

SYSTEMIC BLASTOMYCOSIS (OIDIOMYCOSIS)

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IN 1894, Gilchrist¹ described before the American Dermatological Society, a yeast-like organism which he found in a section taken from a patient with an unusual dermatitis. He classified the organisms as blastomycetes and named the disease blastomycetic dermatitis. A few months later, Busse² described a fatal case and demonstrated the pathogenicity by finding the organism in the internal organs as well as in the skin. He termed the disease saccharomycosis hominis. The bacteriological and clinical features of these two cases are quite identical with those subsequently reported by various men as blastomycosis or oidiomycosis.

The following case is described as a fatal case of the systemic disease, and is unusual because of the small amount of pathology found in comparison to the symptoms.

Clinical History.—A. B. S., age twenty-seven, male, American. First admission March 28, 1922. Discharged May 26, 1922. Admitted again January 3, 1923. Died March 7, 1923.

There was nothing of interest in his family history. He denied luetic infection, but admitted gonorrhœa four years previously. For two years prior to admission he had been employed as a miner in an Illinois coal mine. The onset of his disease dated back to March, 1921, (a year before admission) when he mashed the fourth finger of his right hand. The resulting injury remained a granulating ulcer for 10 months. A few weeks after this injury he became aware of pain in his lumbar spine. Two months after onset of his lumbar pain, he noticed a fluctuating lump in his lumbar region, which was incised and had drained continuously up until admission. A few weeks after incision of this abscess there developed skin lesions, in order of appearance, on the back of his neck, over the right shoulder, on the left buttock and on the right leg.

November, 1921, patient developed a cough which gradually increased in severity, and which was productive of a blood-stained, muco-purulent, grayish-brown sputum. Associated with this he had a definite but slight shortness of breath, but scarcely any pain. About March 5, 1922, (three weeks prior to first admission) he developed a soft fluctuating mass over his right jaw. At about the same time his scrotum began to swell, and two weeks later a sinus developed on the right side. He had lost about 30 pounds of weight since the onset of his disease, and was bedridden at the time of admission.

Physical Examination.—The patient is a well developed, but moderately emaciated and anemic middle aged man. Over the occipital region, left scapular region, left posterior thorax and right buttock are skin lesions varying from 8 to 16 cm. in diameter (Fig. 1). Each lesion has a red irregular cauliflower-like surface, which bleeds readily. The base is reddened and elevated. The centre

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of some lesions show scarring of recent healing. Mild discharge, but no deep ulceration is present. Fresh lesions first show up as small papules or pustules which later coalesce to form the cauliflower-like mass.

Just to the left of the spine of the 5th lumbar vertebra is a mass of granulations (2 cm. in diameter) with a draining sinus in the centre. Within one to two cm. of the edges of the various lesions are tiny miliary abscesses, some of which can scarcely be seen with the naked eye (Fig. 2).

Over the ramus of the right jaw and adjacent tissue is a tense, smooth fluctuant



FIG. 1.—Appearance of skin lesions on neck and shoulder at time of first admission before treatment was started.

mass 5 x 8 x 10 cm. Pus is present and feels superficial. Only slight tenderness is present. On account of this abscess, he is not able to open his jaws more than 1 cm. Below the above mass is a nodular mass suggesting numerous small lymph glands matted together.

Respiratory excursion of the right side of the thorax is distinctly less than the left. Breath sounds are harsh over the right upper lung, where the percussion note is impaired. A few crepitant râles are heard here and at each base.

The liver is palpable 5 cm. below the costal margin and is very tender. The splenic dulness is increased.

There is a discharging sinus over the right epididymis which is 5 cm. in diameter, firm and tender.

A recently healed ulcer is noted on tip of the fourth finger of the right hand at the site of his initial lesion. Definite but slight tenderness is made out over the spines of the 3rd and 4th lumbar vertebræ.

Laboratory Data.—Erythrocytes, 4,600,000. Leucocytes, 12,000 to 25,000. Hæmoglobin, 80 per cent. Differential count: Polymorphonuclear neutrophiles 60 per cent. Lymphocytes, 35 per cent. Large mononuclears, 3 per cent. Eosinophiles, 2 per cent.

Phenolsulphonaphthelein kidney test 75 per cent. in 2 hours. Blood Wassermann

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negative. Sputum:—Consistently negative for tubercle bacilli. Complement fixation for tuberculosis negative.

Urine: Faint trace of albumin. Few white blood cells, no red blood cells. Few granular casts.

Blood culture negative. Culture of aspirated pus from abscess of jaw, hemolytic streptococcus. Culture from miliary abscess of neck, blastomyces.*

Stool: Red blood cells found during attacks of diarrhoea. Benzidin consistently positive. Frequent yeast-like organisms, having a double contoured surface, which, however, could not be established definitely as blastomyces.

X-ray studies of the gastro-intestinal tract were made by Doctor Mills who



FIG. 2.—Skin lesion on buttock before institution of treatment.

reported an unusual gastritis, characterized by massive gastric rougæ.

Course During First Admission.—(March 28, 1922, to May 26, 1922). The patient's temperature persisted irregularly around 100°. Pulse 90 to 110. The abscess of the jaw, was incised shortly after admission, and thin greenish pus obtained. The abscess cavity healed very slowly. He was put on intensive potassium iodide treatment, and was able to tolerate 150 grains per day. One heavy dose of X-ray therapy was given over two of the lesions, but no difference could be seen in the rapidity of healing. Under iodide treatment, his lesions began to heal remarkably fast, and at the time of his discharge, the cauliflower-like granulations had been replaced by a scaly scar which seemed to progress from the centre outward. Over a period of a few days he complained of intense epigastric pain, but without any signs of peritonitis. He was confined to bed when admitted, but regained his strength rapidly and at the end of four weeks was walking around without discomfort.

Microscopical and Cultural Characteristic of the Organism.—Smears were made repeatedly from the various open skin lesions and the sinus over the back,

*Credit is due Miss Ludwig of the bacteriological laboratory of Barnes Hospital, for assistance with the cultures.

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but only occasionally, could one find unquestionable blastomyces. From the miliary abscesses, however, smears consistently yielded a moderate number of organisms and produced a pure culture of blastomyces.

On the third or fourth day of incubation tiny colonies of the yeast could be seen on the surface of the media. These colonies were heaped up, wrinkled, had irregular edges and were of a dark gray color. They grew equally well on blood agar and glucose agar, but seemed to produce a heavier and earlier growth on Russel's media than upon any of the others tried. In broth a granular cloudiness developed in five or six days and by the end of twelve days a grayish granular precipitate of the organisms was formed. As the culture on solid media aged, the color of the growth became darker. When the culture tube was sealed, thus restricting air, the organism invariably formed aerial hyphæ within three weeks, and in gross appearance greatly resembled a mould.

Microscopically, the organism was seen in tissue only in the budding form. Likewise, the minute colonies obtained by transplant directly from patient to media, consisted almost entirely of budding forms for the first few days. As the culture aged, however, mycelia appeared and became more predominant as successive transplants were made. It was also noted that unfavorable conditions during incubation, such as low temperature or dry media tended to produce more and thinner mycelia threads.

The organism in the budding stage is 8 to 18 μ in diameter, is round or slightly oval, and is doubly contoured. No nucleus can be definitely identified, but the protoplasm is coarsely granular and contains highly refractile bodies. Occasionally, vacuoles are seen. The terminal or younger mycelial segments are more homogeneous and contain fewer granules. As the culture ages, there is an increasing tendency toward formation of terminal and lateral conidia which are connected to the main stem by short thick pedicles.

The organism produced no gas in either dextrose, lactose or saccharose broth.

Animal Experiments.—The organism proved consistently pathogenic to guinea pigs. Five were injected intraperitoneally, all of which died in about four weeks. Organisms were demonstrated either in culture or section in all but the first. A mouse which was injected intraperitoneally died in 24 hours, but no organisms could be found. One rabbit was injected intraperitoneally but showed no evidence of disease. In none of the guinea pigs were tuberculous lesions found.

Progress Since First Admission.—On January 3, 1923, seven months after discharge, he was admitted again. He volunteered the information that he had stopped the daily dose of iodide several times, for periods of 2 to 3 weeks, and

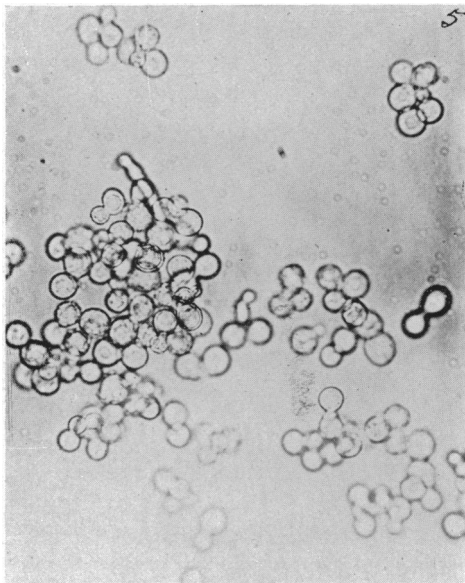


FIG. 3.—Culture four days after transplant from minute abscess to blood agar, showing predominance of budding forms.

had suffered from appearance of new lesions and general ill health. During the last four weeks previous to second admission, he had three convulsions of a generalized type. Two weeks before second entry, his scrotum and ankles began to swell. He had been gradually losing weight.

Examination showed the lesions to be dried but scaly as at discharge of first entry. Scattered over the body were several small fluctuant superficial abscesses, which contained thin greenish pus, in which blastomycetes could be found. The sinus of the epididymis had healed, but the sinus over the 4th lumbar vertebra was still draining. There was marked œdema of the ankles and scrotum, as well as

fluid in his peritoneal cavity. The lung findings remained practically the same.

In addition to heavy doses of potassium iodide by mouth, patient was given several intravenous doses of 50 to 75 grains of sodium iodide. He also received several doses of salvarsan. From none of these procedures did he receive any beneficial effects. He became very weak and died apparently from toxemia on March 7, 1923.

Organisms were again found in his sputum, but were not

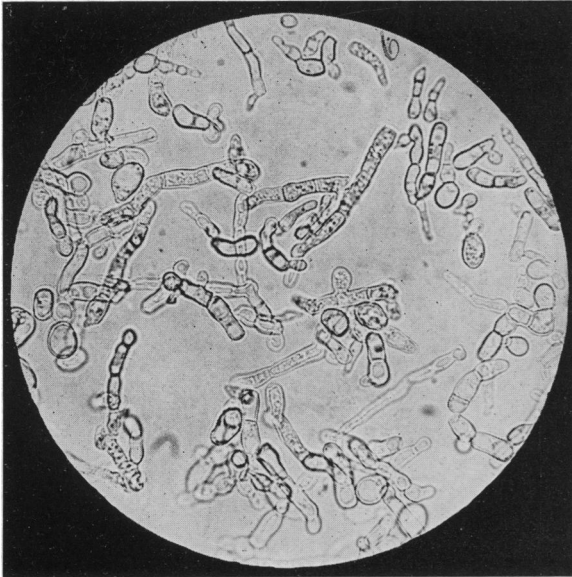


FIG. 4.—Appearance of culture after several transplants. Note predominance of mycelial forms. Occasional terminal and lateral conidia are seen.

demonstrated in the urine as they were on his first admission. His N.P.N. remained normal. Urine gave a very heavy test of albumin and contained many casts, a very few of which were waxy. Blood culture remained negative. Sputum and urine cultures negative for blastomycetes. X-ray of lumbar spine revealed a destruction of the fourth lumbar vertebra, as contrasted to negative bone findings on the last admission.

Autopsy Report.—(By Dr. E. S. Walsh). The body is that of a poorly developed and nourished white male weighing fifty-seven kilos and measuring 154 cm. in length.

Numerous foci are scattered over the body surface in the skin. Possibly the largest is situated over the right scapula; another very large one over the left tibial region. Small suppurating lesions are seen in both groins and over the right scapulo-humeral joint. Pressure on any of these lesions yields a thick creamy pus. The general character of all the lesions is much the same in that there is an elevated nodular periphery with a smooth scar-like centre. Crusts are heaped up in places, and over the suppurating lesions the skin is so thin in places that slight pressure causes rupture with discharge of thick creamy pus. The skin of the scrotum is greatly thickened and indurated and several excoriated areas are seen upon it.

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On opening the head a rather noticeable engorgement of the vessels of the pia arachnoid is seen and there is some œdema.

There are about 2000 c.c. of cloudy fluid in the peritoneal sac. This does not coagulate on standing, but fibrin threads are present in considerable numbers.

The pericardial sac also contains some cloudy fluid and there is a white scar in the epicardium of the right auricle.

The *heart* weighs 220 gms. and the valves measure as follows:

A	7.00 cm.	M	10.0 cm.
P	8.0 cm.	T	11.0 cm.

The left ventricular wall measures 12 mm., the right 5 mm. The myocardium is of a deep red color. The heart is dilated with fluid and clotted blood.

The *lungs* do not collapse when the chest is opened and the right one is loosely bound to the chest wall by delicate fibrous adhesions. Great numbers of shot-like nodules are scattered throughout all lobes of both lungs. In places these nodules have aggregated themselves to form foci of considerable size (2 to 3 cm. in diameter). On section these lesions are only distinguished with considerable difficulty. The places where large numbers of them have gathered together appear as deep red irregular areas. (Lungs fixed for future study.) There is a fibrous lesion at the right apex.

The *liver* is large, pale and smooth, and irregular areas of necrosis are scattered throughout. It weighs 2150 gms. and measures 27 x 19 x 8 cm. There are many spots on the cut surface which have a pale waxy appearance. These are stained brown by iodine but not very distinctly. The gall-bladder is greatly distended with fluid bile which can readily be expressed into the duodenum.

The *spleen* is very large and firm and divided into three lobes by two notches. On section, numerous waxy foci are seen scattered throughout the pulp. These do not seem to bear any definite relation to the Malpighian corpuscles as they are located both within and outside the waxy areas. They are stained brown with iodine. The spleen weighs 530 gms. and measures 15 x 11 x 6.5 cm. Several sharply encapsulated tubercles are found in the pulp and one upon the surface of the organ. The pulp outside of the pale waxy appearing foci is rather bright red in color. The capsule is thickened in several places. In addition to the lesions already described there are many very minute gray opaque areas which have a tendency to occur in clumps. These cannot definitely be differentiated from Malpighian corpuscles.

The *pancreas* appears normal. It weighs 135 gms. and measures 23 cm. in length.

The *right kidney* weighs 360 gms., the left 280. One measures 13 x 8 x 4 cm.,

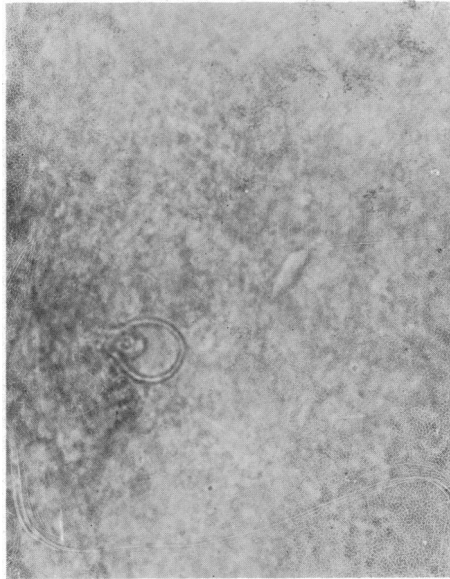


FIG. 5.—High power of a budding organism in the lung of guinea pigs injected intra-peritoneally with the organisms.

cortex 9 mm. They are pale and smooth. The capsules are rather firmly adherent to them and they seem to be very thin. The surface as well as the cut surface is irregularly mottled by small grayish-white opaque areas. The *adrenals* appear normal. The *pelvic organs* appear normal.

Microscopical Examination.—*Myocardium* appears normal. *Lung*: The histological appearance is that of tuberculosis with the following exceptions. Small aggregations of polymorphonuclear leucocytes, sharply circumscribed, are frequently seen and often form the nucleus of what otherwise would appear to be typical tubercles. Giant cells of the type usually associated with tubercles are abundantly formed in and around the lesions. Yeast cells are present but in very

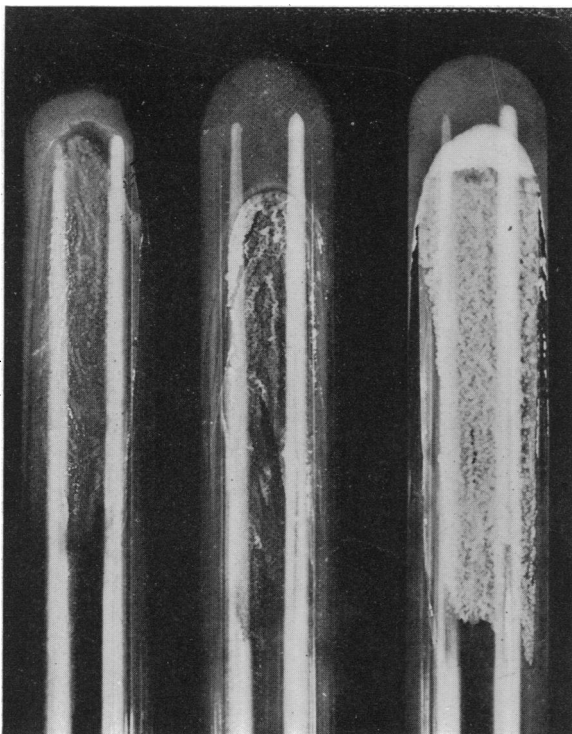


FIG. 6.—Culture two weeks of age. From left to right, glucose agar, Russel's media and blood agar.

scanty numbers, and when found are either in the small polymorphonuclear accumulations or in the giant cells. A few budding forms are found. There is some necrosis but little or none of the dead material has the typical appearance of caseous tuberculous tissue.

Liver: A few focal accumulations of mononuclear leucocytes are seen in the periportal areas. The sinusoids are dilated. Amyloid is deposited rather abundantly in the walls of some of the small vessels. The dilatation of sinusoids is most conspicuous at the centre of the lobules and is accompanied by a moderate amount of atrophy of liver cells.

The *pancreas* appears normal.

The *spleen* is heavily loaded with amyloid which occurs both in and around the Malpighian corpuscles. In the former case the lymphoid elements of the corpuscle are completely replaced by it. The walls of the small blood-vessels are conspicuously involved.

Kidney: There is an abundance of homogeneous material in the glomerular tufts, glomerular vessels, and the walls of many of the larger vessels. This material is stained brown by iodine and red by methyl violet. Hyalin tube casts are frequently seen.

Adrenal: Amyloid seems to be abundantly deposited.

Skin: There is a marked epithelial hyperplasia with numerous papillary downgrowths into the corium. The surface in many places is ulcerated. The corium likewise is thickened and contains numerous plasma cells. Scattered

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about in the corium, adjacent to the distorted finger-like processes of the epithelial layer, are numerous irregularly shaped islands of epithelium. Throughout the entire section, and especially prominent in the Malpighian layer of the epidermis are numerous minute abscesses of varying size. Some abscesses contain only a half dozen or dozen leucocytes; others are large enough to be visible to the naked eye. A relatively large percentage of the polymorphonuclears are eosinophils. In addition to the polymorphonuclear invasion, there is a diffuse mononuclear infiltration. Throughout the section, especially notable in the miliary abscesses, are a moderate number of giant cells. Typical blastomycetic yeast cells, of a

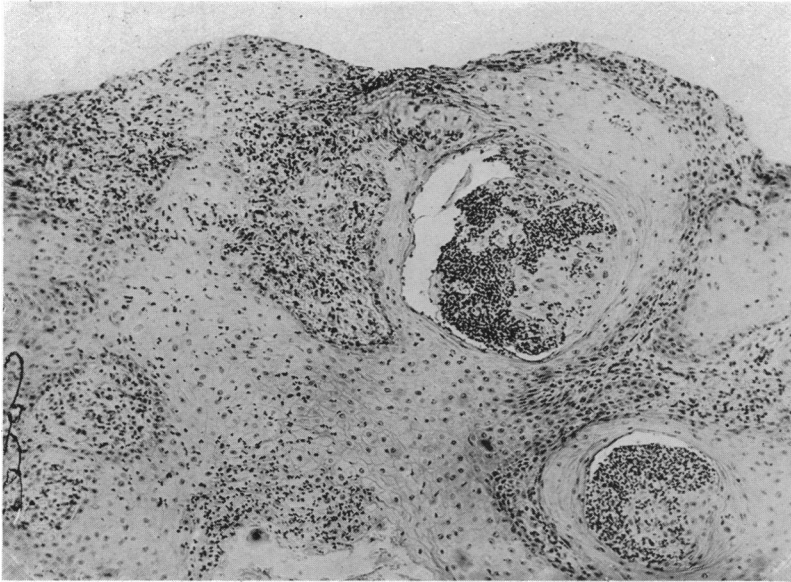


FIG. 7.—Low power of section of patient's skin showing miliary abscesses and hyperplasia of epithelial cells.

description found elsewhere, are seen throughout both layers of skin, usually in the miliary abscesses and frequently in the giant cells.

A set of sections stained with carbol fuchsin and methylene blue are negative for acid fast organisms.

The *brain* upon cut section reveals no abscess cavities or evidence of inflammation. Culture of heart's blood yielded a hæmolytic streptococcus, but no blastomycetes.

Clinical and Pathological Diagnosis.—Pulmonary and cutaneous blastomycosis, blastomycosis of 4th lumbar vertebra, general amyloidosis, fibrino-purulent peritonitis, fibrino-purulent pericarditis, œdema and congestion of pia arachnoid, blastomycosis of epididymis (healed), abscess of jaw, secondary anemia and hæmolytic streptococcus septicemia.

Remarks.—As stated, the peculiarity of this case is the scarcity of lesions found at autopsy as compared to the clinical symptoms. However, the organs affected, including lungs, bone, skin, and epididymis represent common locations for disease, excepting the latter. From a review of twenty-two autopsied

cases, Wade and Bel³ found the organs affected in order of frequency were lung, skin, bone, spleen, kidney, liver, lymph-nodes and brain.

The pathology of the lungs on cut section resembled tuberculosis very closely, except as is usually the case in pulmonary blastomycosis, no cavities were found. The exception to this rule is found in a report by Irons and Graham⁴ of a case which had cavities in the lung.

Pathogenicity.—The portal of entry in this case is undoubtedly through a wound of the finger, sustained in an accident in a coal mine. It seems logical

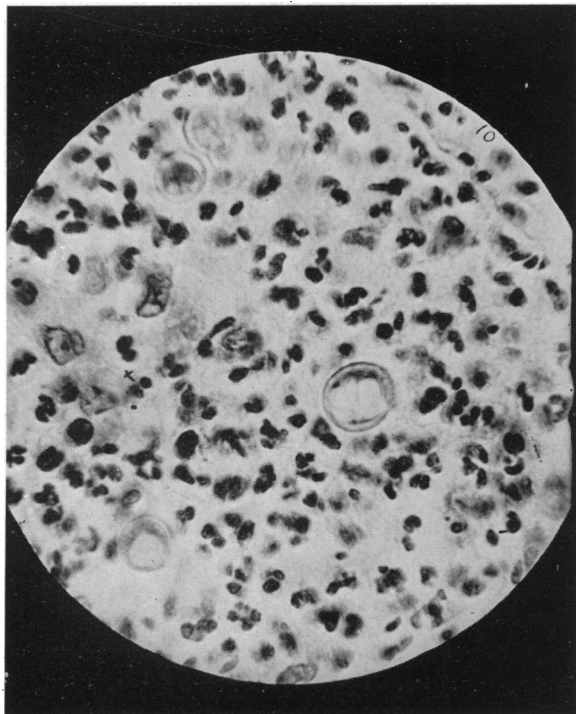


FIG. 8.—High power of a minute abscess containing several organisms. Note the presence of polymorphonuclear leucocytes.

to suppose the mine was the habitat of the organism, but we were unable to obtain history of any similar infection among the miners in this locality. All symptoms of this patient developed after this injury, which produced a stubbornly healing ulcer on his finger. Pulmonary symptoms did not develop until seven or eight months after his initial infection. Study of previously reported cases, however, supports the theory of pulmonary infection as the initial lesion. Montgomery⁵ reported a case whose first symptoms were pain in the chest and which at autopsy revealed blastomycotic abscesses in the lungs.

Christensen and Hektoen⁶ also report a case whose first symptom was pain in the chest. The majority of cases of systemic disease, however, gave a history of an initial skin infection.

Although frequent recoveries are encountered among the cases whose disease is limited to the skin, the fatality of systemic infection is almost absolute. Herrick,⁷ however, reported a recovery from systemic infection. A systemic case under the observation of Boughton and Stober⁸ also recovered, but under heavy vaccine therapy. Davis,⁹ however, offers evidence of a very poor immunological reaction, but he was dealing with a different strain of the organism. Although the disease is comparatively a rare one, no less than two physicians have suffered an infection by contact with infected patients.

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It is quite certain that the infection is a blood-borne disease even though the primary portal in some cases is the lung. Notwithstanding this certainty, it apparently is very difficult to demonstrate the organism in the blood stream. Krost, Stober and Moes¹⁰ observed one of the few cases from which the organism was obtained by blood culture.

Differential Diagnosis.—Undoubtedly, the disease is much older than records show, but was diagnosed wrongly, probably in most cases as verrucous tuberculosis. Most blastomycotic skin lesions develop faster than verrucous tuberculosis. The former will respond to iodide treatment whereas the latter will not. The pathology is very similar to tuberculosis but polymorphonuclear cells are more numerous than in a tubercle, and eosinophils are found in great numbers. The proliferation of epithelium resembles an epithelioma but the miliary abscesses, eosinophils and presence of organisms are distinguishing features. Syphilis rarely simulates it, and can be excluded serologically and by reaction to salvarsan.

Treatment.—This particular case was treated with iodides, salvarsan, X-ray and local application of mercurochrome. The beneficial value of the former is unquestioned, and was probably first used by Bevan. None of the others, except the local application of mercurochrome, which did stimulate scarring of the lesion, had any effect. Copper sulphate has been used for years both externally and internally but with very little if any beneficial effect. On account of the relatively slow growth of the local lesions, excision should be, and has proven to be a curative measure many times. Obviously, to be a suitable case for excision the infection must be confined to the skin and be accessible to the knife.

Classification.—Curiously, practically every organism reported differs in minor details from all the others. This makes it difficult to establish an accurate nomenclature. All of them, however, might be said to be double contoured yeast-like organisms having no definite nucleus, which reproduce in living animal tissue by budding only, and which under certain varying conditions will produce mycelia. One of the important points of difference between the different organisms reported, lies in animal experimentation. Most strains

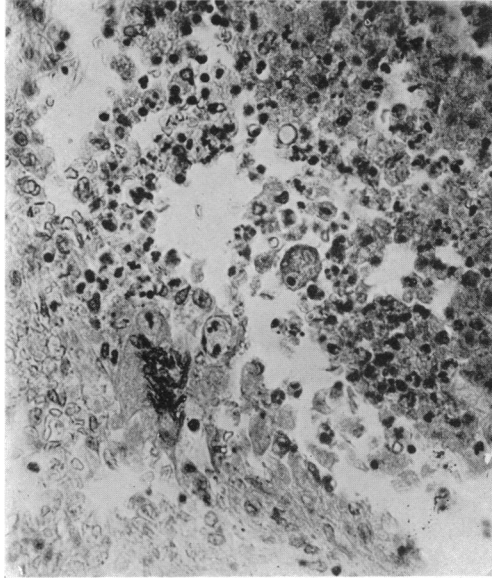


FIG. 9.—Moderately high power of miliary abscess containing a budding organism in the lung of the patient.

are pathogenic to guinea pigs, but Eisendrath and Ormsby¹¹ and many others report negative results from guinea-pig inoculation. An interesting discovery that female guinea-pigs are practically resistant to infection was made by Davis and may in some instances account for negative results.

An organism producing a disease very similar to blastomycosis was described by Rixford and Gilchrist¹² and named *coccidioides immitis* on account of a very slight similarity to coccidia. The striking difference between this organism and the blastomycete lies in its reproduction by sporulation. In many cases, it is difficult to determine whether the causative organism is a blastomycete or the coccidioidal organism. The clinical features are very similar to blastomycosis, but the prognosis is even more serious than in blastomycosis.

On account of the varied cultural characteristics, it has been hard to select a terminology which will include all the various strains of blastomycetes. In view of the fact that a true blastomycete reproduces by budding only, I would prefer to classify these organisms as oidia and call the disease oidiomycosis, especially since oidia present at least a few budding forms. Ricketts¹³ has very satisfactorily divided them into three groups:

1. Blastomycetoid, reproduces by budding, but may produce mycelia.
2. Oidium-like, form submerged mycelia which break up into chains of "spores." Occasional budding form.
3. Hyphomycetoid, produces serial hyphæ in addition to having characteristics of the first two.

Whitman¹⁴ has very aptly classified all coccidioidal as well as blastomycotic cases as *Zymonema*.

Under any circumstances it is an evident fact that the organisms form a stepping stone between the yeasts and hyphomycetes.

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