RAT BITE FEVER*

REPORT OF A CASE

AARON ARKIN, A.M., M.D., PH.D.
MORGANTOWN, W. VA.

DEFINITION

Rat bite fever (Sodoku of the Japanese; Rattenbisskrankheit; toxi-infection par morsure de rat; morbo da morso di topo, etc.) is an acute infectious disease caused by *Spirochaeta morsus muris,* following the bite of the rat (rarely cat, weasel, ferret or other animal) and characterized, after an incubation period, by recurring paroxysms of fever, a blue red exanthem, marked nervous symptoms, emaciation and weakness.

HISTORICAL

The disease is best known in Japan where it has long been endemic. For a review of the history of this extremely interesting and rare disease the reader is referred to the excellent report of the disease in Japan by Miyake,[1] who, in 1900, found no cases recorded in the European literature. In the older Japanese literature appear many references to a disease incident on the bite of the rat, but not fully described. The first good description in modern Japanese publications appeared in 1890, in Katsura's system of surgery.

Not only was the disease recognized early as being related to the bite of the rat in Japan, but it appeared also in the settlement days in our own country. Several reports of an unusual febrile disease, accompanied by severe nervous symptoms, and following the bite of the rat are found in our early medical journals. Of these, perhaps, the first is that of Dr. Whitman Wilcox[2] published in 1840. Reporting an attack following the bite of a rat he states: "Very little notice was taken of the wound until 12 or 13 days afterwards, when it commenced to be painful and tumefied. I was called in on the evening of the 17th, and found him with pain in the back and head, heat of skin, thirst, tongue with a thin white coat, bowels costive, hand painful and swollen, pulse nearly natural, etc." He then describes severe mental symptoms, gangrene of the wound, with sloughing of the skin. He also mentions a relapse occurring three or four days after subsidence of the first

* From the Department of Pathology and Bacteriology of West Virginia University School of Medicine.

1. Miyake, H.: Ueber die Rattenbisskrankheit, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **5**:231, 1899.

2. Wilcox, W.: Violent Symptoms from the Bite of a Rat, Am. J. M. Sc. **26**:245, 1840.

attack and lasting five to six days. This description corresponds closely with our present conception of rat bite fever. The characteristic exanthem and the lymphangitis and adenitis were not mentioned, however; nor was the relapsing type of fever carefully described.

In a study of the French literature, Roger[3] has found an excellent report of the disease made by Millot-Carpentier[4] in 1884, which leaves little doubt that his report of the disease was the first in Europe, and preceded the Japanese study of Miyake. In 1909, Horder[5] reported three cases from England. Crohn[6] in this country, reviewing the literature in 1915, found a total of fifty-two cases, and added one case which he reported. Blake,[7] in 1916, collecting the cases reported at that time, found a total of eighty-one on record in the entire literature.

I have found forty-eight cases reported since 1916 to July, 1919. These reports are given in the list of references. This makes the cases to date, including the eighty-one collected by Blake to 1916, number about 130.

INCIDENCE OF DISEASE

Cases have now been reported from Japan, France, England, the United States, India, Italy, Morocco, Scotland, China, Spain, Germany, Brazil, Australia and the Philippines. It is interestitng to note that medical officers of the army have reported a number of cases among soldiers in the trenches in France and elsewhere. The similarity of the fever to trench fever, and the presence of obscure fevers, makes it necessary to keep this disease in mind in the trenches. A failure to obtain the history of a rat bite, or to recognize the cardinal symptoms of rat bite fever, might more easily occur among soldiers in active warfare.

The greater prevalence of the disease in Japan is probably due to the fact that more people live in wooden houses, where rats are numerous. Whether the percentage of infected rats is higher in Japan than in other countries cannot be known until a study of the prevalence of the spirochete in rats in different countries is made. According to Japanese investigators, the organism is found in from 3 to 12 per cent.

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3. Roger, H.: Erytheme toxi-infectieux et septicemie legere par morsure de rat des tranchees; un cas de sodoku fruste, Marseille méd. **53**:321, 1916. Le cas français de sodoku; toxi-infection par morsure de rat, Presse méd. **25**: 201, 1917. De l'anciennete, en France, de la toxi-infection par morsure de rat (sodoku des Japonais), Rev. gen de clin. et de therap., Par.**31**:323, 1917.

4. Millot-Carpentier: Considerations medico-physiologiques sur un cas de morsure de rat suivie d'intoxication ayant determine des accidents nerveux simulant l'hydrophobie et l'apparition d'un purpura a forme intermittente, L'Union méd., Par. **38**:1069, 1884.

5. Horder, T. J.: Rat Bite Fever, Quart. J. Med. **3**:121, 1909.

6. Crohn, B. B.: Rat Bite Fever, Arch. Int. Med. **15**:1014, 1915; also Ref. Handb. M. Sc., New York **7**:483, 1917.

7. Blake, F. J.: The Etiology of Rat Bite Fever, J. Exper. Med. **23**:39, 1916.

of rats in that country. It is possible that the disease has been carried from Japan to other countries by infected rats. A study of infection in rats in different countries may help to determine this.

PREDISPOSING CAUSES

Age and sex seem to play no part in the occurrence of the disease. It has been found at various ages and in either sex. Occupation is important only in so far as it renders the person more liable to be bitten by rats. Hence more cases have been found among farmers, seamen, and soldiers in the trenches. Previous illnesses have no relationship to infection. Not all persons bitten by rats develop rat bite fever. There are a number of determining factors, such as (1) infection of the rat; (2) location of the wound—a wound on the exposed parts of the body is more likely to become infected than one through clothing, just as in rabies; (3) depth of the wound—in some cases a scratch has sufficed, in others free bleeding may cleanse the wound of infection; (4) mixed infection, which may inhibit growth of the spirochete or aid it. Cases have been reported of several persons bitten by the same rat, one developing the disease, another showing no symptoms (Miyake[1]).

THE CAUSE OF RAT BITE FEVER

Since the recognition of rat bite fever as a distinct disease, several reports of the discovery of a micro-organism associated with the malady have been published. The following may be mentioned: (1) Streptothrix, Schottmüller,[8] Blake, Tunnicliff,[9] Litterer,[10] Tileston.[11] (2) Sporozoon, Ogata.[12] (3) Telosporidia, Shikami. (4) Diplococcus, Middleton; Douglas, Colebrook and Fleming.[13] (5) Spirochaeta morsus muris, Futaki and associates[14] Ishiwara and associates,[15] Ido and

8. Schottmüller, H.: Zur Aetiologie und Klinik der Bisskrankheit, Dermat. Wchnschr. **58**:77, 1914.

9. Tunnicliff, R.: Streptothrix in Bronchopneumonia of Rats Similar to That in Rat Bite Fever. Preliminary Report, J. A. M. A. **66**:1606 (March 25) 1916; J. Infect. Dis. **19**:767, 1916. Tunnicliff, R. ,and Mayer, K. M.: A Case of Rat Bite Fever, J. Infect. Dis. **23**:555, 1918.

10. Litterer, W.: New Species of Streptothrix Isolated from a Case of Rat Bite Fever, J. Tennessee M. A. **10**:310, 1917.

11. Tileston, W.: The Etiology and Treatment of Rat Bite Fever, J. A. M. A. **66**:995 (March 25) 1916.

12. Ogata, M.: Die Aetiologie der Rattenbisskrankheit, Deutsch. med. Wchnschr. **34**:1099, 1908; Mitt. a. d. med. Fakult. d. k. Univ. z. Tokyo **8**:287, 1909; **9**:343, 1911; **11**:179, 1913.

13. Douglas, S. R., Colebrook, L., and Fleming, A.: A Case of Rat Bite Fever, Lancet **1**:253, 1918.

14. Futaki, K., Takaki, I., Taniguchi, T., and Osumi, S.: The Cause of Rat Bite Fever, J. Exper. M. **23**:249, 1916. Spirocheta morsus muris, n. sp., the Cause of Rat Bite Fever, J. Exper. M. **25**:33, 1917.

15. Ishiwara, K., Ohtawara, T., and Tamura, K.: Experimental Rat Bite Fever. First Report, J. Exper. M. **25**:45, 1917.

associates,[16] Kitagawa and Mukoyama,[17] Kaneko and Okuda,[18] Kusama and associates,[19] etc.

That the bite of an animal, especially the rat, may cause infection in man with different micro-organisms is obvious to anyone who makes a careful survey of the literature of diseases produced by animal bites (rat, cat, ferret, weasel, dog, mouse, etc.). This is not at all surprising in view of the demonstration in rats of many parasites (streptothrix in bronchopneumonia of rats by Tunnicliff; *Spirochaeta icterohemorrhagiae* in rats by Ido in Japan; Noguchi,[20] Jobling and Eggstein in America, and a number of investigators in Europe; *Spirochaeta morsus muris,* Futaki and associates, Kusama and associates, Coles;[21] *Spirillum minor* Carter, *Spirochaeta laverani* Breinl and Kinghorn, *Spirochaeta muris* Wenyon, which three may be similar to *Spirochaeta morsus muris* Futaki; spirochetes of Borrel, Calkins, Mezinescu, etc. Still others may be present in the saliva of the rat, such as pathogenic streptococci, virus of rabies, etc.). Mixed infections with more than one organism might, therefore, occur.

From a study of the disease I am of the opinion that rat bite fever is caused by a specific micro-organism first observed by Futaki and his associates, *Spirochaeta morsus muris,* for the following reasons: (1) The disease is a definite clinical entity, as will be described later. (2) *Spirochaeta morsus muris* has been found in the blood and tissues of persons suffering from the disease, in the wild rat and field vole, all three strains belonging to the same species. (3) The disease has been produced in animals by the bite of inoculated rats and pure cultures, and the spirochete found. (4) Specific immune bodies, spirocheticidal and spirochetolytic) are present in the blood of patients. (5) Arsphenamin has a specific therapeutic action in the disease.

There are several difficulties in the way of demonstrating the specific organism in rat bite fever, and it is to aid in overcoming these

16. Ido, Y., Hoki, R., Ito, H., and Wani, H.: The Rat as a Carrier of Spirochaetosis Icterohemorrhagiae, the Causative Agent of Weil's Disease (Spirochaetosis Icterohemorrhagica), J. Exper. M. **26**:341, 1917.

17. Kitagawa, J., and Mukoyama, T.: The Etiologic Agent of Rat Bite Disease. Preliminary Report, Arch. Int. Med. **20**:317 (Sept.) 1917. Kitagawa, J.: Clinical Experience with Cat Bite Disease, Saikingaku Zasshi, No. 260, p. 422, 1917; abstr. in China M. J. **33**:55, 1918.

18. Kaneko, R., and Okuda, K.: A Contribution to the Etiology and Pathology of Rat Bite Fever, J. Exper. M. **26**:363, 1917.

19. Kusama, S., Kobayashi, R., and Kasai, K.: The Rat Bite Fever Spirochete, with Comparative Study of Human, Wild Rat and Field Vole Strains, J. Infect. Dis. **24**:366, 1919.

20. Noguchi, H.: Spirochaeta Icterohemorrhagiae in American Wild Rats, and Its Relation to the Japanese and European Strains, J. Exper. M. **25**: 755, 1917.

21. Coles, A. C.: Rat Bite Fever, Lancet **1**:350, 1918.

that I wish to summarize our present knowledge of the disease. First, the rat that produces the bite is not obtained for examination. I have not been able to find a single report of such an examinatiton. Not infrequently the rat is caught and killed, but there is a failure by the physician or patient, or both, to recognize its relation to the disease. Second, the spirochete is present in the blood, skin lesions and lymph glands in greatest number at the height of the first few febrile attacks, when smears and animal inoculations should be made. In some cases it may be absent from the blood, or there may be so few as to be overlooked. This will be discussed under diagnosis.

MODE OF INFECTION

The spirochete is inoculated in the tissues with the bite. It is present in the mouth of the rat probably from abrasions of the mucous membrane of the gums, as spirochetes have not been found in the mouths of experimentally inoculated rats, even when they have been able to produce the disease in other animals by a bite and when spirochetes have been present in the blood. Abrasions of the gums could easily occur. The germ has been found in the submucosa of the gums and also in the salivary glands of inoculated rats. It is present in the blood of these rats in considerable number about the eighth day after inoculation, also in the kidney and suprarenals.

Rats may also become infected by preying on infected rats and then transmit the disease by biting man or lower animals.

SPIROCHAETA MORSUS MURIS

This organism was first discovered by Futaki, Takaki, Taniguchi and Osumi in 1915. These investigators found a spirochete in the skin lesions, local lymph glands and blood of two of four cases. In the study of six other cases the following year they found the spirochete in five; in two of these it was found in the blood. Two types of spirochete were found, one, a short form, in the blood, the other a long form, in the tissues. Ishiwara and Ohtawara found a similar spirochete in animals infected by the bite of rats, confirming the findings of Ogata on infection by rat bite. In 1916, Futaki found that the two types are probably the same spirochete, intermediate forms also occurring. Kaneko and Okuda came to the same conclusion from the study of the pathologic anatomy of human cases in which they found the spirochete. Kitagawa and Mukoyama were able to infect rats, guinea-pigs and monkeys with an axillary lymph gland from a patient and found the same spirochete. Row[22] has observed a spirochete in rat

22. Row, R.: On a New Species of Spirochete Isolated from a Case of Rat Bite Fever in Bombay, Indian J. M. Res. **5**:386, 1917.

bite fever in Bombay. Sano,[23] and Costa and Troisier[24] have also found a spirochete in this disease. The organism has not yet been seen in cases in this country.

The spirochete varies in length from 2 to 6 microns, with its flagella it is from 6 to 10 microns long. The short form is usually found in the blood of patients and in experimental animals, and is probably the young form. The long form is found chiefly in human tissues, and in culture mediums. Intermediate forms and degenerating forms also appear. In cultures the organism is from 1.5 to 19 microns in length, thicker than the *Spirochaeta pallida,* and possesses one curve per micron. The curves are regular and sharp. There are usually from one and one-half to six curves, occasionally as many as nineteen. It stains readily with Giemsa's stain, also with Loeffler's methylene blue and gentian violet. It is gram-negative. Burri's india ink method is very satisfactory. Levaditi's method is best for staining the organism in tissues.

The organism is motile, having a rapid movement. Cultivated ones are less active. Infection occurs in the mouse, wild rat, guinea-pig and monkey. The guinea-pig and monkey develop the characteristic fever and other symptoms, whereas the other animals present the spirochete in great number in the peripheral blood without definite symptoms. In the mouse spirochetes appear in the blood in from five to fourteen days after inoculation, and the animal usually survives. Mouse inoculation is a valuable aid in isolating the spirochete. In the guinea-pig the infection usually results fatally with swelling and congestion of the bitten part, enlargement of lymph nodes, fever, loss of weight and alopecia. Acute inflammatory changes are found in the kidney, and hyperemia and hemorrhages occur in the suprarenal where spirochetes are usually most numerous. Hyperemia of the lungs and catarrhal inflammation of the gastric mucosa also occur. In the monkey the symptoms are very similar to those in man and the infection is often fatal. However, a monkey recovered from the infection shows no symptoms on reinoculation.

In a very recent study by Kusama, Kobayashi and Kasai, which shows the human, wild rat and field vole strains of spirochete to be the same, the authors find that on inoculation of a rat or guinea-pig the spirochete for the first two weeks is found chiefly in the blood. Then it appears in the connective tissues of various parts of the body

23. Sano, T.: Rat Bite Disease. Case Report, Iji Shimbun, No. 981, p. 1153, 1917; abstr. China M. J. **32**:469, 1918.

24. Costa, S., and Troisier, J.: Un cas de sodoku (fievre par morsure de rat), Bull. soc. med. de hôp de Par. **40**:1931, 1916. Un nouveau cas de sodoku. Spirochetes a l'examen direct du sang, Bull. et mem. Soc. med. de hôp. de Par. **42**:616, 1918.

(submucosa of eyelids, lips, nose and tongue; capsule of lymph glands and salivary glands; adventitia of large blood vessels; parenchymatous organs). None are present in the normal saliva, intestinal contents or bile. They may appear in the urine.

That a streptothrix may be found in cases of rat bite fever was first demonstrated by Schottmüller, and later observed also by Blake, Tileston, Tunnicliff and Litterer. The fact that in some of these cases arsphenamin was used with prompt cure makes it very likely that the streptothrix was not the specific cause, but only a secondary invader. Recognizing the difficulties in finding the spirochete in blood smears, and also in obtaining positive animal inoculations when the blood and tissues are examined late in the disease or between paroxysms of fever, sometimes even during the attacks, one is not surprised at failure to find the spirochete in most cases of rat bite fever. Also the ulcerative endocarditis, and degenerative and infiltrative changes found in the organs in Blake's fatal cases are not demonstrable in experimental rat bite fever in animals, and have not been found in the other necropsies done on rat bite fever victims. I think that the specific action of arsphenamin, as found by Tileston, rules out the streptothrix as the cause of the disease in his cases.

SYMPTOMS

A. The Bite.—The bite is usually a small punctiform area which heals readily in a few days, the time depending on its size. It usually does not suppurate. In some cases, however, necrosis of the skin and subcutaneous tissue with sloughing, followed by slight pigmentation, occurs. Pus formation is due to secondary infection.

B. Incubation Period.—The average length of the incubation period is twelve days; it varies from five to thirty days. A few cases have been reported with symptoms manifested in less than five days, and some months after the bite. The latter cases were not controlled carefully, and probably were incorrect. In severe and prolonged cases, which seem to be more common after bites on the face or head, the incubation period is usually shorter than the average.

C. Prodromata.—As a rule, within two weeks after the bite the patient complains of pain and heat in the bitten area, which is swollen, of a bluish red color and somewhat indurated. The pain may become severe, being sharp or pulsating.

About the area of acute hyperemia may be a slight edema of the skin, giving a ring-like appearance about the central bluish red induration. Sometimes the bite resembles closely an extra-genital primary lesion of syphilis. Reddish streaks appear in the direction of the local lymph glands, which soon become enlarged, tender, hard, but discrete.

The patient begins to complain of headache, pains in the muscles of the back and extremities and malaise. Soon the most constant symptom, the fever, appears.

D. Fever.—With the prodromal symptoms, inflammation of the bitten area, and lymphangitis and adenitis there usually occurs a sudden rise of temperature, from 102 to 105 F. It is ushered in with severe chills, great pains in the limbs, and headache. The pulse is rapid, full and soft. The patient often complains of great thirst, nausea and vomiting and a feeling of anxiety. The skin is pale, and the extremities are cold. In severe cases hallucinations, and even delirium or coma may accompany a fatal outcome during the first paroxysm of fever. The paroxysm usually lasts from three to six days, when it falls by crisis with profuse perspiration and great improvement in the condition of the patient.

After an apyrexia of from two to six days another attack occurs. In fatal cases the attacks may become more severe until death results. As a rule, subsequent attacks become less severe and less frequent until in a few months they disappear. The average duration of the disease is two months. However, Kitagawa and Mukoyama have seen a case with recurrences fifteen years after the first attacks, and Kusunoki states that one or two relapses per year occur for ten years after recovery from rat bite fever. The patients treated with arsphenamin seem to be entirely free from recurrences.

The fever not infrequently shows irregularity. At first it may be continuous or remittent. Later the attacks are of shorter duration and do not reach as high. On account of the variability of the fever, the cases may be classified into the following types:

1. Febrile form with exanthem:
   (a) Intermittent fever.
   (b) Continuous fever.
2. Febrile form with nervous symptoms:
   (a) Acute.
   (b) Subacute.
3. Afebrile form with marked nervous symptoms.
4. Abortive form.

The paroxysms may vary from one severe fatal attack, or one mild prolonged attack with continuous fever for as long as twenty days, to as many as thirty attacks. The average is about from five to ten attacks. They occur at least once a week at first. As already mentioned, they last from three to six days, to a day or less later in the course of the disease. The interval also varies somewhat, averaging four days.

E. Nervous Symptoms.—Involvement of the nervous system occurs in most cases of rat bite fever. There is usually severe headache, dizziness, ringing in the ears, blurring of vision, especially during the paroxysmal attacks of fever. In the acute cases delirium or coma may develop. Hemicrania, neuralgic pains and especially pains in the muscles of the extremities, mostly in the lower, occur. Beginning with the first or second attack of fever the pain may be generalized, and later remain localized in the lower extremities. In some cases persistent neuralgic pains have been recorded for months or years.

Motor disturbances may develop in the form of paresis of the lower extremities, rarely the upper, and they may become very marked. This usually disappears with recovery from the fever. The tendon reflexes may be exaggerated, less often abolished. Progressive atrophy of the extremities has been reported.

Sensory changes occur in most severe cases, from paresthesias to complete anesthesia in some areas, mostly the extremities. These usually last through the febrile period. Hyperesthetic or hypoesthetic zones may be found in different parts of the body.

The febrile type, with acute nervous symptoms, is suggestive of the symptoms of rabies. The patient complains of severe pain in the bite, dizziness, great anxiety, headache. Dyspnea, rapid and small pulse, sensory and motor disturbances of the extremities, collapse, delirium or coma and even death may follow.

There is also a subacute form. After the incubation period, with or without any exanthem, the patient complains of severe, persistent, muscular pains; there may be paralysis of the lower extremities, with loss of patellar reflexes. The motor and sensory disturbances may be of long duration.

In the abortive type the patient may have only a few mild attacks of fever; the exanthem may be confined to the region of the bite, or it may be entirely absent. There are vague general symptoms, malaise, headache, slight weakness. Recovery is rapid, usually in a week or two.

F. Skin Manifestations.—The exanthem is rarely absent, as in the mild or abortive cases. It usually makes its appearance with the first attack of fever and lasts several days, when it may disappear, leaving a slight pigmentation or desquamation. With the recurrence of the fever the exanthem usually reappears, or new eruptions become visible. Sometimes the rash is not visible until the second, third or later attack of fever.

It may affect the skin about the bite, or an extremitiy, or more frequently it appears on the face, neck, back, chest, abdomen and extremities and less often in the palms of the hands and on the soles of the feet. A rash on the mucosa of the mouth has also been

described. The rash is not symmetrical. It begins as a macular eruption, red to blue red in color, varying in size from 5 mm. to 10 cm., usually round or oval and well defined. Later the spots become elevated; the center may be higher than the periphery and paler in color. The color does not entirely disappear on pressure or only on deep pressure, which causes some pain. The areas are slightly indurated.

In cases where the rash is localized near the bite or on the extremity, large, bluish red, elevated, indurated areas appear, from a dime to the palm of the hand in size. They often are distributed along the course of the lymphatics and over the enlarged lymph glands. They are slightly painful on pressure.

Miyake has described an acute urticaria, which he states is very characteristic of the disease toward the end of its course. It is spread over the entire body, often accompanied by fever. It may be overlooked unless the patient is kept under observation until recovery is complete.

G. Lymphatics.—That the spirochete infection spreads at first by the lymphatics is indicated by the frequent occurrence of lymphangitis. Reddish streaks are seen extending from the bite to the lymph nodes of the area. These appear just before the first attack of fever and usually disappear entirely in a few days. Then the local lymph glands become enlarged, sometimes reaching the size of a hen's egg, though usually smaller than this. After the first three or four attacks of fever the glands return almost to normal; in some cases they remain large throughout the disease, enlarging and becoming painful with each attack of fever.

The glands do not suppurate. They are elastic, rather soft, and later become harder. There is pain on pressure, and often considerable tenderness. The enlargement is usually confined to the regional glands, though the others may also become affected.

H. Gastro-Intestinal Tract.—The gastro-intestinal symptoms are not severe. A white coated tongue, nausea and vomiting are not uncommon. Constipation is more often present than diarrhea. In a few cases severe dysphagia, almost resembling that of rabies, has been reported. The appetite is usually poor during the acute attacks, but may return to normal between the paroxysms.

The liver and spleen are not, as a rule, enlarged.

I. Genito-Urinary Tract.—Evidence of nephritis is found in about 10 per cent. of the cases. It may vary from an acute fatal parenchymatous nephritis to a mild attack. In the severe form there is a reduction in the urinary excretion, albumen, casts and some red cells are present in the urine. In other cases there is only a slight amount of albumen with few casts. That the spirochete has a tendency to attack

the kidney is also shown by its presence there in large number in experimental animals after inoculation.

J. Circulation.—The pulse usually varies with the height of the fever. It is rapid and small. There may be evidence of myocardial weakness, probably due to the toxemia as well as the secondary anemia. In severe cases there may be palpitation of the heart, and a hemic murmur is often heard at the apex.

K. Respiratory Tract.—The respiratory system is little affected. Slight bronchitis may develop. In prolonged and fatal cases terminal pneumonia may occur. The dyspnea in severe cases develops with the high fever, and may be toxic in origin.

PATHOLOGY

Little is known of the pathologic anatomy of this interesting disease. Miura[25] examined one case seventeen hours postmortem, and found only an increase in the amount of cerebrospinal fluid and hyperemia of the pia mater. There were no specific changes in the internal organs. Histologic examinations were not made. Blake's case was a streptothrix septicemia, with localization of the streptothrix in the mitral valve, producing an acute endocarditis followed by infarct formation in kidney and spleen. Subacute lesions of the parenchymatous organs also were present. These degenerative and infiltrative changes have not been observed in experimental rat bite fever, nor in other postmortems in human cases, hence we are forced to conclude that they do not represent the picture of true uncomplicated rat bite fever.

In 1917 Kaneko and Okuda reported the findings in two cases. There were parenchymatous changes in the organs. In the kidney occurred hyperemia, swelling and degeneration of tubular epithelium. They report the presence of spirochetes in the kidney, in the cortex of the suprarenal and in the interstitial cells of testis. The liver presented fatty degeneration, necrosis chiefly in the centers of the lobules, hyperemia and hemorrhage. The local lymph nodes were hyperemic, with an inflammatory cellular hyperplasia, hemorrhages and erythrophagocytosis. Other lymph glands were swollen and hyperemic. Catarrhal changes in the mucosa of the stomach and urinary bladder, congestion of the lungs, and hyperemia and edema of the meninges occurred. Slight degeneration of muscle and nerve cells was found. At the site of the bite cellular infiltration, edema and degeneration (acute exudative inflammation) appear. There is frequently a lymphangitis extending from the bitten area to the lymph glands, shown by the presence of reddish streaks along the course of the lymph channels. This is followed by the lymphadenitis already mentioned.

25. Miura and Toriyama: Tokyo med. Ztschr. **11**: No. 23, 1897.

In experimental guinea-pigs Ishiwara and others found swelling of the bitten area and lymph glands; acute inflammatory changes in the kidneys, hyperemia and hemorrhages of the suprarenals, hyperemia of the lungs and catarrh of the mucosa of the stomach. Ido[26] has found similar changes in guinea-pigs infected by the bite of rats. Futaki and his associates record swelling of the spleen, hyperemia, congestion and swelling of the liver, hemorrhages in kidneys and lungs of inoculated animals.

The blood changes have been reported by several writers. A leukocytosis occurs in most cases of rat bite fever, most marked during the attacks of fever. It usually reaches from 13,000 to 20,000 cells, and varies with the different attacks. In most cases the count returns almost to normal between paroxysms. The increase is often in the mononuclear cells, which may reach from 35 to 40 per cent. of the white count. However, others have reported a polymorphonuclear increase. Eosinophils have been found by some to reach from 5 to 15 per cent. In the case reported by me we found a leukocyte count of 16,000 one month after the bite of the rat, and during an attack of fever. The differential count showed 80 per cent. of polymorphonuclears, 4 per cent. of eosinophils; the rest were mononuclears. During the afebrile condition the white blood count dropped to 9,600 and rose again to 15,000 at the next attack.

There is usually a reduction in the red blood count with the development of the weakness and cachexia. The red count in most cases examined has been about four million, and the hemoglobin, proportionately reduced, about 80 per cent. Later an advanced anemia may develop.

The Wassermann test is of interest because of the close relationship of *Spirocheta morsus muris* to the *Spirocheta pallida*. Kitagawa and Mukoyama report a negative Wassermann in their case, and quote Kunusaki, who found the Wassermann negative in four of five cases of rat bite fever. They also quote Inada as obtaining a negative Wassermann in Weil's disease, a spirochete infection. On the other hand, Costa and Troisier, and Mauriac[27] obtained positive Wassermann in their cases. The Wassermann was negative in the case reported by me. It seems, therefore, that the Wassermann test is not to be depended on as an aid in the diagnosis of this disease. In cases with a positive reaction, syphilis must, of course, be considered, as in the case reported by Brennemann[28] in a child with indications of congenital syphilis, whose mother gave a positive test.

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26. Ido, Y., Ito, H., Wani, H., and Okuda, K.: Circulating Immunity Principles in Rat Bite Fever, J. Exper. M. **26**:377, 1917.
27. Mauriac, P.: Rat Bite Disease, J. de méd. de Bordeaux **89**:93, 1918.
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DIAGNOSIS

The diagnosis of rat bite fever is based on:

1. History of bite by rat or other animal.
2. Cardinal symptoms, of which one or more are usually present.
   (a) Characteristic fever, usually relapsing.
   (b) Exanthem.
   (c) Muscular pains.
   (d) Nervous symptoms.
   (e) Lymphangitis and adenitis.
3. Demonstration of *Spirochaeta morsus muris.*
   (a) In blood during febrile attack.
   (b) In area of bite, skin lesions or enlarged lymph glands.
   (c) Animal inoculation, preferably mouse in which spirochetes can be demonstrated in blood in from five to fourteen days, or guinea-pig, etc.
4. Therapeutic test—administration of arsphenamin.

In the differential diagnosis we must consider (1) erysipelas; (2) pyogenic infection (phlegmon or pyemia or septicemia); (3) relapsing fever; (4) trench fever; (5) malaria; (6) syphilis; (7) erythema multiforme.

1. *Erysipelas.*—This disease can be differentiated by finding the streptococcus; absence of characteristic exanthem of rat bite fever; temperature curve; course of the disease.

2. *Pyogenic Infection.*—In rat bite fever blood culture is negative; absence of suppuration in the bite, unless secondary infection occurs; characteristic fever; incubation period; eruption; history of bite.

3. *Relapsing Fever.*—Finding of spirochete of Obermeyer; number of attacks rarely more than three; short incubation period.

4. *Trench Fever.*—Spread by body louse; fever, relapsing or irregular, or continuous; sudden onset like influenza; nystagmus on extreme lateral rotation of eyeballs; enlarged spleen, harder than that in typhoid; macular rash; shin pains; painful joints without swelling; no laboratory diagnosis at present. Caused by resistant filterable virus.

5. *Malaria.* — Blood examination (*Plasmodium malariae*); therapeutic test by use of quinin; enlarged spleen; endemic character of disease.

6. *Syphilis.*—History of infection; examination of lesion for *Spirocheta pallida;* Wassermann test; clinical manifestations.

7. *Erythema.*—Symmetrical arrangement of lesions; absence of history of external injury; recurrence of lesions; lesions of vivid color, often edematous; frequent association with rheumatism.

PROGNOSIS

The prognosis is usually favorable. The mortality has been about 10 per cent. The outcome depends on the severity of the disease. Cachexia, edema, nephritis, or severe anemia are bad signs. The patient is often incapacitated for a long time. The disease is more serious in very young or old people. A short incubation period followed by severe nervous manifestations usually indicates danger Death may occur during the first few attacks of fever from severe toxemia. As already stated, attacks of fever may occur for years after the bite. The average course of the disease is from two to three months. With the use of arsphenamin the prognosis is very favorable, the symptoms usually disappearing after one or two injections. No recurrences follow this treatment, as a rule.

TREATMENT

Prophylactic treatment consists of immediate cauterization of the bitten area with fuming nitric acid. The acid should be applied thoroughly in the bite, incision being done if necessary. Such treatment within an hour will usually prevent the disease and should be practiced in all animal bites. The ancient Japanese tried numerous odd cures, such as the use of poultices of herbs, filling the wound with gunpowder and then exploding it, applying raw meat and feeding it to a cat. Later reports have appeared in which quinin, iodid, salicylates and arsenic compounds by mouth were tried, but with no definite effect. In 1912, Hata[29] reported the use of arsphenamin in eight cases with complete recovery and disappearance of all symptoms in all but one case. Others have reported equally happy results. One or two injections usually suffice. The specific curative value of arsphenamin led Hata and others to suspect a spirochete as the cause of the disease. Mercury also seems to have a definite curative value (Borelli[30]). Arsphenamin has been found to have a curative value in experimentally inoculated animals. It should be given in all cases of rat bite fever.

REPORT OF CASE

CASE.—An American boy, 9 years of age, was first seen by Dr. P. A. Gibbons, April 8, 1919. The history was as follows: March 25 the patient was bitten on the right index finger by a large gray rat while playing near his father's printing office. He reached his hand down into a barrel when the rat caught his finger, and according to the patient did not release its hold until it was killed by a person attracted by the screams of the boy. When the boy reached home the finger was painted with tincture of iodin. After

29. Hata, S.: Salvarsantherapie der Rattenbisskrankheit in Japan, München. med. Wchnschr. **59**:854, 1912.

30. Borelli, E.: Mercurial Treatment of Rat Bite Disease, Policlinico **25**: 25, 1918.

the bite he made no complaint and the wound seemed to heal nicely. On the fourteenth day he began to complain of pain in the finger and a burning sensation. The finger had become reddened and swollen. A physician was then called. He found the finger reddened, swollen, and at the site of the bite a slightly elevated blue red papule surrounded by a lighter edematous zone. The finger was painful on pressure. Examination revealed enlargement of the lymph glands in the right axilla. The supratrochlear glands were slightly enlarged. The physician made an incision but no pus was found. The area was swabbed with tincture of iodin. The boy returned to school the following day. Three days later (seventeen days after the bite) he complained of not feeling well, and the physician was again called and again incised the finger, finding very little pus. The symptoms were drowsiness, weakness, headache, diarrhea and vomiting. The gastric symptoms lasted for four days. April 11 the temperature was 102 F. The boy complained of chills and went to bed.

The patient was seen by me April 28. On this day his temperature was 99 F. He had suffered three attacks of fever, accompanied by severe headache, nausea and vomiting, pains in the back and extremities. These occurred at intervals of six days and lasted two to three days. During the third attack he became dizzy and fell. He was then sent to bed.

Physical Examination.—April 28. Patient was pale, rather thin and had an anxious look. Temperature, 99 F.; pulse, 90. The right index finger was bluish red, the color extending over the terminal phalanx. It was swollen and somewhat indurated. The incision had completely healed. On the right forearm were several bluish red, slightly elevated, well defined areas or nodules varying in size from a quarter to one inch in diameter. They were present on the flexor and extensor surface. Between them could be seen very faint reddish streaks. The supratrochlear glands were enlarged, measuring almost an inch in the greatest diameter. They were somewhat elastic and painful when compressed. The right axillary glands were also large, about the size of a walnut and not very hard. On questioning the patient and mother I learned that the skin nodules had first been seen about three weeks after the bite. A rash on the chest and abdomen was also reported to have been present. The rest of the body presented no eruption at this time. There was slight edema of the lower eyelids.

Heart and lungs: Negative.

Abdomen: Somewhat distended; suggesting slight ascites.

Liver: The lower edge was palpable along the free margin of the ribs, and flatness extended to the fifth interspace.

Spleen: Not enlarged.

Lymph glands: Right axillary glands enlarged, also supratrochlears. Other glands normal.

Head and neck: Negative.

Extremities: Negative, except for right arm already described.

Temperature: 99 F.; pulse,·90; respiration, normal.

Urine: Amount, normal; acid; clear; specific gravity, 1.025. Albumin: trace. Casts: a number of hyaline and granular; no red blood cells.

Blood Examination: April 28, 1919: Erythrocytes, 4,100,000; leukocytes, 16,000. Differential count: polymorphonuclears, 80 per cent.; mononuclears, 16 per cent.; eosinophils, 4 per cent.; hemoglobin (Sahli), 75 per cent.

Blood smears: Smears of blood obtained by puncture of the lobe of the ear were stained with Giemsa stain, Wright's stain, Jenner's stain and india ink April 29 when the temperature had dropped to 99 F. All examinations were negative.

Blood cultures: April 29, 10 c.c. of blood were drawn from the arm, and 3 c.c. were placed in 200 c.c. each of plain bouillon and glucose bouillon, and

an equal amount in glucose agar (50 c.c.) for plating. The cultures were all negative aerobically. Unfortunately pressure of other work prevented animal inoculations at this time.

May 2: Temperature, 98.6 F. Erythrocytes, 4,600,000; leukocytes, 9,600; polymorphonuclears, 70 per cent.; mononuclears, 27 per cent.; eosinophils, 3 per cent. Blood smears stained with Giemsa and Jenner stain were negative.

Patient feels much better, but complains of weakness and loss of appetite. The skin nodules are much smaller and have almost disappeared. The right axillary glands are still enlarged. No rash is present on the body.

May 10: I was called to see the patient who had a severe chill and high fever on the evening of May 9. Temperature, 101 F.; pulse, 100. The patient complained of nausea and severe headache. The nodules on the right arm were somewhat larger than on May 2, and pressure on the right axillary glands caused pain.

Blood examination: Erythrocytes, 4,400,000; leukocytes, 15,000; polymorphonuclears, 75 per cent.; mononuclears, 23 per cent.; eosinophils, 2 per cent.

Blood smears stained with Giemsa and Jenner failed to show any spirochetes after prolonged search. I inoculated two guinea-pigs with blood obtained from the left arm vein, using 3 c.c. intraperitoneally. The animals remained well for four weeks and showed no signs of illness whatever.

June 25: The patient felt much better but tired quickly. He complained of gastric disturbance. The nodules on the right arm had entirely disappeared. The right axillary glands were only slightly enlarged. The edema about the eyes had disappeared. The mother stated that the patient had lost about 20 pounds during his illness. From May 9 to June 25 the patient had two attacks of fever, but much less severe than the earlier attack and lasting only a day or two. I advised the administration of neoarsphenamin intravenously. The patient had been treated symptomatically and was given Fowler's solution, from 3 to 6 drops, three times a day.

September 30: The patient felt well. The glandular enlargement had disappeared, and the patient had been free from attacks since July 28, when his temperature rose to 101 F.

Blood examination: erythrocytes, 4,800,000; leukocytes, 9,000; polymorphonuclears, 76 per cent.; mononuclears, 22 per cent.; eosinophils, 2 per cent.

SUMMARY OF CASE

A boy, aged 9 years, was bitten on the right index finger by a rat, which instead of escaping, had to be killed in order to release its hold. The wound was shortly afterward painted with tincture of iodin and healed. After a period of fourteen days, inflammation, edema and induration occurred, accompanied by lymphangitis and lymphadenitis, and the appearance of a blue red exanthem. There were also high fever and chills, and gastric disturbances. This attack was followed by three others at intervals of about six days, each characterized by chills, fever, nausea, headache and pains in the extremities. Reappearance of the exanthem with these attacks was noted. There was marked lymphadenitis of the trochlear and axillary glands. The spleen was not enlarged. Slight nephritis existed. Blood examination revealed a leukocytosis, which reappeared with subsequent febrile attacks and returned almost to normal between paroxysms. Spirochetes or other organisms were not found in the peripheral blood, but the patient was not seen until thirty-four days after the bite. Inoculation of two guinea-pigs with blood obtained forty-six days after the bite proved negative. Cultures or animal inoculations were not obtained from the skin nodule or the local lymph glands. Blood smears made from the ear failed to reveal any spirochetes on several examinations, the first being made thirty-four days after the bite (twenty days after first paroxysm). The subsequent history reveals recurring attacks of fever at longer intervals, and less severe. No attack has occurred in the last two months.

The case is typical of rat bite fever, and of special interest because it calls attention to the presence of rats infected with the virus of the disease in this community. A study of rats for the presence of *Spirocheta morsus muris* is now under way.[31]

519 Front Street.

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