

Tularemia: Experience in the Hamilton area

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Tularemia is a specific infectious disease of wide distribution. It is not as rare as the official reports suggest and its mortality without treatment is significant. Since 1931, according to the Dominion Bureau of Statistics,¹ 220 cases have been reported in Canada. There have been 11 deaths since 1941, a mortality of 6.4%² (Table I). In the United States 33,084 cases have been reported since 1927.³ The incidence of cases reported in that country has been decreasing in recent years, whereas in Canada there appears to have been an increase (Table II). This increase has been most striking in Ontario where, in the last 10 years, almost two-thirds of the Canadian cases have been reported (Table III). During this period none were reported from British Columbia or the Maritime provinces. Only one has ever been reported from Newfoundland, and the incidence in Prince Edward Island is unknown since tularemia is not a reportable disease in that province.

This paper describes the first three cases which have been reported in Wentworth County, Ontario.

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Case 1

Mr. V., a 32-year-old salesman, was admitted to St. Joseph's Hospital, Hamilton, on the evening of April 3, 1969. He had wakened early that morning with rigor, throbbing headache, weakness and anorexia. The rigor was followed by fever and sweating. Five days earlier he had skinned and mounted a muskrat which he had shot a few miles northwest of Hamilton. While being hunted the animal had acted somewhat stupidly and had not run for cover as quickly as expected, but the patient did not attach much importance to this unusual behaviour at the time. During the skinning operation he had cut his left thumb with the scalpel and this cut had not healed.

On admission he appeared ill. His temperature was 39.7° C. and his pulse rate was 84 per minute. On his left thumb there was a small, linear, punched-out ulcer with thickened, red edges. An epitrochlear lymph node was palpable and there were also many large, tender nodes in the left axilla. A presumptive diagnosis of tularemia was made and treatment was started with oral tetracycline, 2 g. daily, on April 4. His temperature remained elevated for two days and then returned to normal. He was discharged four days after admission, feeling well except for tender lymph nodes in his left axilla. Tetracycline was continued in the same dosage for a total of 10 days.

Laboratory tests showed a normal hematocrit and blood film. Leukocyte count was 6100 with a normal differential. The sedimentation rate was 20 mm. in one hour. Urinalysis was normal. Blood cultures were negative and the culture from

the lesion on the thumb, on glucose cystine blood agar, was negative for *Francisella (Pasteurella) tularensis*. Chest radiograph was normal. Agglutination tests for tularemia were negative on the first and fifth days after admission. Forty days after admission the titre was 1:400; 13 months later it was 1:100. Widal agglutination tests were negative.

Seven days after completion of tetracycline treatment his symptoms recurred, with fever and increased soreness in the left axilla. Oral tetracycline was again prescribed for 10 days, with prompt resolution of symptoms. The axillary lymphadenopathy persisted for several weeks, but since then the patient has remained in good health.

Case 2

Mrs. V., a 30-year-old housewife (wife of Case 1), developed symptoms similar to those of her husband, but less severe, five hours prior to the onset of her husband's

TABLE I
Reported cases and deaths from tularemia in Canada

Year	Cases	Mortality
1931-1939	48	No data
1940-1949	40	9
1950-1959	69	2
1960-1969	63	0
Total	220	11

TABLE II
Comparison of reported cases of tularemia in Canada and the U.S.A.

Year	Canada	U.S.A.
1927	No data	219
1931	8	675
1939	3	2291
1955	17	584
1965	1	264
1967	10	184
1968	12	186
1969	15	149

illness. She too was interested in taxidermy and while her husband was skinning the muskrat she and a friend had skinned a duck. She cut her left hand with one of the bony spicules from the duck before helping her husband skin the muskrat. A small ulcer appeared at the site of the injury. Her friend, who did not handle the muskrat, did not become ill.

She was not admitted to hospital but was given the same treatment as her husband—oral tetracycline, 2 g. daily for 10 days. She felt well after a few days and had no recurrence of her infection.

At the time of her illness, agglutination tests were negative for tularemia. These were not repeated until 13 months later, when the titre was 1:200. Widal agglutination tests were negative.

Case 3

Mr. H., a 38-year-old farmer, became ill in April 1969 after trapping and skinning about 500 muskrats. He developed fever and painful lymph nodes in his right axilla. There were a few cuts on his hands, but these were not bothering him. He was treated at home with penicillin for four days without any improvement and then with erythromycin for one week without any remission in his symptoms. He was then given tetracycline, 1 g. daily for one week, and apparently recovered. However, two months later the symptoms recurred. Agglutination tests for tularemia showed a titre of 1:400. He was treated with tetracycline orally, 4 g. on the first day and then 2 g. daily for two weeks. His symptoms cleared and have not recurred. A repeat agglutination test one year later gave a titre of 1:200.

Historical background

Tularemia was originally described in 1911 in ground squirrels in Tulare County in California. The organism was first isolated in man three years later, and because the infection resembled the plague, the organism was classified as a *Pasteurella*. However, since it proved to be different from the *Pasteurella* species, it has been renamed *Francisella tularensis*,⁴ in honour of Dr. Edward Francis, who

pioneered in the study of tularemia. This disease is found in Europe, Africa and Asia as well as in North America, but it is not known in South America or Australia. The natural occurrence of tularemia has not been reported from the British Isles.

An early reference to tularemia in Canada was made in an editorial in *The Canadian Medical Association Journal* in 1924.⁵ This alluded to an outbreak which occurred among research students at the Lister Institute in London, England. The admonition was expressed that "Tularemia must be reckoned with as a disease that may possibly be met with in the ordinary course of practice." In April 1929 another editorial in *The Canadian Medical Association Journal*⁶ stated "We, in Canada, have been fortunate in escaping for a time at least some of the ills that affect our neighbours to the South, but how much longer this happy state will continue is problematical. Already undulant fever, regarded as an exotic disease, has gained a foothold here, and tularemia bids fair to follow its malign example." A few months after this editorial was written the first case of tularemia was reported by McNabb.⁷ This was in a man from Timmins, Ontario, presumably infected while skinning and dressing a wild rabbit. Since then, numerous case reports have appeared in the Canadian literature.⁸⁻²⁴ The most extensive study was made in 1949 by Rand,²⁵ who reviewed 65 cases reported in Canada up to that time. The most recent report is by Gattereau, Gareau and Diallo²⁶ in which they describe in detail two cases of tularemia acquired from muskrats in the Province of Quebec in 1969.

Epidemiology

Tularemia is primarily a disease of wild animals spread by blood-sucking

insects. Man becomes secondarily infected by direct contact with the animal or by a bite from an infected arthropod, usually a tick. Less frequently, he is infected by inhaling the organism, drinking infected water or eating improperly cooked meat which has been contaminated by the organism. Most animals, both wild and domestic, and some birds and reptiles are susceptible to tularemia, but only a few are involved to any degree with its transmission of the disease to man. Dogs and cats have occasionally been incriminated. Many arthropods have been shown to be infected (ticks, flies, mosquitoes, fleas, lice, mites and bed-bugs), but only the tick appears to play a significant role in perpetuating the disease. The source of human infection varies considerably in different parts of the world and even within each country. In Europe the principal source of infection is rats. Most of the infections in the United States are acquired from rabbits and ticks. However, the largest human outbreak in the United States was linked with muskrats, and occurred in the State of Vermont in 1968 when 47 cases were reported.²⁷ Canadians become infected chiefly from wild rabbits and muskrats. Forty-four per cent of the 65 cases in Canada reviewed by Rand²⁵ in 1949 originated in wild rabbits. In Ontario, on the other hand, of the 39 cases reported in the last 10 years, 19 were acquired from muskrats and only two from rabbits.²⁸ In 10 cases the tick, deer fly, beaver, weasel, hamster and drinking water were possible sources of infection; in eight it was unknown.

In Ontario the muskrat has been suspected as the source of tularemia for humans since 1933, but proof was lacking until 1951. In that year Labzoffsky and Sprent²⁹ isolated the organism from beavers and muskrats in widely separated areas in Ontario. In 1955, Fyvie, Ross and Labzoffsky³⁰ studied the muskrat population on Walpole Island in Lake St. Clair, Ontario, where they found a high incidence of tularemia. In some parts of the island the infection had killed up to 80% of the muskrats. A high mortality was noted in 1960 among the muskrats in Castor Swamp, 35 miles southeast of Ottawa. This area was studied by Ditchfield, Meads and Julian,³¹ and tularemia was identified in the muskrats as well as in the rabbit ticks.

Although the epidemiology of this disease has not been completely

TABLE III
Reported cases of tularemia, Canada, by province, 1960-1969

	Canada total	Quebec	Ontario	Manitoba	Saskatchewan	Alberta
1960	8		6			2
1961	4		3			1
1962	3		3			
1963	3		2		1	
1964	4		3			1
1965	1		1			
1966	3		2			1
1967	10	6	1	1	2	
1968	12	3	8		1	
1969	15	2	10	3		
Totals	63	11	39	4	4	5

worked out, there seems little doubt that *F. tularensis* is well established in the rodent and tick population of Ontario. The rabbit tick, although it rarely attacks man, probably disseminates the disease among the wild animals and even among the ground-frequenting birds. Francis³² has shown that there is hereditary transmission through the egg of the tick. Streams become contaminated by the excreta of infected animals and by the carcasses of muskrats dying of tularemia. It has been demonstrated that the organism can survive in carcasses for several months and in water for three months.³³ Ice from water contaminated with the organism has been shown to contain viable bacteria.³⁴ The durability and infectivity of the organism probably explain why the infection seems to follow certain watersheds and why the muskrat and beaver become depleted in local areas from time to time. The farmer (Case 3) had no difficulty trapping about 500 muskrats in the spring of 1969, but in 1970 he did not bother to set any traps because so few muskrats were seen. Undoubtedly tularemia killed many of the muskrats in the Hamilton area. However, the animals multiply rapidly and their numbers will probably increase in the next year or two.

Prevalence

Studies on the Indian population in Ontario indicate that tularemia is much more common than is reported. Greenberg and Blake³⁵ reported that 8.4% of the Indian population in the Hamilton area had agglutination tests positive for tularemia. In the James Bay area the figure is 29%. Wood³⁶ reported an incidence of 11.7% among the Indian population of Manitoba and northwestern Ontario, but no clinical cases of tularemia were seen. In this part of Ontario, where trapping is not an integral part of life, exposure to infected animals is sporadic and depends on the availability of muskrats and the price of their pelts.

Unless the patient is carefully questioned, the illness may be mistaken for simple influenza. Even if diagnosed, the disease is often not reported to the public health authorities. Two deaths from tularemia were reported from Alberta in 1941, yet no cases were reported to their public health authorities in that year.³⁷ Undoubtedly there were many cases at

that time which were either not recognized or not reported. These studies suggest that human tularemia is not a rare disease.

Clinical features

Tularemia is a very infectious disease, as evidenced by Cases 1 and 2, in husband and wife who handled the same muskrat. Also, the two cases recently reported from Quebec²⁶ had both handled the same muskrat. As few as 10 organisms by the cutaneous or respiratory route have been shown to produce infection.³⁸ Over 100 cases in laboratory workers have been reported in the United States, presumably from inhaling the organisms. The organism, a pleomorphic bacterium, can penetrate the unbroken skin.³⁹ In spite of the infectiousness of the disease, there is no confirmed report of spread from man to man.

There is no problem in diagnosing the classical case of tularemia from the history of handling an animal, an ulcer on the finger, painful regional lymph nodes and an influenza-like illness. It may not be as readily thought of when there is an eye infection which can be caused by squeezing an infected tick or handling an infected animal and then rubbing the eye. Sometimes lymph nodes may be enlarged in the absence of any lesion at the site of inoculation. Infections which are acquired by ingestion or inhalation can easily be missed unless there is a high index of suspicion. Occasionally there may be subcutaneous nodules along the arm which may simulate sporotrichosis. The onset is invariably sudden, after an incubation period of usually three to five days. Of 531 cases reported by Foshay,⁴⁰ 75 had an incubation period of one day or less. The infections in the husband and wife (Cases 1 and 2) began within a few hours of each other, five days after contact with the same muskrat.

The early symptoms are similar to a severe attack of influenza and if untreated the initial fever often lasts two or three days. There may then be a remission of symptoms and fever, followed by a recurrence a few days later, the entire acute illness lasting two to three weeks. Pneumonia may occur regardless of the method of infection, and the prognosis is then much more serious. Convalescence is slow, sometimes lasting months or even a year. Regional lymph nodes suppurate in about 50% of patients. In others they may remain tender and

painful for several months, and occasionally they may suppurate as long as two years after the onset of the disease. Some strains are more virulent and may cause death in a few days. Francis⁴¹ reported a family of four who all developed tularemia and of whom three died within six to eight days. Simpson⁴² reported the death of a young Negro four days after the onset of illness. Pneumonia is the commonest cause of death, and the usual finding at autopsy is a necrotic or granulomatous lesion affecting principally lymph nodes, spleen, liver and lungs. Because it may run a prolonged course, the disease may be confused with tuberculosis or undulant fever. Tularemia may occasionally be misdiagnosed as cat scratch fever, typhoid fever or even infectious mononucleosis.

The mortality rate reported in Canada prior to the availability of antibiotic treatment was more than twice that for the United States, 22.9% in contrast to 9.5% (Table IV).

TABLE IV
Comparison of mortality from tularemia in Canada and the U.S.A.

Year	Canada (%)	U.S.A. (%)
1940-1949	22.9	9.5
1950-1959	3	1.2
1960-1968	0	0.9

This discrepancy is probably related to the method of reporting in Canada rather than to a more virulent infection. Of the 11 deaths reported in Canada, two were from Ontario, the last one in 1945. The most recent death reported in Canada occurred in Saskatchewan in 1956. Because of incomplete reporting it is difficult to estimate the true mortality rate in untreated patients, but Foshay⁴³ postulated this to be about 6%. In severely ill patients the mortality rate has been reported to be as high as 19% even with antimicrobial treatment.³³

The diagnosis is made by demonstrating agglutinins against *F. tularensis* and doing serial estimations to demonstrate at least a fourfold change in titre. This is a very specific test for tularemia, but because agglutinins may persist indefinitely in a patient who has had this disease, a positive test does not necessarily indicate an active infection. There may be some cross-agglutination with *Brucella* agglutinins, but this is usually of low titre. Early treatment may abort a high titre of agglutinins. The ag-

glutination reaction is usually positive by the second week and maximal in three or four weeks. However, occasionally a positive reaction may not appear until the fourth week, particularly if treatment were started early in the illness. Special media are required for culturing the organism, since it is difficult to grow. Any material, whether it is sputum or blood or scraping from an ulcer, should be sent to a laboratory which is familiar with handling this organism. Live cultures of *F. tularensis* are very hazardous to the laboratory personnel, and special precautions have to be taken. More accurate results of culture are obtained by injection of the suspected material into a susceptible animal, such as a mouse or guinea pig. If the animal becomes infected it will die within a week, and the material from the lesion seen at autopsy can be inoculated on the proper media.

Treatment

The most effective antibiotic for the treatment of tularemia is streptomycin. The dose for adults is 1 g. intramuscularly every 12 hours for seven days. There is a rapid response, usually within 24 to 48 hours. Tetracycline is also effective. Dangerfield⁴⁴ recommends 1 g. of tetracycline every six hours for four doses and then 0.5 g. every six hours for 14 days. He states that he has had no relapses with this dosage. Our cases 1 and 2 both received 2 g. of tetracycline a day for 10 days. The husband had a recurrence and required a second course of treatment. Relapse is not uncommon with tetracycline, particularly if treatment is started early in the disease before a good immune response can develop. Relapse is not associated with development of resistance to the antibiotic, so that the same agent can be used again if a relapse should occur. Tetracycline is more convenient than streptomycin, particularly if the patient is not ill enough to be admitted to hospital. Strains resistant to streptomycin but not to tetracycline have been encountered. Both kanamycin and chloramphenicol are effective in the treatment of tularemia, but because of their potential toxicity are not used except in special circumstances. Any patient with tularemia complicated by pneumonia should be admitted to hospital and should receive streptomycin.

Case 3 did not respond to penicillin, erythromycin or a short course of tetracycline, but only to larger doses

of tetracycline given for two weeks.

An infection with tularemia produces lifelong immunity. With early treatment mortality should be negligible.

Prevention

It seems apparent that *F. tularensis* is well established in nature. Ticks, flies and mosquitoes, even though they do not seem to be important vectors in spreading the disease to humans, undoubtedly form the main reservoir capable of infecting animals. Since there is no way to control the arthropod vectors, the disease will be controlled in humans only by education of the public, particularly of persons who are likely to come in contact with infected animals. The most susceptible groups are hunters, trappers, butchers and taxidermists. These people should wear protective gloves when handling animals. Laboratory workers who are likely to come in contact with the organism should wear masks and gloves. Meat, especially from wild animals, should be well cooked, for it is known that heating to 60° C. for 10 minutes will readily kill the organism, as will chlorination of water. An attenuated live vaccine has been developed which is moderately effective in preventing tularemia.^{39, 44} This may prove useful in selected groups in areas where the incidence is high, such as some of the sheep-ranching areas in the United States.

Summary

Three cases of tularemia are presented, the first such cases to be reported in Wentworth County, Ontario. All were acquired from infected muskrats. Tularemia is a very infectious disease, but transmission from man to man has never been proven. It is usually acquired through a superficial cut or abrasion, although other modes of infection occur, including even inhalation of the organism.

Diagnosis is suggested by the history and clinical findings, and can be confirmed most easily by the agglutination test. The causative organism, *Francisella tularensis*, is difficult to grow without special media and hence diagnosis from isolation of the organism is somewhat more difficult. Inoculation of mice or guinea pigs followed by culture on glucose cysteine blood agar is more likely to result in isolation of the causative agent.

The treatment of choice is strepto-

mycin, although tetracycline is also effective. The three cases described were all treated successfully with tetracycline, although two had to receive a second course of the antibiotic. Usually an illness which may otherwise last for months, and which carries a mortality rate of about 6%, can be cured within a few days.

Since it is impossible to eradicate the blood-sucking arthropods which spread tularemia to animals, control in humans depends on education of the public, particular the groups most likely to encounter animals, i.e., hunters, trappers, butchers and taxidermists.

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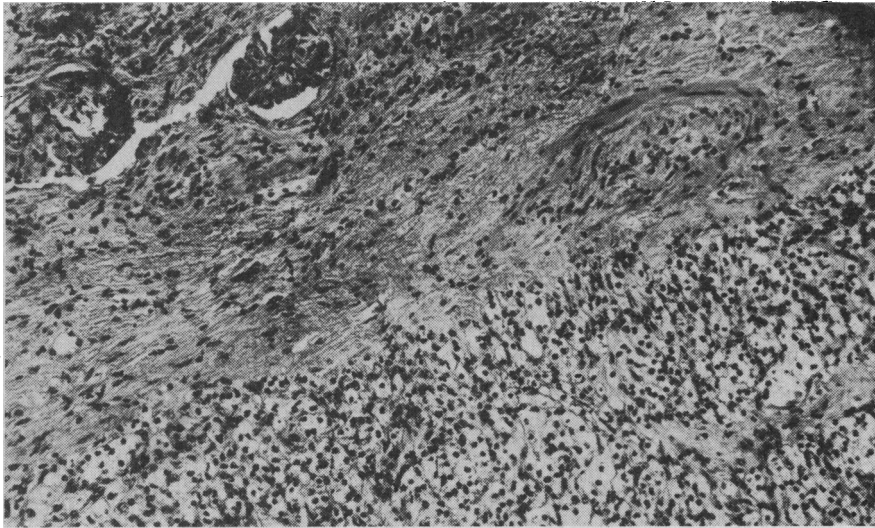


Fig. 2—(Rein gauche) Hypernéphrome. La tumeur est composée de cellules claires typiques. (Héματοxyline-phloxine-safran. x 400.)

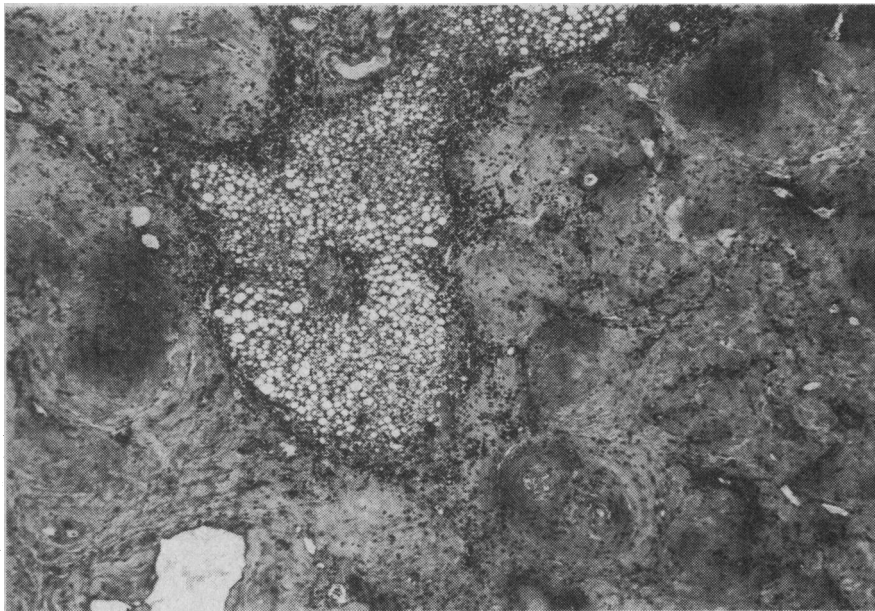


FIG. 3—(Foie) Hémangiome sclérosant. (Héματοxyline-phloxine-safran x 80.)

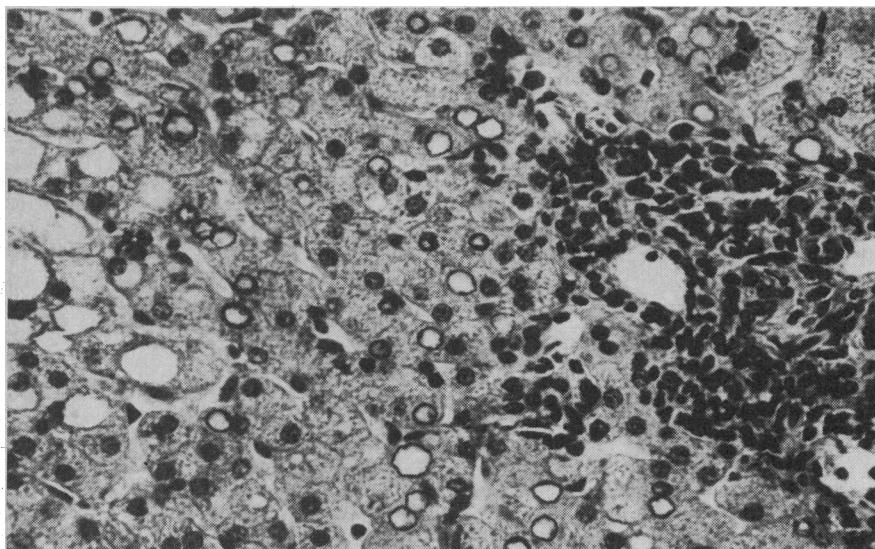


FIG. 4—(Foie) Il existe de la stéatose hépatique, des vacuoles de glycogène et une infiltration mononucléaire des espaces portes. On note aussi une prolifération minimale des cellules de Kupffer ainsi que la présence de lipofuscin dans les cellules hépatiques. Absence de métastases. (Héματοxyline-phloxine-safran. x 500.)

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