# A UNIQUE INFECTION IN MAN CAUSED BY A NEW YEAST-LIKE ORGANISM, A PATHOGENIC MEMBER OF THE GENUS SEPEDONIUM *

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A middle-aged white man who had had an irretractable skin disease for 15 years attracted our attention because the extent and the gross features of the lesions were unlike anything we had ever observed. A survey of the literature convinced us that the clinical manifestations of the ailment indicated a new disease. Unique papular lesions with a small crater of necrosis capping each, which yielded a few drops of sticky pus, covered the entire skin. The lesions were heavily set on a much thickened, wrinkled and scaly skin, which had a tendency to become ulcerated. The ulcers were deep and crusted and progressed slowly. The regional lymph nodes were increased markedly in size. The features enumerated led us to believe that a moderately strong injurious agent was the cause of the disease. The extension of the lesions over the entire surface of the body, followed by enlargement of the regional lymph nodes, led us to suspect an infectious form of microbiological life, possibly a fungus, as the etiological agent of the disease. Sections of the pathological skin and lymph nodes revealed the presence of minute yeast-like bodies chiefly within endothelial phagocytes. The organism was isolated on artificial culture mediums. Mycological and animal pathogenicity studies of the pure culture were made. According to the taxonomy of Saccardo, the organism belonged to the genus *Sepedonium*. Our species did not belong to any of the described members of the genus. No pathogenic member of the *Sepedonium* has been described.

## REPORT OF CASE

*Clinical History:* H. J., a steel welder, was observed on Feb. 9, 1931. He complained of a generalized skin eruption which was accompanied by intense itching. In 1917 dry scaly skin lesions developed in the regions of the popliteal

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spaces from which the remainder of the skin eventually became involved. He had been a sailor for 3 years, a railroad switchman for several years, and a welder of steel flues for the past 14 years. No flux or brass was used and the shop in which he worked was well ventilated. In September, 1929, lesions began to appear on the thighs. Progression of the lesions continued until he was unable to work because of involvement of the palms of the hands.

Physical examination revealed a man whose general condition was quite good. He had a generalized, dry, papular skin eruption which caused him considerable distress from itching. One buccal lesion was observed. Many types of local and general therapeutic agents were tried but these served only to relieve symptoms and had no effect upon the progress of the disease. He was discharged on March 29, 1931, with a diagnosis of dermatitis exfoliativa.

The patient was rehospitalized on July 7, 1932. Since his last hospitalization, ending on March 29, 1931, he had visited numerous physicians and health resorts but had received no aid. He had received a course of eight X-ray treatments in September, 1931, with no benefit, and a biopsy of the skin and an inguinal lymph gland was made in the institution where he had received the X-ray treatments. A diagnosis of dermatitis and lymphadenitis was made, but because of the heavy infiltration of the skin with lymphoid cells the question of leukemia of the skin was raised. Until May, 1932, the skin of his back was fairly smooth but since then the old lesions became more elevated and many new papules appeared. This was accompanied by loss of weight and weakness. He had difficulty in keeping warm even during the summer months. The right small toe became gangrenous and sloughed off in July, 1931. Several fingers of the right hand had been lost in an accident.

Physical examination revealed a weak, emaciated male, whose entire skin was involved in an extensive dermatitis. The lesions varied from scaliness and papule formation to ulcerated lesions measuring 3 to 4 cm. in diameter. The most recent lesions were papules measuring 0.5 to 1 cm. in diameter, which were somewhat irregular in outline and had a tendency to become confluent. The pruritus was intense. The thickened mucous membrane of the mouth presented several small, granular, ulcerated lesions. The heart, lungs and abdominal viscera were normal.

*Laboratory Studies:* The urine was normal. Red blood cells 4,200,000; white blood cells 10,200; hemoglobin 82. Blood Wassermann negative. Blood studies for evidence of changes in the bleeding time, coagulation time, fragility of the red blood cells, clot retractibility and prothrombin time showed no abnormalities. The blood platelets were 0.35 per cent (Van Allen). The $CO_2$ combining power of the plasma was 60.7. No lesions were demonstrable roentgenologically in the chest, or dorsal or lumbar vertebrae. Biopsies of the skin, the left inguinal lymph gland and the buccal mucosa were made on July 9, 1932. Each of these tissues was cultured and the yeast-like organism isolated. The tissue sections revealed definite evidence of a chronic inflammatory process and the presence of numerous yeast-like bodies in phagocytes. A few were free in the tissue and in the epithelial cells.

Therapy consisted of massive doses of potassium iodide and ionized copper treatment. X-ray was also applied to a small area of the lesions, all of which seemed to progress under treatment.

Under observation the patient developed new skin lesions and a punched-out ulcer of the tongue. Many of the older firm papules became ulcerated. His temperature, which had been of a mild septic type since admission, gradually

became more elevated. Three days before death friction rubs and râles were heard in the chest. Death occurred Aug. 7, 1932, presumably 15 years after the onset of the disease.

### Postmortem Examination

The body was that of a well developed, emaciated male, whose entire skin was thickly studded with papular and macular lesions measuring 0.5 to 1 cm. in diameter. Many deep ulcers from 1 to 4 cm. in diameter were found, as well as numerous shallow ulcerations which represented the recent liquefaction of the summits of papules. Large decubitus ulcers were present over the sacral and scapular regions. The skin was thickened, reddish purple in color and fissured in many areas. No areas of the skin escaped involvement. The lesions were found in the scalp, eyebrows, palms of the hands, soles of the feet and the scrotal sac, as well as over the larger skin surfaces. Papular and ulcerated lesions were also found on the roof of the mouth, the tongue and the mucous membranes of the cheek.

Except for fibrous adhesions between the gall-bladder and the colon, the peritoneal cavity appeared normal. The left pleural cavity contained 150 cc. of cloudy sanguineous fluid. Fibrin covered the pleura. The right pleural cavity appeared normal. The lower lobes of both lungs were firm and not crepitant. The cut surfaces were granular and yielded a purulent fluid. The medium sized vessels were occluded by red, friable blood clots. The heart weighed 360 gm. No endocardial lesions were present. The spleen appeared somewhat fibrotic. The liver weighed 2670 gm. The cut surface had a yellowish color and yielded an abundance of greasy material. The gastro-intestinal tract, gall-bladder, pancreas and kidneys appeared normal. The adrenals were somewhat enlarged and showed small areas of necrosis in the medulla. Numerous atheromas and ulcerations were present on the intima of the aorta. The bladder and prostate appeared normal. The brain showed no lesions. All superficial lymph nodes were firm and enlarged, the largest being about 4 cm. in diameter.

### Histological Examination

Except for slight myocardial scarring, the heart appeared normal. Sections obtained from the lower lobes of the lungs showed the alveolar sacs filled with polymorphonuclear leukocytes, fibrin and red blood cells. Many bronchioles showed partial or complete destruc-

tion of their walls. Several of the smaller branches of the pulmonary artery were occluded by organizing thrombi which showed canalization at their peripheries. Both old and recent infarcts were present. Occasionally yeast-like bodies were found which were engulfed by large mononuclear phagocytes. These organisms were found in the alveolar sacs and not in well defined lesions, as observed in the skin and the adrenals. The yeast-like bodies were not numerous. A few spiculated forms of the infectious agent were present. The spleen showed some thickening of the sinusoidal walls. The malpighian corpuscles were atrophic and many plasma cells were noted throughout the pulp. No lesions due to the presence of the organism were noted. The pancreas and gall-bladder appeared normal. The liver showed a moderate fibrosis and a chronic inflammatory cell infiltration of the supporting connective tissue of the portal canals. Fatty metamorphosis of the periphery of the lobules was present and a few small areas of focal necrosis were noted. The kidneys, except for a few small arteriosclerotic infarcts, appeared normal. The adrenals presented medullary and cortical areas of caseation necrosis resembling those produced by *Mycobacterium tuberculosis*. A few yeast-like bodies were present in the central portion of these caseous areas but they were found in great abundance in the phagocytes and the adrenal cells at the periphery. Myriads of microörganisms were found in the adrenal cells proper, in areas where no necrosis had as yet occurred. This was a conspicuous finding in all the early lesions. The largest adrenal lesion measured about 0.2 cm. in diameter. Large subintimal deposits of atheromatous material were observed in the aorta. Organizing thrombi were attached to the bed of some of the atheromatous ulcers. The skin sections taken before and after death, as well as the sections taken at another institution in September, 1931, revealed large numbers of microörganisms engulfed by large mononuclear leukocytes. A papule consisted of a collection of large mononuclear phagocytes located directly beneath the epidermis and confined to the corium. The infectious agent caused very little connective tissue proliferation. The larger, non-ulcerated lesions showed only slight evidence of liquefaction necrosis. Up to twenty or twenty-five rounded organisms, each surrounded by a distinct capsule, were contained within one phagocyte. A few organisms were noted in the epithelial cells themselves. Sections of the lymph glands, which were obtained before and after death, as well as the one removed elsewhere in September 1931, also revealed large

numbers of organisms. Scarring distorted the architecture of the glands so that no evidence of germinal centers was observed. Large numbers of plasma cells were present and a hyperplasia of the endothelial cells was in evidence. The latter contained the organisms. In a few instances collections of phagocytes heavily laden with yeast-like bodies were observed but as a rule they were scattered diffusely throughout the gland. Giant cells were abundant in the lymph glands, as compared to the other tissues involved, but they were not a prominent feature in any of the tissues. They contained relatively few organisms. The brain sections revealed no pathological changes.

## Mycological Study

The appearance of the organisms in the tissues was that of rounded, yeast-like bodies. They varied little in size, and together with the chitinous fungus-cellulose capsule measured from 3 to 5 microns in diameter. There were a few swollen hyaline bodies which were judged to be empty capsules. The organisms were, for the most part, enclosed in monocytes but many were present in adrenal cells proper. A few were free in the tissues and some were present in epithelial cells of the epidermis and in giant cells. They were very numerous in injured adrenal cells at the periphery of a lesion. The organism stained better with various modifications of hematoxylin, (phosphotungstic acid hematoxylin and iron hematoxylin) than they did by the Giemsa method. In the lungs the organisms were larger than they were in the lymph nodes, the skin and the adrenals, measuring about 6 microns in diameter. Some of the yeast-like bodies in the lungs had a thick spiculated capsule, such as was later seen on artificial culture medium.

A biopsy of skin and lymph node was made on July 21, 1932. The tissue from each site was divided into two equal portions. One portion was washed in 6 changes of sterile broth. The other half was first treated momentarily with alcohol and then washed in 6 changes of sterile broth. The pieces of tissue were then macerated in a small amount of broth and test tubes of medium were then inoculated. What remained of the macerated tissue after inoculation of artificial mediums was inoculated into the peritoneal cavities of guinea pigs and mice. No evidence of disease developed in the animals after several months of observation.

Meat infusion agar, blood agar, brain agar, chocolate agar, Sabouraud's medium, 25 per cent rabbit blood agar, and beer-wort

agar were employed. The inoculum of a single loop was passed down a series of several large tubes of medium. The number of contaminating organisms was thus diminished so that isolated colonies of the fungus were readily obtained. In 7 days, there being no particular food requirement for the organism, numerous, small, flat, arborescent, icy-appearing colonies were barely visible on many of the tubes. At times there was no contamination, the tube being thickly set with colonies of the fungus. Even before the colonies appeared, smears from the surface of the medium revealed mycelial threads springing from the yeast-like bodies in a phagocyte. There seemed to be little difference in the rapidity of growth between the temperature range of 22° to 38° C. Under anaerobic conditions the growth was retarded. Colonies appeared first regularly on meat infusion and blood agar. On these mediums mycelial threads were more abundant. This was particularly true of the meat infusion agar. The growth on the mediums with a high percentage of serum and the mediums cultivated under anaerobic conditions developed more slowly, was butter-like in consistence and was composed almost entirely of large, round, yeast-like bodies.

Hanging drop cultures showed branching septate mycelium with the development of a large spore within a long mycelial thread, but much more frequently these spores were found within and at the end of a short mycelial branch. The surface of the spore was at first smooth, but later it took on a distinct spiculated appearance. Conidiospores were observed and there was no dissemination, indicating that the spores were well contained within the mycelial threads. Round, hyaline bodies, which were quite uniform in size and appeared as spores, were frequently seen within these large chlamydospores. They disappeared upon heating and absorbed fuchsin and sudan III. We were convinced of their lipoidal nature. These globules were especially abundant in cultures containing serum or those grown under anaerobic conditions. None of the globules survived fixation and staining methods.

Colonies grown directly on cover glasses showed a thallus of delicate mycelium. The flexibility of the filament is interpreted by the way its direction of growth is diverted when it encounters even the smallest particle on the cover slip. When a mycelium branches, the angle formed between the two mycelial threads is usually more than 45°. Usually after 10 days the large spiculated chlamydospores develop within and at the ends of the short lateral branches near the

center of the thallus. These spores extend peripherally as the thallus grows. After 3 weeks spores are about all that is left of the thallus. The mycelia are for the most part degenerated.

The mycological study in our case included a consideration of the various organisms which appear in tissue as yeast-like bodies. Leishman-Donovan bodies, Darling's *Histoplasma capsulatum*, *Oidium gilchristii*, *Monilia albicans*, *Coccidioides immitis*, *Torula histolytica*, *Phialophera verrucosa*, and the organism of pseudofarcy were compared with our organism. It appeared somewhat like Leishman-Donovan bodies in tissue. Giemsa's stain failed to bring out a kinetic nucleus. Unlike the organism of leishmaniasis, it was not pear-shaped and the chitinous cellulose material about the nuclear substance indicated a fungus rather than an animal parasite. The size of the organism in our case suggested the *Histoplasma capsulatum* of Darling, more than any of the above mentioned yeast-like organisms. It was much smaller than the other yeast-like bodies which appear in tissue. However, in the case here reported, there was no involvement of the spleen and the organism was culturally unlike the organism of pseudofarcy which has been presumed to be similar to Darling's *Histoplasma capsulatum*. The cultural characteristics were also quite unlike any of the above named organisms which appear in tissue as yeast-like bodies.

## Animal Pathogenicity

Inoculation of macerated skin and lymph nodes into the peritoneal cavity of mice and guinea pigs produced no disease. The inoculation of guinea pigs and rabbits subcutaneously with the isolated fungus resulted in local lesions after 7 days. The lesions progressed for 7 days, when definitive evidence of regression was noted. The animals were killed after approximately 4 weeks. The organism was still alive in the lesion but there was no dissemination of the infection and it seemed definite that the lesions would have healed in these animals. The dog and the rat developed progressive lesions. The animals were killed, but judging from the extensive lesions in the lungs, spleen, adrenals and liver, it appeared relatively certain that these animals would have died of their generalized infection. The small yeast-like bodies were found in the granulomatous lesions of these experimental animals. Pure cultures of the yeast-like organism were isolated from the lesions 3 to 4 weeks after the inoculation of the animal.

## Summary and Conclusions

A case of a chronic infection produced by a yeast-like organism belonging to the genus *Sepedonium* has been reported. The infectious agent was apparently localized in the skin and the regional lymph nodes for a period of about 15 years. The skin was thickened and scaly throughout the course of the disease, except during the last 3 months of life when the characteristic papular lesions developed. It is possible that this fungus infection could have been a secondary infection ingrafted upon a non-specific scaly dermatitis, but the presence of the yeast-like organism in the skin and lymph glands for at least a year and a half before the lesions became papular, and the fact that the enlargement of the lymph nodes was an early observation, make this possibility seem quite improbable. It is our opinion that the disease was initiated by the fungus.

The appearance of the organism in tissue, the large spiculated chlamydospores on artificial culture medium and the animal pathogenicity of the organism are the characteristic features by which subsequent cases may be recognized.

The infecting organism is similar in the chronicity of the infection it produced, the macroscopic appearance of its growth upon artificial culture medium and the formation of spores upon lateral branches to the so-called oidium mentioned in medical literature. However, the large spiculated spores, the delicate mycelium and the animal pathogenicity are distinctly different from the *Oidium gilchristii*.

Although we appreciate that the taxonomy of this large group of imperfect fungi, to which this organism belongs, is artificial and often very unsatisfactory, it would appear that this organism could not be more satisfactorily classified for the present than with the genus *Sepedonium*, since no spore formation from the copulation of hyphae was observed.

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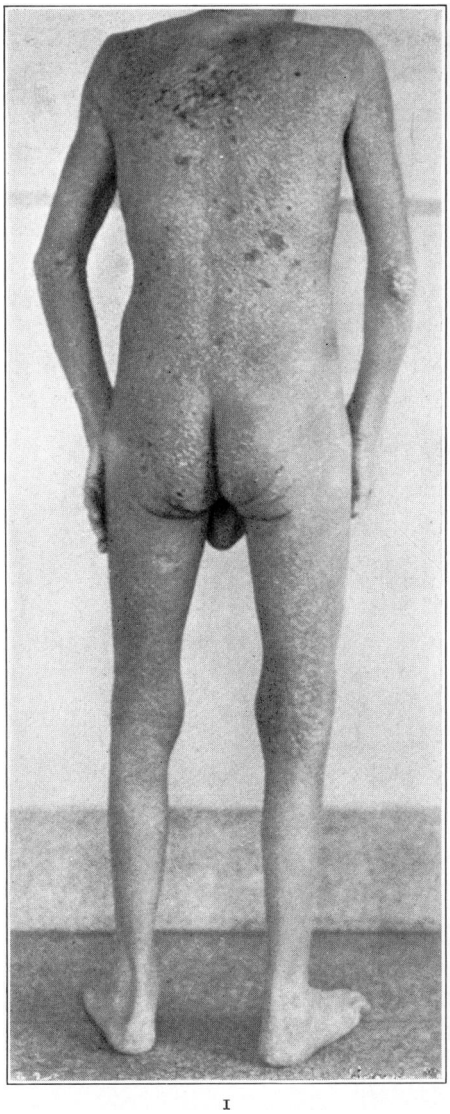
## Description of Plates

### Plate 158

Figs. 1 and 2. Photographs showing the distribution and nature of the skin lesions.

Fig. 3. Photograph of the thickened, wrinkled, scaly skin which shows many papules with crater-like ulcerations of their summits.



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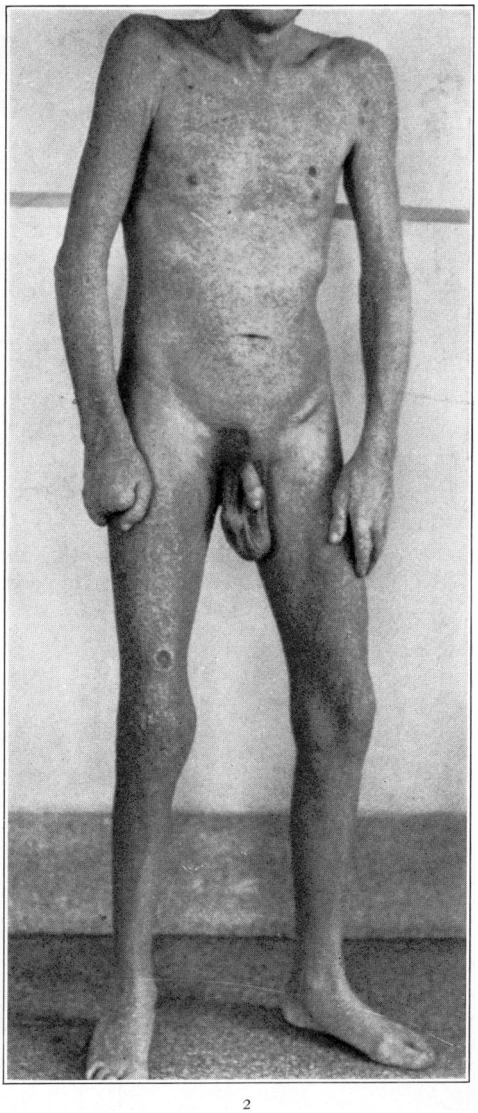

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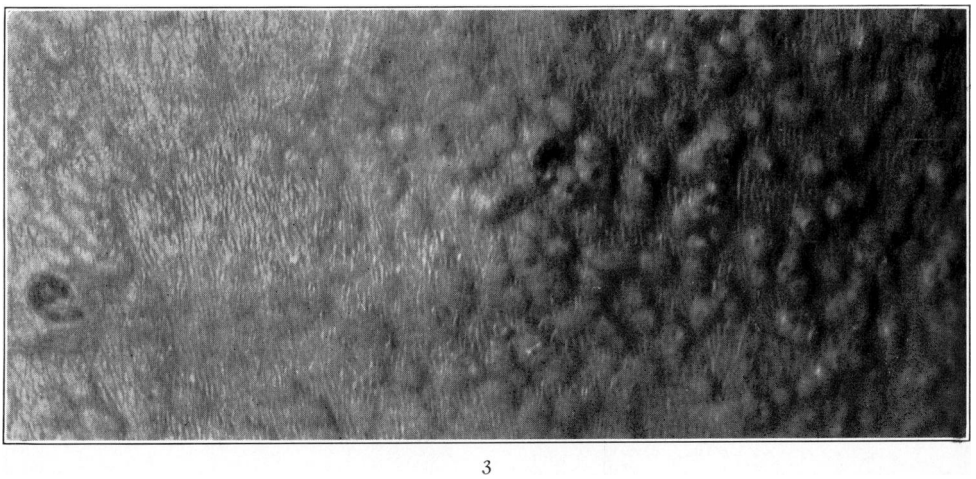

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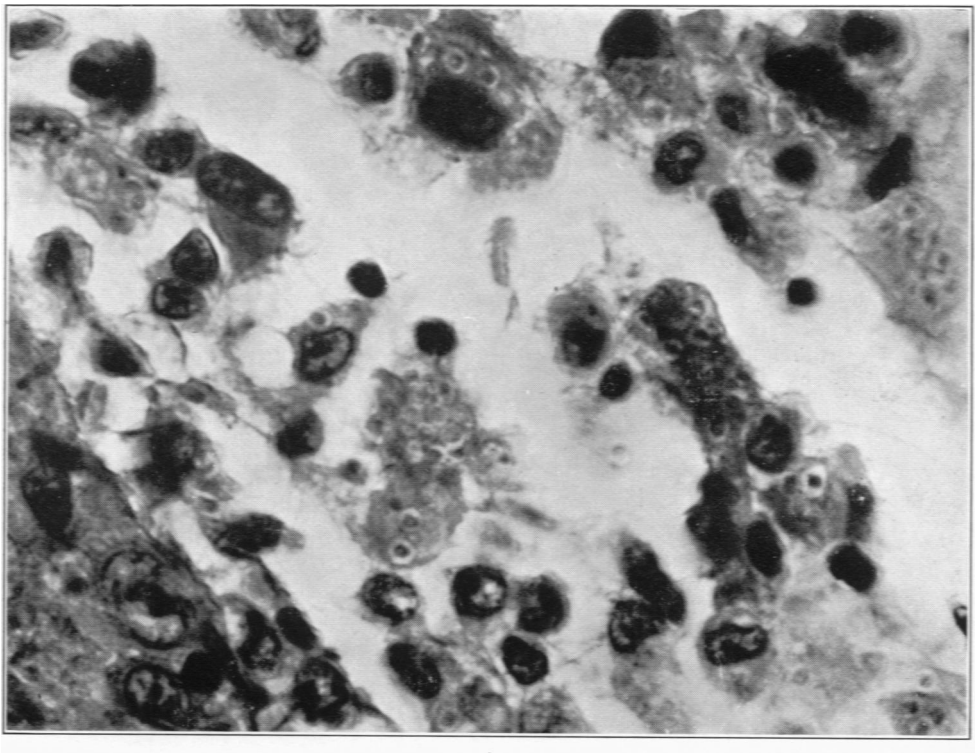
Hansmann and Schenken Infection Caused by New Yeast-Like Organism

## PLATE 159

FIG. 4. Photomicrograph of the yeast-like organism in the large mononuclear cells in the corium of the skin. × 1200.

FIG. 5. Photomicrograph showing the large, thick-walled, spiculated chlamydospores which are so characteristic of the organism upon artificial culture medium. × 1200.



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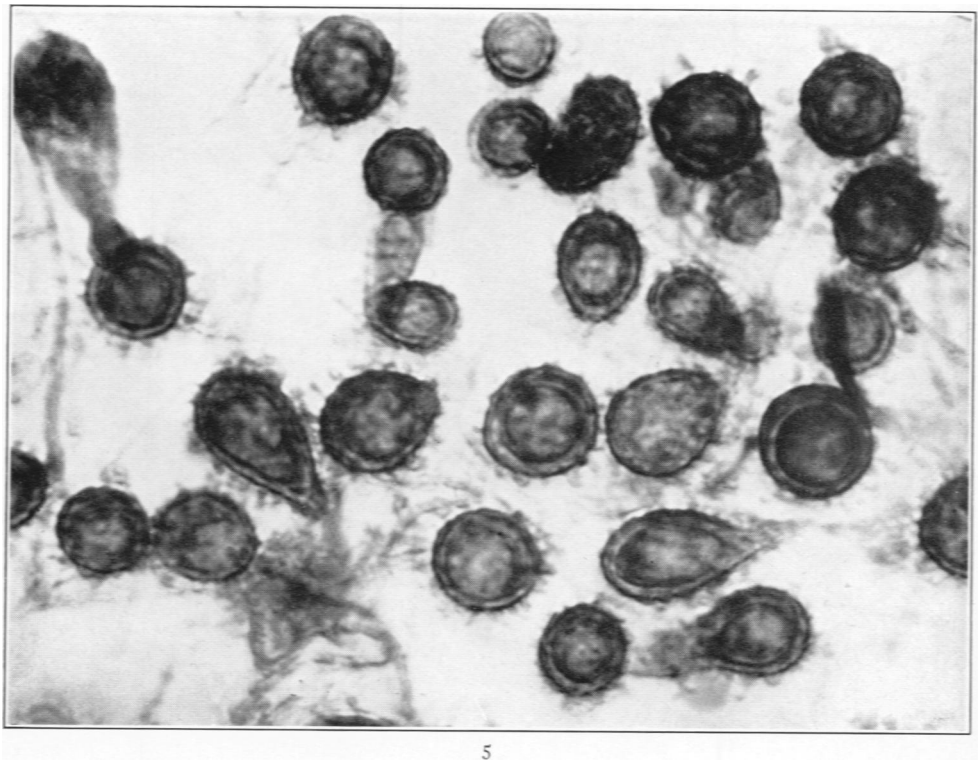

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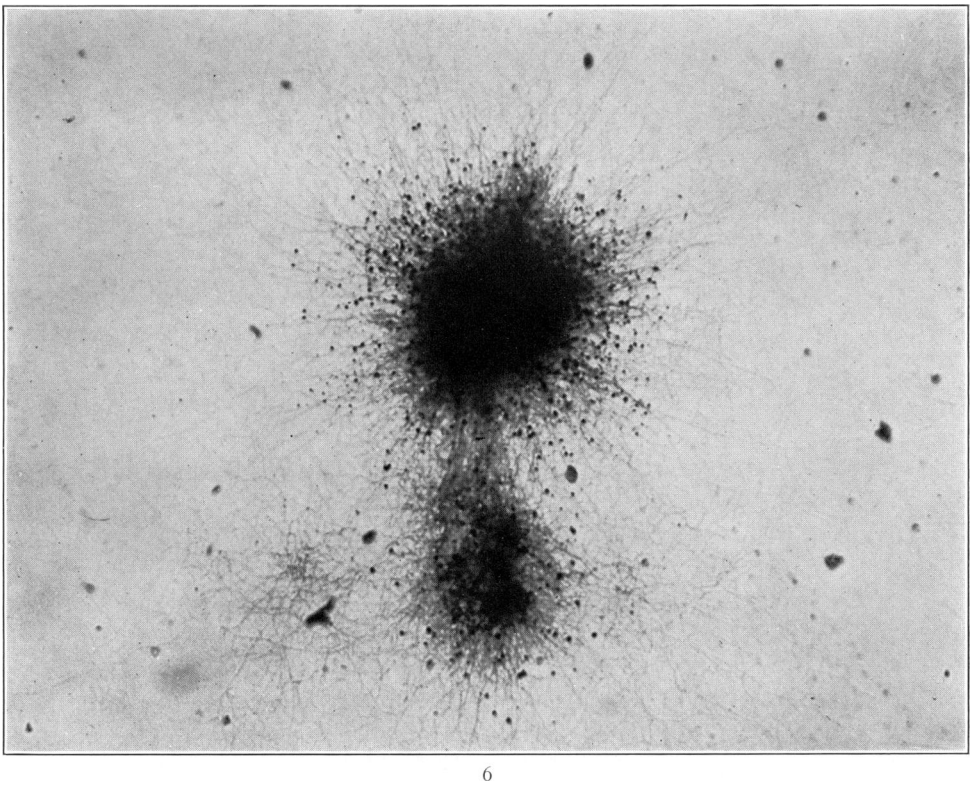
## PLATE 160

FIG. 6. Photomicrograph of a thallus of the organism grown on a glass slide. Note the large spores near the center of the thallus and the delicate, tangled mycelium. × 60.

FIG. 7. Photomicrograph of the adrenal of the human showing an area of caseation necrosis in which many organisms were found. × 70.



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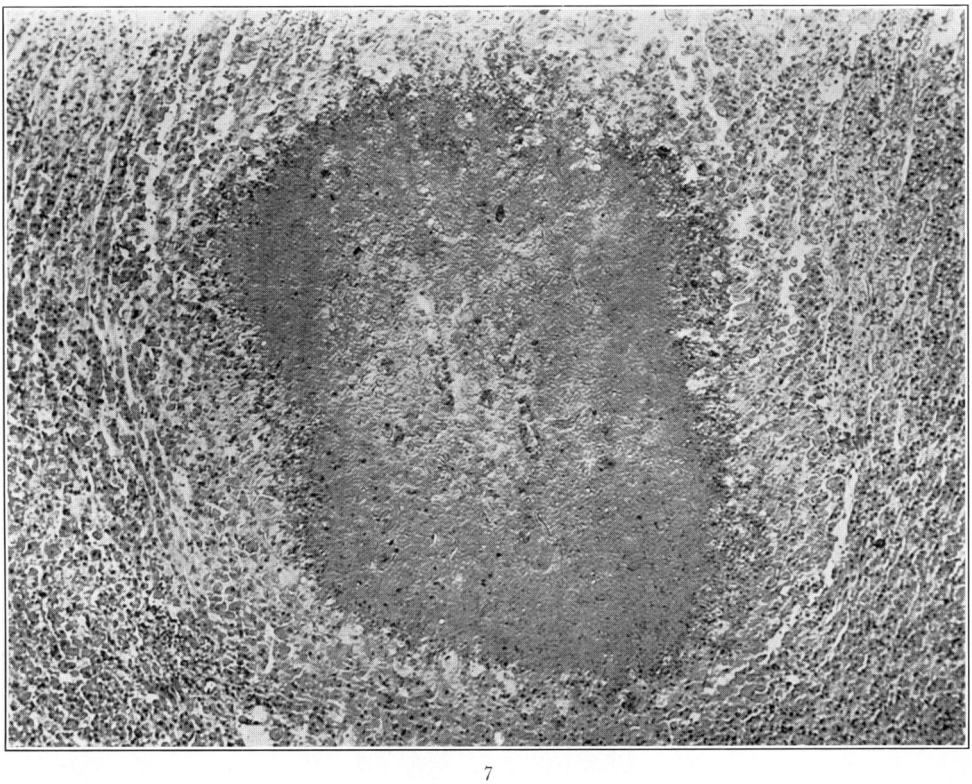

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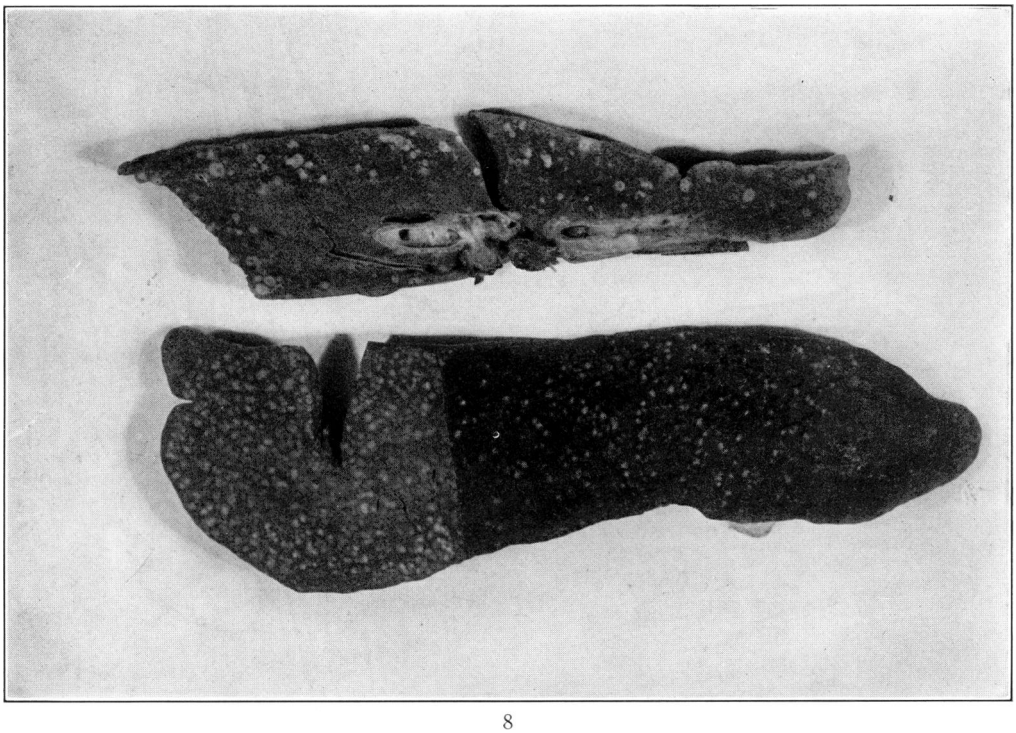
PLATE 161

FIG. 8. Photograph of the lesions in the lung and the spleen of the dog inoculated with the organism.

FIG. 9. Photomicrograph of the lung of a dog showing a granulomatous lesion of the disease. × 60.



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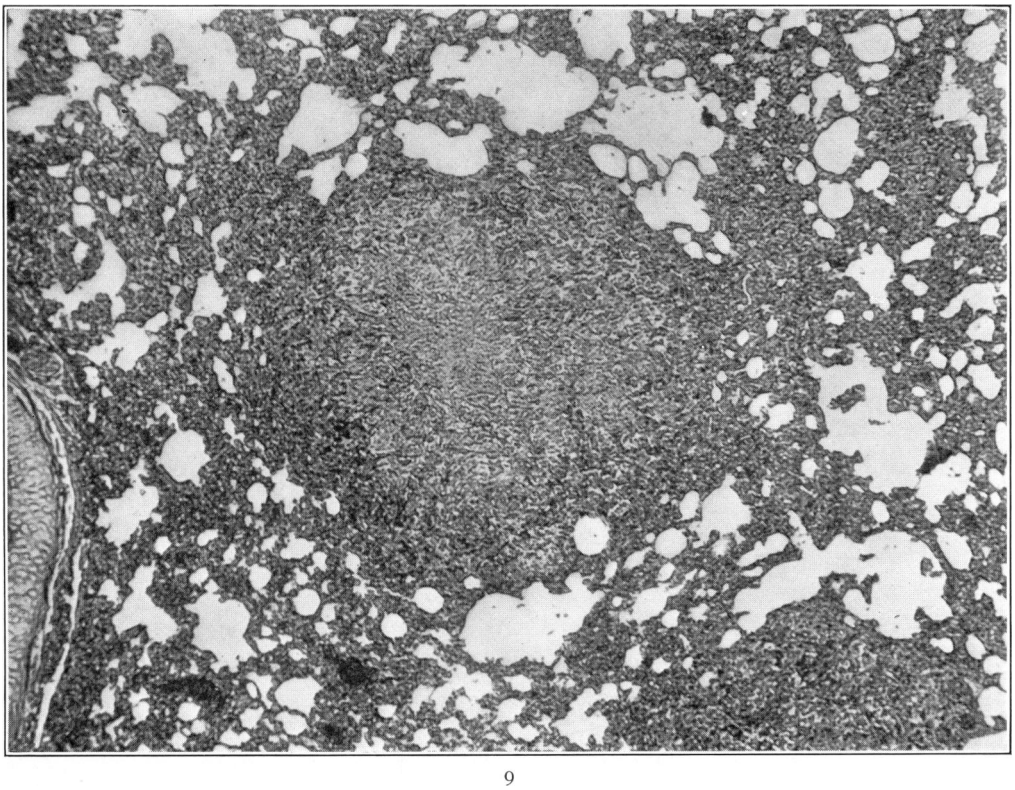

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Hansmann and Schenken Infection Caused by New Yeast-Like Organism