TULAREMIC ENCEPHALITIS *

PATHOLOGY OF ACUTE TULAREMIA WITH BRAIN INVOLVEMENT AND COEXISTING TUBERCULOSIS

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Since Francis [1] accumulated the reports of twenty-four deaths from tularemia in 1928, at least five additional reports of death have been published. Of these five cases autopsies were done in two instances, bringing the total number of reported autopsies, to date, to ten. An additional case, with two unique features and in which an autopsy was performed, is the basis of this report. The unique features are, first, involvement of the brain without involvement of the meninges, and second, the presence of active tuberculosis of the left kidney and right epididymis.

REPORT OF CASE †

Clinical History: Patient admitted December 22, 1930 at 11.30 P.M., with a complaint of fever and delirium. He had had measles and influenza, but there was no history of tuberculosis. His habits were good. Family history unimportant. On December 10, while working in a butcher shop, he lacerated his hand at the base of the left thumb. He was cleaning fish at the time of the accident, but just previous to this had been skinning rabbits. He covered the wound with iodine and continued his work. December 14, the hand became swollen and the axillary glands enlarged and quite painful. At this time he felt "feverish" and consulted his physician, who told him the injury had become infected and treated him accordingly. For three days there was local and general improvement, but December 18 more fever and malaise developed, with delirium and profuse sweats which lasted for four days. The temperature ranged from 101 to 103° F. His physician noted stiffness of neck.

Physical examination showed a well nourished and well developed adult male breathing loudly but regularly, and aroused with difficulty. The pupils were dilated and reacted to light and accommodation. The lips were cracked, dry and bled easily; the mucous membranes were coated. Throat clear. Teeth in good repair. Definite rigidity of neck was present. Lymph glands and thyroid of

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† The history and clinical course are briefly abstracted, as they will be given in a detailed report from the Department of Medicine at a later date.

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usual size. Chest expansion normal, resonant throughout, respirations wheezing with few dry râles. Heart sounds regular, no murmurs. Blood pressure 118/80. The abdomen was on a level with the chest and there was no muscle spasm or tumor masses. The extremities were not unusual except an ulcer 2.5 cm. in diameter on the left thenar eminence. There was no visible lymphangitis but the axillary glands were enlarged. (Physician stated lymphangitis could be readily seen and that one axillary gland had been the "size of a lemon.") Kernig and Babinski signs negative. Hemoglobin 14.7 gm., red blood cells 4,830,000, white blood cells 11,500, polymorphonuclear leucocytes 84, small mononuclears 14, transitional cells 2. Urine: amber, specific gravity 1.018, acid, albumin 1 plus, sugar negative, no red blood cells, white blood cells or casts. Blood culture negative at thirty-six hours.

Progress: On December 29 the patient was drowsy and stuporous, the temperature 101.2° F. Many râles, especially at left base, were noted. The wound was clean and granulating. Blood culture agglutinated *B. tularense* 1:640. December 31, red blood cells were 4,790,000, hemoglobin 13.9 gm., white blood cells 11,400. Urine, albumin 2 plus. Agglutination with *B. tularense* 1:1280. January 1, 500 cc. of blood from a convalescent patient with a titer of 1:640 was given to the patient. January 2 the temperature was only slightly lower, but patient was rational. Three days later a papular eruption appeared, covering the back from scapulae to buttocks. The next day, January 6, he had a slight convulsion. On January 9 a spinal puncture was made which showed bloody fluid, negative culture, sugar 42 mg., white blood cells 145. January 20 the temperature was 104° F, râles were noted over right base and impairment over left base. The respirations became irregular and death took place.

Autopsy Report

Body: Middle-aged, white male 163 cm. in length. Skeleton slight, poorly nourished. Axillary glands on left enlarged. At base of left thumb there is healing ulcer 3 by 1.5 cm.

Abdomen: Surfaces smooth and glistening. Liver reaches costal margin. Spleen enlarged.

Thorax: No excess of fluid or adhesions. Pericardial sac contains 100 cc. clear fluid.

Heart: Weight 320 gm. Subepicardial fat moderate in amount, vessels tortuous but not sclerotic, right auricle and ventricle dilated and filled with liquid blood, valves intact. The myocardium is pale, but of good consistency.

Lungs: Left lung weighs 600 gm., right 650 gm. There are no scars at the apices. The peribronchial lymph nodes are enlarged and show small grayish white areas of necrosis. On the right side small grayish areas of necrosis are seen beneath the pleura and scattered through the parenchyma. Sections from the peribronchial lymph nodes show small areas of necrosis and polymorphonuclear infiltra-

tion. The epithelioid reaction is slight and no giant cells are found. Gram-Weigert and Ziehl-Neelsen stains show no bacteria. Sections from lungs show necrosis with little epithelioid or other cellular reaction and no giant cells. Gram-Weigert and Ziehl-Neelsen stains negative for bacteria.

Spleen: Weight 300 gm. The capsule is bluish red in color and shows no wrinkling, but there are a few grayish areas of necrosis shining through. On section the pulp is very soft and bloody. The necrotic areas cannot be made out. On microscopic examination the areas of necrosis are small and difficult to find. They are sharply outlined and there is some epithelioid reaction at the periphery. No giant cells are found. Stains for bacteria are negative.

Liver: Weight 1900 gm. The capsule is smooth and a few small grayish yellow areas of necrosis are seen shining through. On the dorsal surface, at the junction of the right and left lobes, is a soft necrotic area 8 mm. in diameter filled with grayish homogeneous material. The parenchyma is brick red in color and the cut surface is finely granular. Lobulation is distinct and there is no increase in fibrous tissue. Microscopic examination shows minute areas of necrosis infiltrated by leucocytes. There is no epithelioid reaction and no giant cells. Gram-Weigert and Ziehl-Neelsen stains reveal no bacteria (Fig. 1).

Kidneys: Weight, right 200 gm., left 200 gm. The capsules strip readily, leaving smooth, unscarred, cortical surfaces. On section the cortex ranges from 7 to 10 mm. and the usual architecture is well made out. In the upper pole of the left kidney the calyces are lined by grayish granulation tissue and are enlarged. Microscopic sections through involved calyces show whorls of epithelioid cells with giant cells forming typical tubercles. Acid-fast bacilli are readily demonstrated (Fig. 2).

Testicles: The left testicle is missing. The right epididymis is enlarged and indurated with a caseous abscess 1 cm. in diameter. Microscopic sections show whorls of epithelioid cells with giant cells and necrosis forming single and conglomerate tubercles. As many as ten acid-fast organisms to a single field are demonstrated by Ziehl-Neelsen stains.

Brain: Dura is of usual thickness and translucent. The convolutions are broad and flat and the sulci are correspondingly narrow. The inner meninges show no edema or infiltration. On section

through the fixed specimen the corpus callosum, basal nuclei, pons and the adjacent tissue show soft, grayish yellow, necrotic or hemorrhagic areas ranging from 0.5 to 3 mm. in diameter (Fig. 3). Microscopic sections taken through the brain and necrotic lesions in various places show a necrosis similar to that seen in glands, lungs, spleen and liver, except that it is much more extensive and that there is hemorrhage in places. There is more leucocytic infiltration also. The blood vessels within and near the necrotic areas show marked proliferation of the lining endothelium with narrowing, and in some cases, obliteration of the lumen. Gram-Weigert and Ziehl-Neelsen stains fail to reveal bacteria (Fig. 4).

Discussion

With active tuberculosis demonstrated in the left kidney and the right epididymis by finding the tubercle bacillus in the lesions and by reproducing the disease in guinea pigs, the question naturally arises as to whether all the pathology and particularly that in the brain could be explained on the same basis. Aside from the clinical history which is typical of tularemia, and the high agglutination titer (1: 2480) of the patient's serum for *B. tularense*, the lesions in the lymph nodes, spleen, lungs, liver and brain are quite different from those in the left kidney and epididymis, in that the former show more necrosis, less epithelioid reaction and no giant cell reaction. Furthermore, sections from lymph glands, spleen, lungs, liver and brain were stained by the Ziehl-Neelsen method at the same time as sections from the kidney and epididymis, but no acid-fast bacilli were found in the former, while as many as ten acid-fast bacilli were found in a single oil immersion field in the latter.

Brain involvement has not previously been reported in man. However, Francis and Callender [2] record a negro with swelling and suppuration of the axillary glands who died after several days of stupor and coma. The clinical diagnosis was tuberculous meningitis. The autopsy showed bronchopneumonia and the spleen, liver and meninges showed opaque firm nodules. Although the pathology was interpreted at the time as tuberculous meningitis, tubercle bacilli were not demonstrated, so the possibility of tularemia was suggested later.

Experimentally Dwijkoff [3] has produced hemorrhagic lesions of the brain stem in guinea pigs with *B. tularense*.

On the other hand, it is doubtful if tuberculosis ever produces a general inflammation of the brain substances as seen in this case, that could properly be called encephalitis, at least in the absence of meningeal and ependymal lesions. Roque, DeChaume and Ravault [4] report a single case of "tuberculous meningo-encephalitis," and describe the principal lesions in the meninges and ependyma with involvement of only the brain substance immediately adjacent.

In addition to lethargic encephalitis, encephalitis is known to occur in measles, scarlet fever, whooping cough, mumps, typhoid fever, typhus fever, variola, varicella and diphtheria. In tularemic encephalitis, if judged by this single observation, the lesions are even more extensive than in most of the diseases mentioned and are characterized by proliferation of the endothelium of the blood vessels, endarteritis, extensive necrosis, particularly of the white matter, and hemorrhage.

Summary

1. A case of acute tularemia with diffuse encephalitis and coexisting tuberculosis of the kidney and epididymis is described.

2. The brain lesions are readily seen as areas of yellow necrosis and hemorrhage throughout the base.

3. Microscopically there is patchy necrosis with round, wandering cell and polymorphonuclear infiltration.

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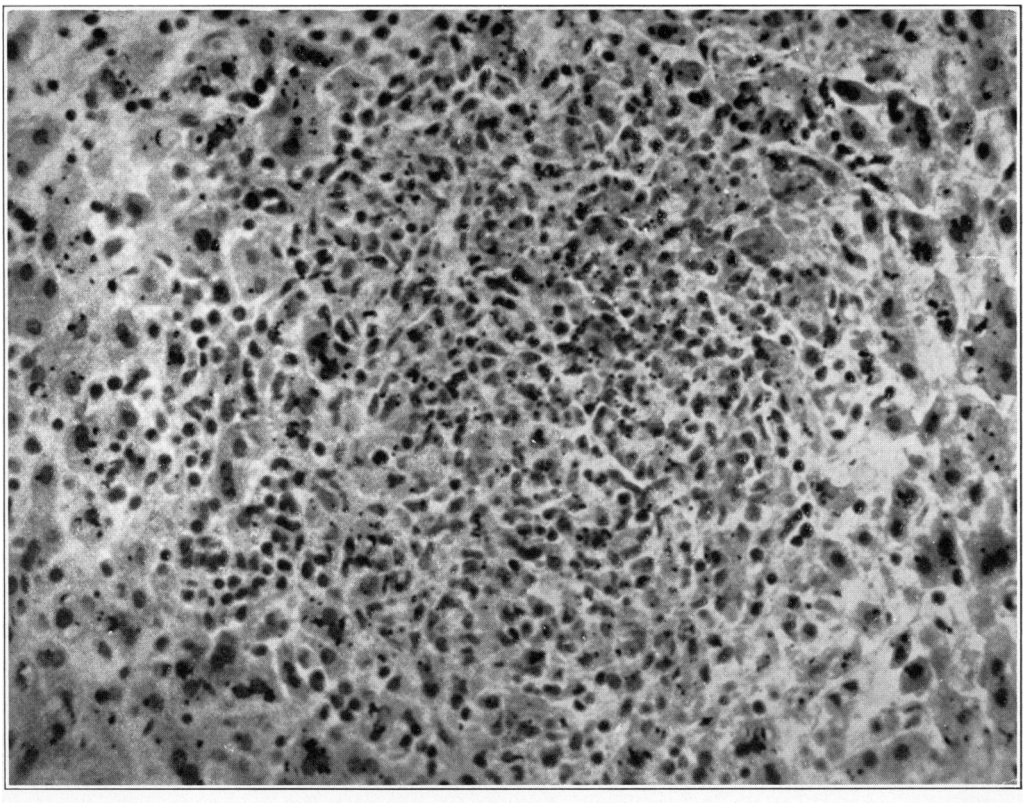
DESCRIPTION OF PLATES

PLATE 8

FIG. 1. Photomicrograph of liver showing area of necrosis without giant cells.

FIG. 2. Photomicrograph of left kidney showing typical tubercle.



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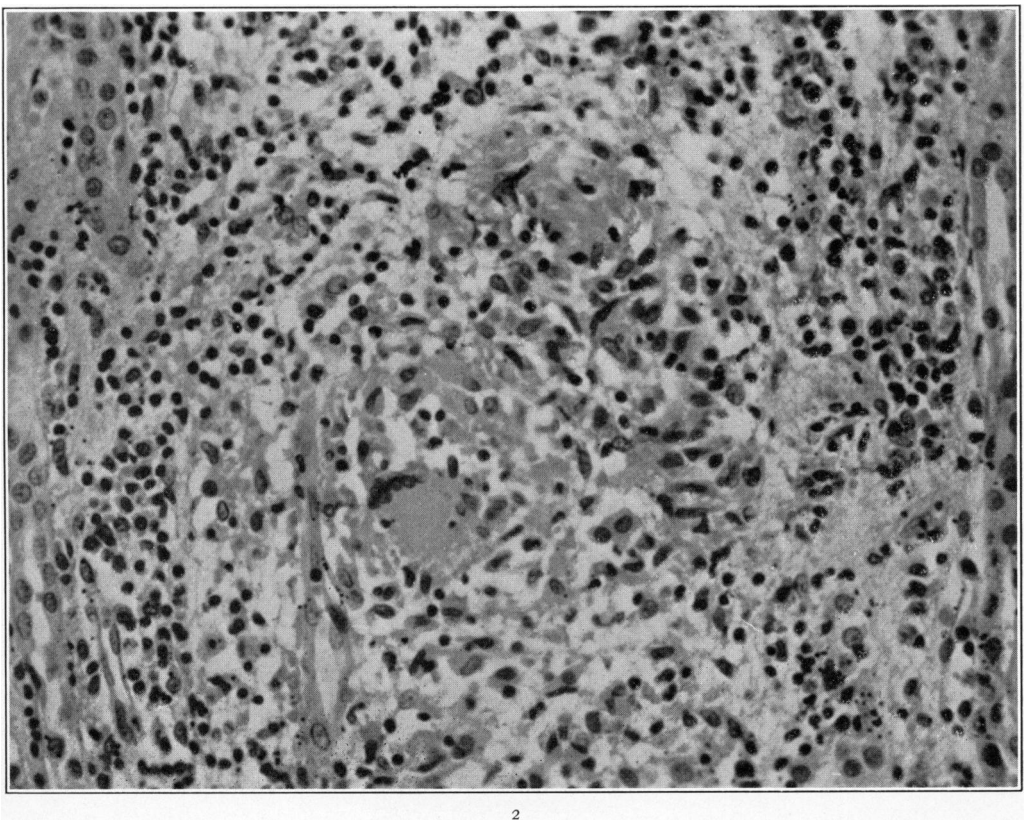

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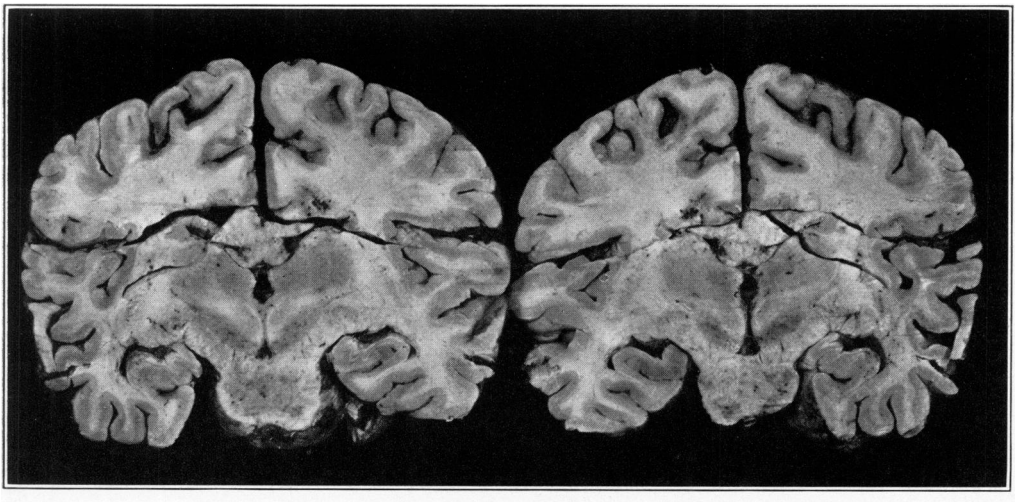
PLATE 9

FIG. 3. Coronal sections of brain showing areas of necrosis and hemorrhage.

FIG. 4. Photomicrograph of brain showing area of necrosis with leucocytic infiltration at periphery.



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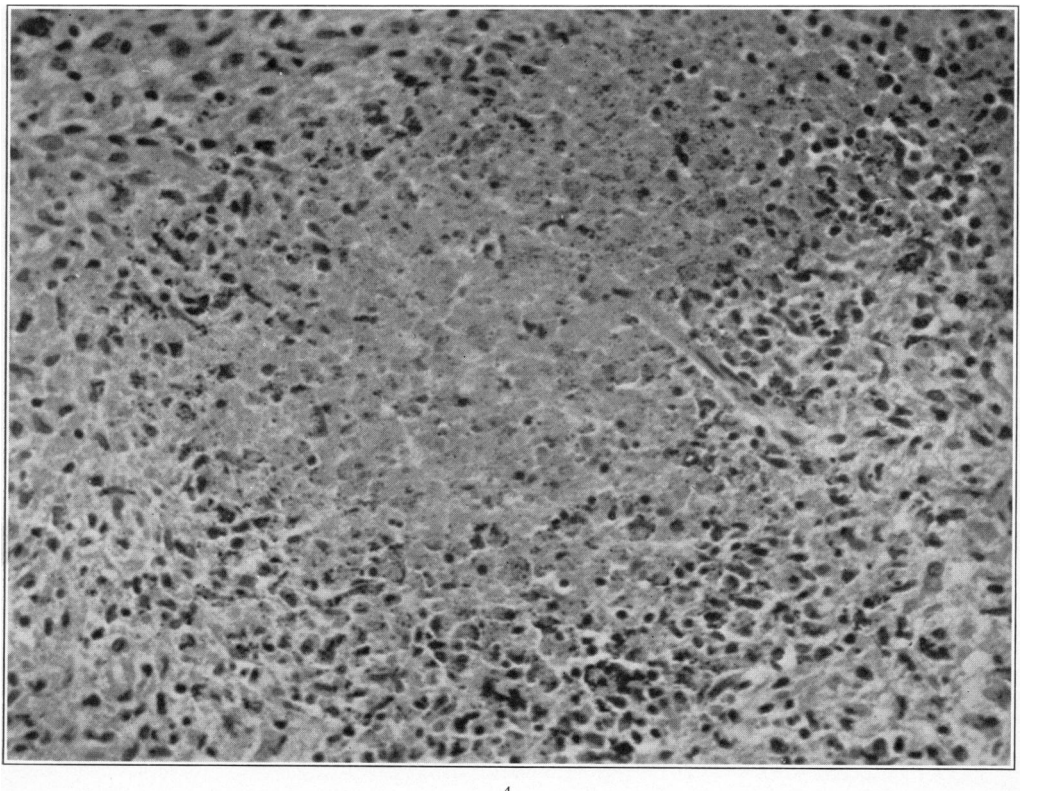

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