason to doubt that the specific cause of rat-bite fever is *Streptothrix muris ratti*.

The pathology of rat-bite fever has hitherto been largely a matter of surmise. One autopsy only has been recorded in the literature (Miura (22)), and nothing abnormal was noted other than injection of the pial vessels. The autopsy in the case here reported has proved of considerable interest in the extent and character of the lesions found. A streptothrix septicemia with the localization of the organism in the mitral valve producing an acute ulcerative endocarditis is the most striking feature of the case. The infarcts of the spleen and kidney are a natural sequence of the endocarditis. The subacute lesions of the myocardium, liver, adrenal, and kidneys, glomerular and interstitial, are all of a similar nature, consisting of areas infiltrated with leukocytes, lymphocytes, plasma, and endothelial cells with varying degrees of degeneration of the normal cells of the affected area. In no instance has the presence of the streptothrix in these lesions been demonstrated, and it is not unreasonable to assume that they are toxic in origin.

The data here presented may be correlated with the clinical features of rat-bite fever to give us a clear understanding of the course and nature of the disease. The patient is inoculated by the bite of a rat with *Streptothrix muris ratti*. After a variable incubation period a non-suppurative inflammatory reaction occurs at the site of the wound with extension to the neighboring lymphatics and lymph nodes. Invasion of the blood stream follows, accompanied by the onset of severe toxic symptoms. Clinically the nervous system and frequently the kidneys seem to be especially involved. That the myocardium, liver, and adrenals may also suffer is shown by the autopsy findings in the case reported above. Ulcerative endocarditis is probably a rare occurrence. In the majority of cases after a more or less prolonged course, the disease terminates spontaneously and so may be considered a self-limited infection. This is presumably brought about by the development in the body of a protective mechanism against the streptothrix. That such a process does occur is evidenced by the demonstration of agglutinins in our case. Whether a permanent immunity is acquired after one attack of rat-bite fever is not known. No instances of a second infection are recorded in the literature.

Although rat-bite fever varies somewhat in its symptomatology in individual cases, the picture is sufficiently characteristic to make the diagnosis not a difficult matter. The history of a rat-bite, latent incubation period with subsequent non-suppurative inflammatory reaction of the wound, lymphangitis, and enlarged lymph nodes, severe chill at onset, high fever of the relapsing type, intense muscular pain and nervous symptoms, and the characteristic bluish red exanthem, present a symptom-complex not easily overlooked. The disease is frequently complicated by a severe nephritis, and prolonged cases develop a high grade of anemia and cachexia. In the case here reported ulcerative endocarditis occurred.

In the large majority of cases the prognosis is favorable for a successful termination. The patients, however, are often incapacitated for a considerable period of time The mortality is about 10 per cent, death usually occurring in the first febrile period apparently from a profound toxemia, or at a later stage due to the development of a severe nephritis.

Until recently treatment has been entirely symptomatic and has been of little avail in altering the course of the disease. Miyake has found immediate treatment of the wound by cauterization or with carbolic acid highly efficient as a prophylactic measure. Hata (30) in 1912 introduced salvarsan therapy and reported eight cases so treated, seven of which showed marked and rapid improvement. One case was apparently unaffected. Two of the cases receiving only small doses had a subsequent relapse. Surveyor (31) and Dalal (18) also have reported success with salvarsan injections. It is to be hoped that further experience with this method of treatment will yield equally favorable results.

CONCLUSIONS.

1. Rat-bite fever is a specific infectious disease following the bite of a rat. It occurs in Asia, Europe, and America.

2. The etiological organism is *Streptothrix muris ratti*, first described by Schottmüller in 1914. His observation is confirmed by the isolation of an identical streptothrix in the case here reported.

3. Invasion of the blood stream by *Streptothrix muris ratti* occurs in rat-bite fever.

4. The case here reported developed a powerful agglutinin for *Streptothrix muris ratti.*

5. Pathological changes occur in the myocardium, kidneys, liver, and adrenals showing areas of degeneration and infiltration with polynuclear leukocytes, lymphocytes, plasma cells, and endothelial cells.

6. Ulcerative endocarditis may occur in rat-bite fever and be caused by the *Streptothrix muris ratti.*

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EXPLANATION OF PLATES.

PLATE 8.

FIG. 1. Stained preparation of *Streptothrix muris ratti* from a 15 hour Loeffler's blood serum culture, showing branching, homogeneously stained filaments and the non-radial arrangement at the margin of the colony.

FIG. 2. *Streptothrix muris ratti* from a 24 hour Loeffler's blood serum culture, showing irregularly swollen filaments and beginning formation of coccus-like chains.

PLATE 9.

FIG. 3. Fragmentation of mycelial threads appearing as chains of bacilli (24 hour culture).

FIG. 4. Complete fragmentation into rod-like forms (30 hour culture).

FIG. 5. Fragmented forms showing beading and terminal swellings.

PLATE 10.

FIG. 6. Twenty-four hour culture of *Streptothrix muris ratti* on Loeffler's blood serum and in ascitic bouillon.

FIG. 7. Agglutination of *Streptothrix muris ratti* by patient's serum. Dilutions 1 : 20, 1 : 40, 1 : 80, and control (Table I).

PLATE 11.

FIG. 8. Section of myocardium from patient.

FIG. 9. Section of liver from patient.

PLATE 12.

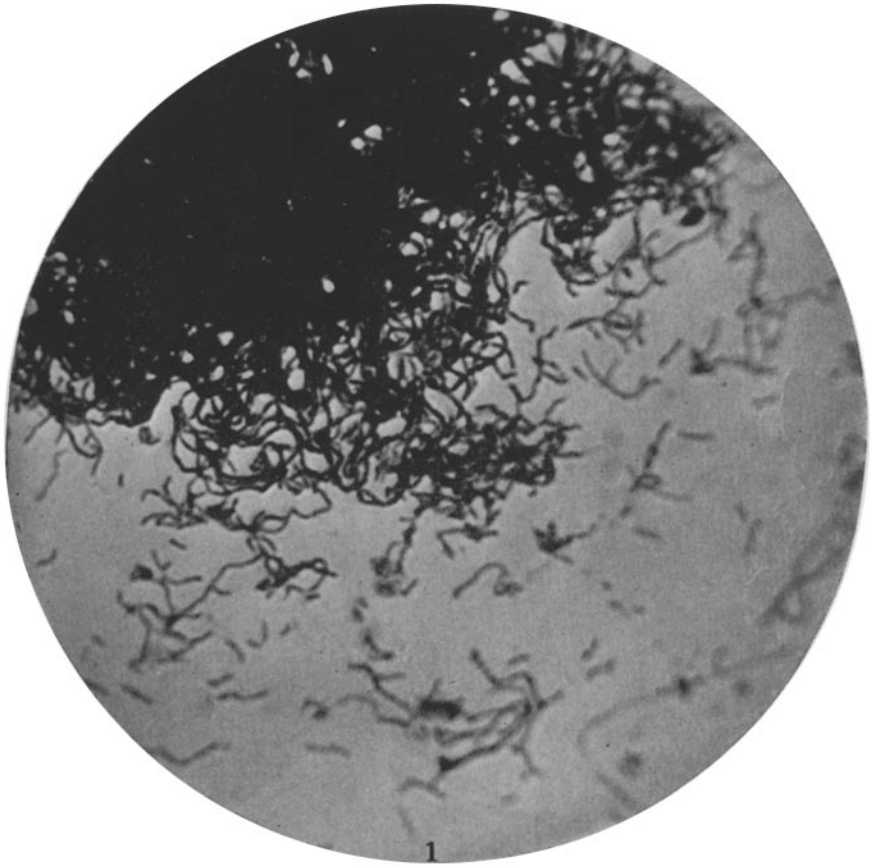
FIG. 10. Section of kidney from patient.

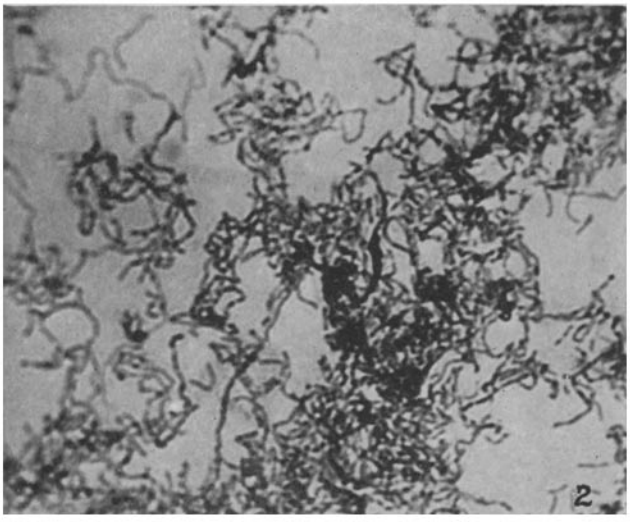
PLATE 13.

FIG. 11. Section of mitral vegetation showing necrotic material, infiltration with polymorphonuclear leukocytes, and masses of organisms.

PLATE 14.

FIG. 12. Section of mitral vegetation showing clumps of organisms. The rod-like form of the organisms is indefinite in the single focal plane represented in the microphotograph, but can easily be demonstrated in microscopic study of the actual section.





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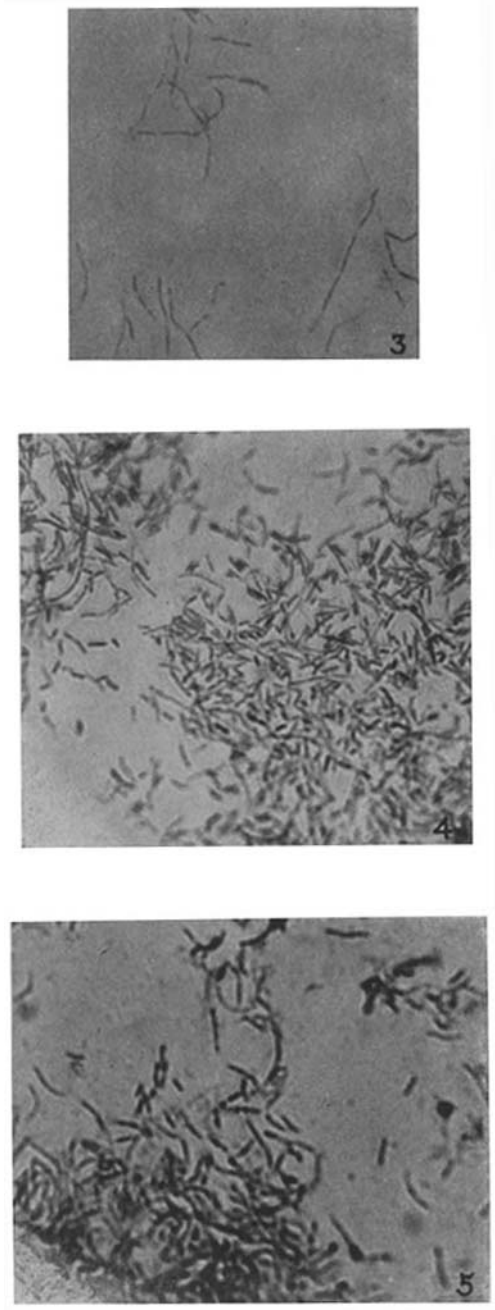

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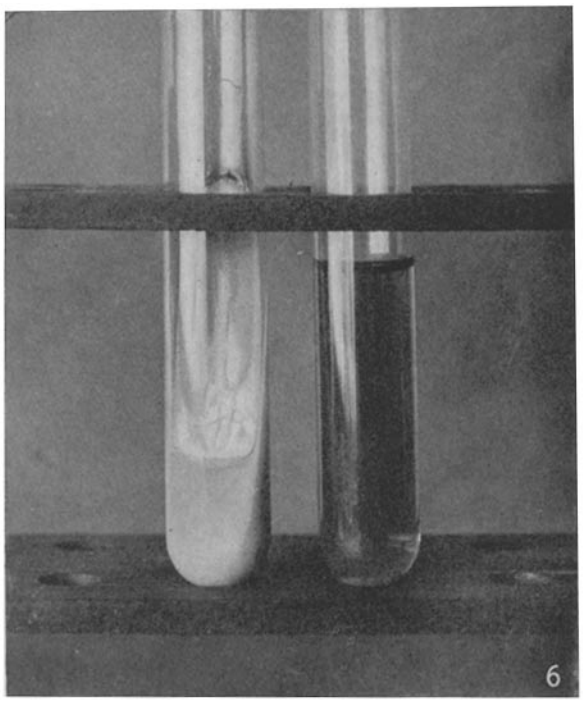

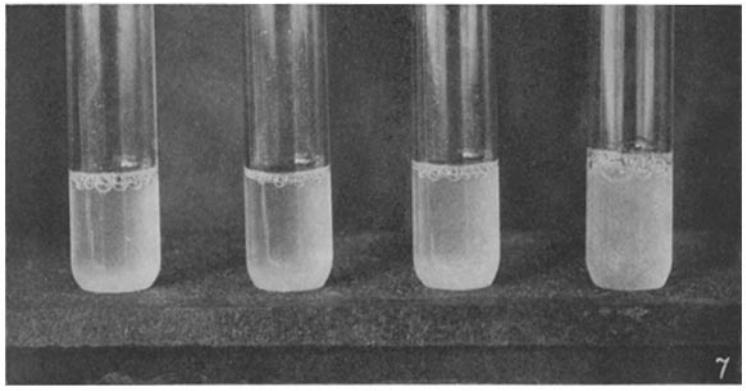

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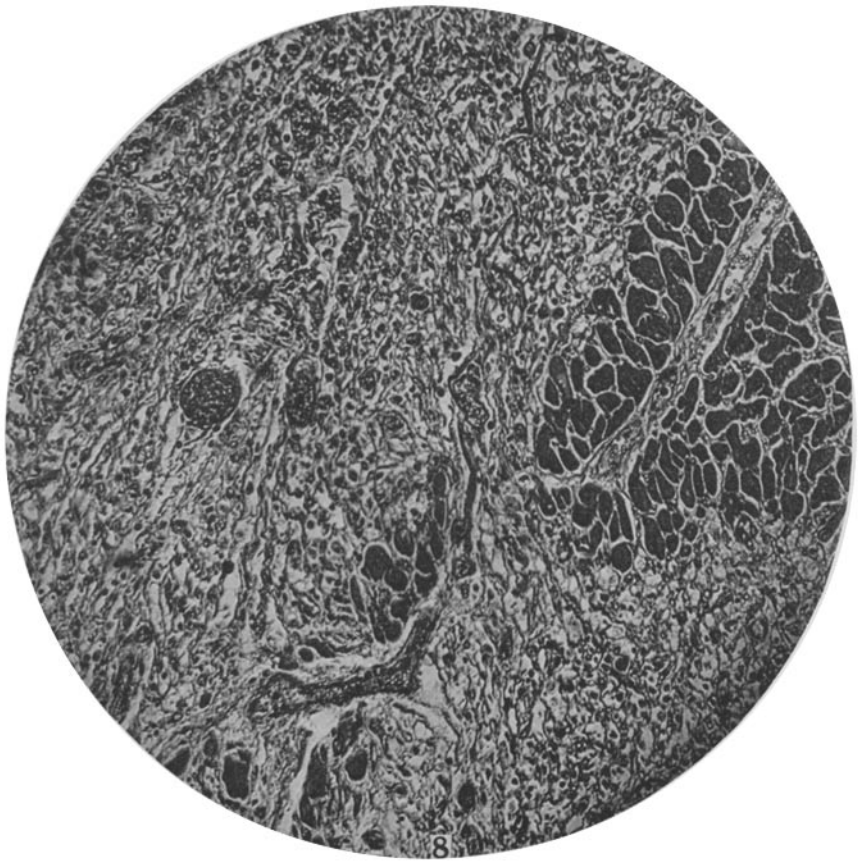

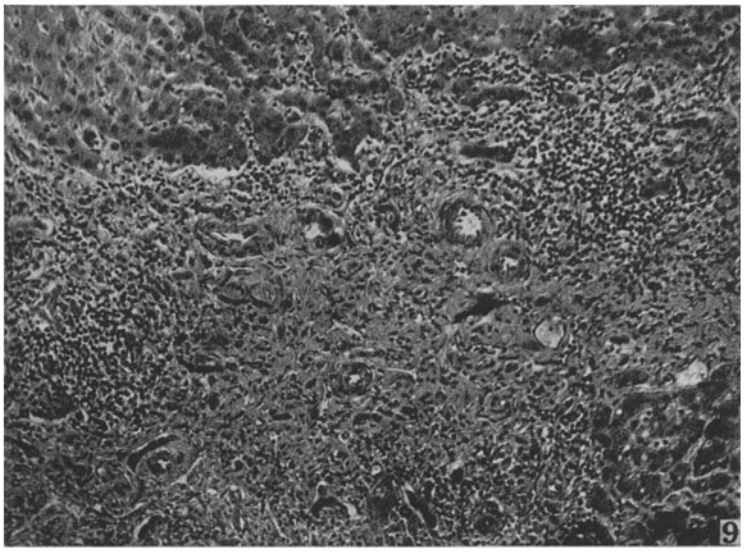

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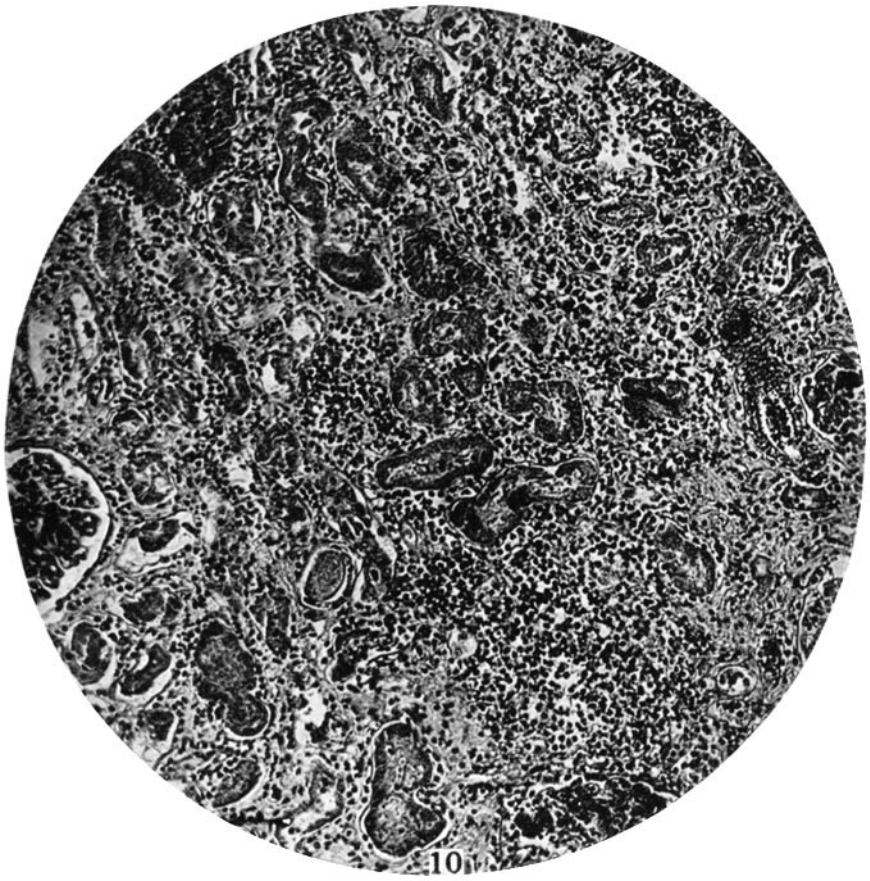

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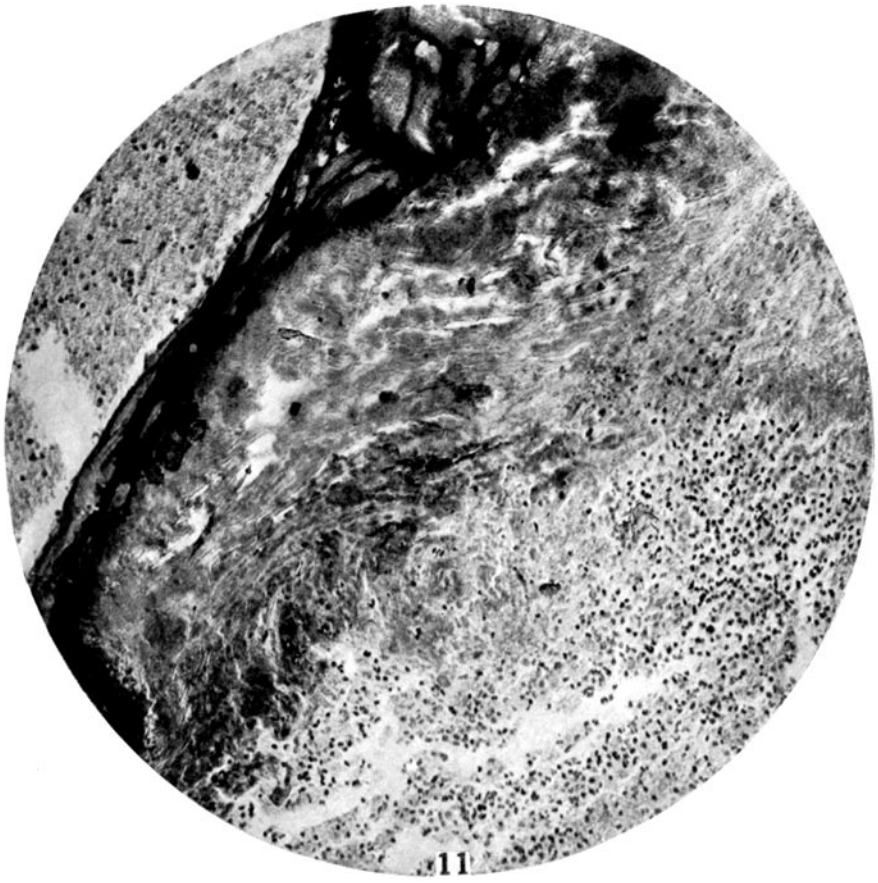

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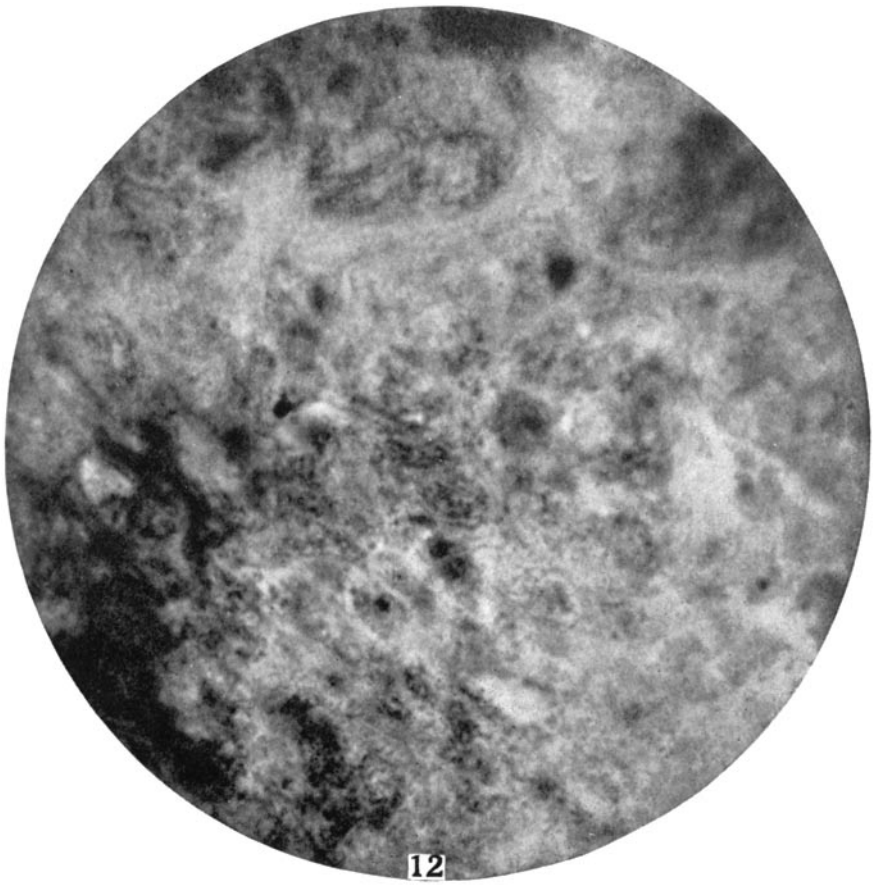

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