

began again. Radium was again inserted, in dose of 30 milligrams for 24 hours. There has been no bleeding since. The persistent high blood pressure has made operative procedure out of the question in this case; otherwise the uterus would have been removed long ago. Although we have made a diagnosis of cancer of the

fundus uteri, we have endeavoured to carry the patient along with the divided doses of radium. The results seem to have justified this course. After nearly six years the progress of the carcinoma appears to have been arrested, and the patient is in as good health as the persistent high blood pressure will permit.

TULARÆMIA

WITH REPORT OF A CASE

BY R. M. SHAW, B.A., M.D., D.P.H., F.R.C.P. (C.),

Provincial Laboratory, University of Alberta,

AND HEBER C. JAMIESON, M.B., F.R.C.P. (C.),

Department of Medicine, University of Alberta Hospital,

Edmonton

TO the practitioner of fifty years ago fever without a rash or apparent organic change in the body was an enigma. Several diseases in which this phenomenon was the outstanding manifestation were looked upon as varying degrees of the same morbid process. "You may believe that when we speak of fever generally, secondary lesions are either wanting or are inconstant in their amount or in their nature." So wrote Stokes, and he further stated that there was a tendency for fevers to change from a sthenic to an asthenic character. So typhoid, typhus, malaria, and other diseases characterized by rise of temperature were parts of a confused group of symptomatic fevers. Later, some were found to be due to specific organisms and assigned proper places in the catalogue of human morbidity. Out of those that remained obscure new diseases have from time to time been identified and carefully studied.

One of these "new" diseases is tularæmia, the causative agent of which was described by McCoy and Chapin in 1912 in a disease of rodents and first reported in a human case by Wherry and Lamb¹ in 1914. Since then many hundred cases have been discovered in Asia, Europe, and America, and tularæmia can now no longer be looked upon as a rare disease.

In Canada reports on 3 human cases have been published. In none of these was a culture obtained, all having been diagnosed by agglutination tests. The first was reported by McNabb² in Ontario in 1930; the second by Ootmar³ in British Columbia; and the third by Cramer⁴ in Ontario. In Ootmar's case the diagnosis was made more than a year after the acute attack,

and the agglutination titre of the serum ran to complete agglutination in 1-80, with partial agglutination in 1-160 and 1-320. McNabb's case was one of an acute illness without glandular enlargement, and with symptoms referable to the abdomen, particularly to the right upper quadrant, where there was pain, tenderness and muscular rigidity. There were also fever, chills and an icteric tinge in the sclera. The agglutination titre of the serum for *B. tularensis* reached only 1-160, though two examinations were made. A fact to be kept in mind in the diagnosis of tularæmia by serological methods is, that after an attack of this disease the agglutinins remain in the blood for many years in appreciable titratable amount, (the average for 21 cases at one year after infection was 1-140, [Francis⁵]).

Cramer's patient became ill on July 6, 1931, and pursued a typhoidal course. The serum, after showing negative reactions in agglutination tests with *B. tularensis* on July 11th and 14th, became positive in dilution 1-20 on July 17th, 1-160 on July 22nd, and 1-640 July 29, 1931.

Parker, Hearle and Bruce⁶ reported isolating *B. tularensis* from a rabbit taken in British Columbia in the spring of 1930, and from ticks infesting this animal.

Francis, from a study of 679 cases has divided tularæmia into four clinical types—ulceroglandular, oculoglandular, glandular, and typhoidal. In the first two varieties enlargement of regional glands is found with suppuration in about 50 per cent of the cases. Adenitis, without lesions on the skin to account for infection, characterizes the glandular type. In the typhoid form,

which comprised only 28 out of 679 cases reported by Francis, no glandular enlargement was seen. Unless complications arise, a diagnosis in this variety is made with difficulty; in fact it can only be made with certainty by animal inoculation or agglutination tests. As already pointed out, the presence of specific agglutinins in small amounts in a patient's serum is not, *ipso facto*, sufficient evidence to diagnose an acute attack. Francis states that these antibodies appear in the second week of the disease and increase in quantity to the fourth or seventh week, when they soon begin to decline. The increase in titre of specific agglutinins for *B. tularensis*, rather than the mere presence of these antibodies in the patient's serum, signifies existing infection.

Another point to be kept in mind with regard to diagnosis by agglutination tests is that *B. tularensis*, *Br. abortus* and *Br. melitensis* are antigenically related. The serum of a patient suffering from tularæmia, besides agglutinating *B. tularensis*, may also agglutinate these other organisms, though usually only in much lower dilutions. The converse also holds true, *viz.*, the serum of an undulant fever patient may agglutinate *B. tularensis*, but in lower dilution than it does the causative agent of this disease. From this it is apparent that *B. tularensis* and either *Br. abortus* or *Br. melitensis* should be used as antigens in agglutination tests on the sera of patients suspected of suffering from either of these infections.

The common complications of tularæmia as listed by Francis are ascites, pneumonia and pleurisy with effusion.

The following case emphasizes the necessity of being watchful for this disease in fevers of an obscure nature, and is an example of a not infrequent occurrence, where the presence of a complication leads one to a diagnosis. In this instance the diagnosis was suggested by the gross pathological findings in an inoculated laboratory animal and was confirmed by cultural and serological methods.

CASE HISTORY

P. B., a halfbreed, aged 52, married, a farm labourer, was seen first on September 19, 1931, by Dr. Frank F. Law, of Tofield, at his office, complaining of sore throat, general aches and pains, headache and constipation, the symptoms being of one week's duration. The patient was dull and apathetic; temperature 102°; pulse 110.

Physical examination showed only some generalized abdominal tenderness. He was informed that the

diagnosis was not clear and told to return home and report progress. One week later he requested the doctor to visit him as he was not better. Living conditions were found to be deplorable. The patient, his wife, and six children, in ages from two to fifteen years, were existing in a tent, 8 feet by 10 in size. The chief article of diet appeared to be rabbit, there being numerous skins and many piles of rabbit entrails lying about, fed upon by myriads of flies. (This information concerning rabbits was obtained from Dr. Law only after diagnosis was made on bacteriological and serological findings, and after repeated statements by the man that he had had nothing to do with rabbits for a period of two years.)

The patient at this time had a non-productive cough and said he was passing green stools. The abdomen was not distended, but was again generally tender. The temperature was 102°. Some dullness and diminished breath sounds were noted in the right chest. He was advised to enter hospital for diagnosis and treatment, and was admitted to the Royal Alexandra Hospital, Edmonton, under the care of Dr. N. L. Terwilleger, to whom the authors wish to acknowledge indebtedness for the privilege of reporting this case in full.

On admission, the patient complained of headache, vague abdominal pains, constipation, and general malaise of three weeks' duration. He had a cough, bringing up a small amount of thick greyish sputum. Temperature, in a.m. 98°; in p.m. 101° to 102°, for about one week after admission, then subsiding by lysis to normal. Pulse 80 to 100; respiration 18 to 22; blood pressure 110/80.

Physical examination showed a throat hyperæmic and covered with mucus. The chest was poorly developed, both apices flattened, and with limited movement, more marked on the right side. The base of the right lung was dull on percussion. The breath sounds, vocal resonance, and tactile fremitus were absent over this area. The right chest, above this, showed some impairment of breath sounds and vocal resonance. Heart, normal. Abdomen, negative. Nervous system, normal. An x-ray of chest showed the right side to be dense from apex to base. The blood Wassermann test was negative. Sputum negative for *B. tuberculosis*. Widal, T. A. and B., negative. Leucocyte count, 9,600. Polymorphonuclear cells, 89 per cent; lymphocytes, 6 per cent; endothelial leucocytes, 5 per cent. The urine showed a trace of albumin and a few pus cells.

Paracentesis was done three days after admission, 54 ounces of sanguinous fluid being withdrawn. A second specimen of fluid was obtained on October 22, 1931.

Following the second paracentesis the patient's general condition became better, the lung expansion improved, and the evidences of pleurisy diminished. His cough abated and he left hospital on November 23, 1931, with normal temperature, but still complaining of general weakness and some dyspnoea on exertion.

Cultural and serological findings.—Fluid collected from the pleural cavity on September 30, 1931, was submitted to the Provincial Laboratory, University of Alberta, Edmonton, with a request for guinea pig inoculation. The fluid was slightly blood stained and had a coagulum. Inoculation was made subcutaneously into the left hind leg of a guinea pig on October 2, 1931. This pig died on October 9, 1931, seven days after inoculation. At autopsy the glands of the groins and axillæ were found necrotic. The spleen was enlarged and closely studded with minute white areas, each about a millimetre in diameter; the liver showed a similar, though less marked, condition. The lungs appeared healthy. The gross general picture suggested tularæmia.

Inoculations were made from the spleen on Francis' glucose-cystine-agar, enriched by the addition of filtered human serum. The spleen was ground up with sterile saline and inoculated into two fresh guinea pigs, one by the subcutaneous route, and the other by rubbing

into the freshly shaven skin of the abdomen. These pigs died on the fourth and fifth days respectively, and showed at autopsy a condition similar to pig No. 1, but with smaller foci in the spleen and liver.

The procedure outlined above, *viz.*, the inoculation of culture media and re-inoculation into fresh animals was repeated. The infection was passed from pig to pig through several series, with a view to keeping it alive until a culture could be obtained. Tubes of Francis' glucose-cystine-agar enriched with defibrinated rabbit blood, inoculated from the fifth pig in direct passage, were the first to show growth. The growth was scant and appeared only after three days' incubation. This culture, emulsified in broth, was inoculated into a fresh guinea-pig which died within forty-eight hours. Autopsy revealed a fine mottling of spleen and liver, and moderately enlarged congested glands in groins and axillæ. Cultures with good growth in 4 days were obtained from spleen and heart blood on Francis' medium enriched with defibrinated rabbit blood. A second specimen of pleural fluid and a specimen of blood were requested and were received on October 22, 1931. This pleural fluid failed to produce infection when inoculated subcutaneously into healthy guinea pig though 3 c.c. were used.

The blood serum of the patient agglutinated the freshly isolated organism completely in all dilutions up to 1-5,000, showed partial agglutination in 1-10,000, but failed to agglutinate in 1-20,000. When tested, using a known *B. tularensis*, (*B. tularensis* No. 38, isolated by Francis, and obtained by us from the National Health Institute, Washington), as antigen, the agglutination titre was the same as with the freshly isolated organism. This serum also agglutinated *Br. abortus* in dilutions 1-20, 1-40, and 1-80, but not in 1-160. A second specimen of serum obtained on November 19, 1931, agglutinated *B. tularensis* in dilutions up to 1-5,000 and *Br. abortus* up to 1-40.

Smears from pleural fluids did not reveal the presence of *B. tuberculosis*. The pig inoculated with the second specimen of pleural fluid was killed on December 3rd, and showed no evidence of tuberculosis.

COMMENTS

The following points are of special interest and importance in this case.

1. The advisability of doing serological tests in fevers of uncertain origin, not only for typhoid and undulant fevers but for tularæmia as well.

2. The importance of examining carefully guinea pigs dying within a week of inoculation with ascitic or pleuritic fluid.

3. The need for close scrutiny in a good light of the liver and spleen of such animals, since the lesions are sometimes very minute.

4. The evidence of the non-contagiousness of the disease for guinea pigs, as shown by the fact that the first animal lived in a pen with seven others for seven days and they remained apparently well.

5. The disappearance of the organism from the pleural fluid between the first and second paracentesis in this case, a period of 23 days.

6. The report herein given appears to be the first record of the isolation of *B. tularensis* from man in Canada.

Francis,⁵ in 1928, stated that cultures have been obtained from 24 human cases by guinea pig inoculations. Isolation from pleural fluid is not mentioned among these, though he says the organism was obtained from ascitic fluid in one case, three months after onset of disease, and has been obtained at autopsy from lungs. The knowledge that rabbits will be increasing greatly during the next few years, and that this disease can be diagnosed serologically, should make the medical practitioner alert, especially in those districts of Canada where contact with rabbits or other rodents might suggest the possibility of tularæmia.

The following points emphasized by Francis should aid in the diagnosis. First, a history of having dressed or dissected a wild rabbit, or being tick-bitten or fly-bitten; secondly, a primary lesion of the skin in the form of a papule followed by a persistent ulcer, or a primary conjunctivitis; thirdly, persistent glandular enlargements in the region draining the primary lesions, and fourthly, fever of from two to three weeks' duration.

REFERENCES

1. WHERRY AND LAMB, *J. Inf. Diseases*, 1914, 15: 331.
2. McNABB, *Canad. Pub. Health J.*, 1930, 21: 91.
3. OOTMAR, *ibid.*, 1931, 22: 207.
4. CRAMER, *ibid.*, 1931, 22: 568.
5. FRANCIS, *J. Am. M. Ass.*, 1928, 91: 1155.
6. PARKER, HEARLE AND BRUCE, U. S. Pub. Health Reports, 1930, Vol. 46, No. 2, p. 45.

DIPHYLLOBOTHRIUM LATUM: INFESTATION ON EASTERN SEABOARD.—Twenty-one cases of infestation with *Diphyllbothrium latum* are reported by Milton Plotz from New York City. These are the first cases reported in the literature from New York State and include five patients born in the United States, bringing the total number of reported native cases to thirty-one. All but two of the patients were females and all but two Jewish.

Mild to severe anæmia was found in all of fifteen cases in which blood studies were made. One is not justified in concluding from this series that there is a definite relationship between primary anæmia and this disease. Eosinophilia was found in five of eleven cases in which differential counts were made. The author hopes that this report will stimulate further search for this parasite on the eastern seaboard.—*J. Am. M. Ass.*, 1932, 98: 312.