BLASTOMYCOSIS: REPORT OF A CASE, WITH A STUDY OF AN ETIOLOGIC FACTOR AND A CLASSIFICATION OF THE ORGANISM

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Introduction

It is the purpose of this paper to describe briefly the disease known clinically as blastomycosis, and to try to clarify the recognition of the organism involved. The literature of the field is at present too extensive for an entire review, and since numerous workers have already given excellent discussions on the clinical aspects of the infection, as to its gross pathology, microscopic histo-pathology or cellular reactions, and the biological or rather immunological phenomena, a review would be unnecessary here. However numerous such papers may be, there is still much work to be done on the subject.

The author has attempted to clear up, at least in his own mind, several undecided points in the disease: first, the establishment of the etiological agent of blastomycosis; second, the determination of the exact classification of the organism. In the past, and even at the present, medical men have grouped under one general heading all organisms which were responsible for the same clinical condition. Good as this system may be for general diagnosis, much difficulty is encountered because of the fact that physicians are inclined to devote very little time to a study of the organism, thus rendering any therapeutic measures, if available, indefinite, inasmuch as several of the fungi present varying degrees of pathogenicity and require different therapeutic measures.

Thus we find that numerous species of the genera *Saccharomyces*, *Monilia*, *Cryptococcus*, *Endomyces*, *Sporotrichum*, and others have, at one time or another, been considered etiological agents of blastomycosis. A review of the history will illustrate these facts.

History

Years before the first case was definitely described as blastomycosis, investigators had performed a certain amount of work on

fungi involved in cases of infection and had established these organisms as etiological factors, particularly the yeast and yeast-like groups.

Chronologically, the list is quite long, but it is worthy of note. According to Hufschmitt, Sartory, Sartory, and Meyer ('31), we find that in 1845 Remak, and in 1853 Robin, in his 'Histoire Naturelle des Végétaux Parasites de l'Homme et des Animaux,' discovered the normal existence of the yeast *Cryptococcus guttulatus* in the rabbit intestine. A few years previously, Hannover (cited in Buschke and Joseph, '28) had found yeast in the urine of diabetic patients. Investigations then tended to turn to the parasitism of these organisms in animals, with the result that Bernard during the course of his work on fermentations attempted the first animal experiment by injecting beer yeast into these subjects. Following this work, Popoff, Grohe, Roussy, and several others showed the pathogenic actions of the yeasts on mammals, and Rivolta in 1873 in his 'Parasiti Vegetali' demonstrated for the first time a yeast infection in a horse. In the meantime, Metchnikoff and Weismann showed the parasitism of the Saccharomycetaceae in the lower animals. In 1892 Wernicke showed the first mycosis in man and named it "maladie protozoique de la peau." The following year Troisier and Achalme ('93) definitely established the relation between yeasts and man. In the meantime, several workers attempted to show the destructive ability of these organisms on the animal tissues. Popoff in his work had used dogs as his subjects, but impure cultures. Raum ('91) inoculated animals with large amounts of yeasts, and a rise in their temperature, shortness of breath, and death resulted. Neumayer ('91) fed animals with cultures and also inoculated them subepidermally. His feeding developed a gastro-enteritis which he believed due to fermentation, since the skin inoculations were of no value. The yeasts of these workers were probably of the non-pathogenic types, for L. Rabinowitsch ('96), a few years later, showed fifty various yeast-like organisms with seven pathogenic for animals. Nesczadimenko ('99) made peritoneal injections of yeasts in a physiological saline solution into rats, mice, guinea-pigs, and dogs, with death ensuing from eight to twelve days. He concluded, however, that these organisms were not so deadly, although causing this mortality.

The first actual case of blastomycosis, so-called, was reported by Gilchrist at the June, 1894, session of the American Dermatological Association. His paper resulted from the finding of peculiar yeast-like bodies in the diseased tissue of a patient. The doctor attending the patient had given the diagnosis as a typical case of chronic scrofuloderma. Several months after Gilchrist's report, Busse ('94) brought to light the extraordinary case to which he later gave the name "Saccharomycosis hominis." The patient was a woman thirty-one years of age who had suffered from a localized subperiosteal inflammation of the left tibia. An examination of the abscess, which opened spontaneously, revealed "numerous doubly contoured, very refractive, roundish and ovoid bodies," and these were found to be situated both intracellularly and extracellularly in the pus and abscess wall. These organisms when isolated in pure culture and then inoculated experimentally in animals proved to be what were later known to be blastomycetes. The patient later developed superficial ulcers on the face, subperiosteal swellings on the right ulna and the left sixth rib near the axillary line, with death ensuing. Busse cultured the yeast from the ulnar swellings and from the bottom of the ulcers.

Approximately two years later, the first case reported by Gilchrist was published in detail in the Johns Hopkins Hospital Reports of 1896. In the meantime, however, several others had noticed similar cases among guinea-pigs, horses, mice, and other lower animals (Sanfelice, '95, '96, '96a, Roncali, '95, Corselli and Frisco, '95, Tokishige, '96, and others).

In 1896, Curtis isolated a fungus similar to that described by the former writers from a myxomatous tumor of the leg. In the same year, Gilchrist, in conjunction with Stokes, published a short paper on a second case of blastomycosis, and this was published in detail two years later (Gilchrist and Stokes, '98). Simoni ('97), working on the diseased tonsils of patients, found budding yeast-like cells in twenty tonsils. Maffuci and Sirleo ('98) examined numerous tumors and found budding cells in a great number of tissues. Many other reports followed, as that of Hyde, Hektoen, and Bevan ('99) with a supplement by Hektoen ('99) later in the year, Hessler ('99) with a case report, and

several during the same year and 1900. In the following year appeared the elaborate work of Ricketts ('01), with a study of the organism from a case of systemic blastomycosis by Otis and Evans ('03). Eisendrath and Ormsby ('05) described a systemic infection, and Irons and Graham ('06) reported a severe generalized systemic disorder. Hektoen ('07) gave a comprehensive review of the literature, and from that time on the medical journals have published too great a number of cases of infection due to yeast-like organisms, under the heading of blastomycosis, to render a complete survey of literature a matter for a paper of this length.

Etiology and Clinical Manifestations

The disease known clinically as blastomycosis is very likely due to a plurality of organisms and not species of the same genus as indicated by previous writers. This is clearly evident as seen by the great number of papers published and the cases reported, involving such fungi as *Saccharomyces*, *Oidium*, *Monilia*, *Endomyces*, *Cryptococcus*, *Coccidioides*, and even such a form as *Sporotrichum*. The clinicians have referred to the category of blastomycosis any clinico-pathological condition which may be due to yeast-like or budding fungi. It must be understood, therefore, that the term as here used refers only to the clinical aspect of the condition.

In America, clinicians and medical men, more especially medical mycologists, are inclined to class as the cause of blastomycosis only that organism which was described originally by Gilchrist and Stokes in 1894 and in this view the author is greatly in accord. On the other hand, European workers consider only that organism which was reported by Busse ('94) and so elaborated on by Buschke ('98). However, by reason of priority, the organism of the former workers should hold the position so designated and be established as such. Further remarks on the Gilchrist organism will be found in the discussion.

Blastomycosis presents numerous clinical manifestations and in this respect it is protean, being found in practically every organ of the human body either in biopsy or autopsy material. No immunity towards the invading organism is established by any

of the anatomical structures. Clinically, the condition presents lesions which are alike both for the *cutaneous* type of the disease, that is that group of infections which may be found occurring superficially, or for the *systemic* type of the disorder, occurring in the lungs, bones, meninges, liver, or other viscera. This division is based on the work of Jacobson and his associates ('32), who further separate the cutaneous type into that of *primary* in character, as occurring in the epidermic layers or the cutis, as shown by Hagiwara ('22) and Hashimoto ('22), whose organisms, although not of the Gilchrist type yet coming under the general heading of blastomycosis as known clinically, also the work of Grschebin ('27); and *secondary*, due to an infection of the deeper tissues, internal viscera, or bony structures, as shown by Irons and Graham ('06), Ryerson ('09) for bones, and many others.

The *primary* form or the cutis infection Jacobson further designates as presenting one of three varied appearances: papulo-ulcerative; verrucous or papillomatous; gummatous.

The papulo-ulcerative type Jacobson designates as being initial lesions which are papulo-pustular in character and of epidermic origin (shown by Hessler, '99, Hektoen, '99, Ricketts, '01, Engelhardt, '24, and Fabry, '27, '28). These lesions rupture in the course of time and empty out the purulent exudate on the surface of the skin, with the probable ultimate formation of crusts. The process may be proliferative and involve a great area of the immediate vicinity. The lesions usually show a violaceous border with the involution of the peripheral surfaces and perhaps consequent scarring and atrophy.

The verrucous or papillomatous type (Froilano De Mello and Rodrigues, '29) is characterized as being nodular or papular in character and present on a normal or deep-red, infiltrated skin. Several of the lesions may coalesce to form papillomatous patches which resemble verrucous tuberculosis. These lesions may break up into healing areas which upon drying present irregular scars. The characteristic color as noted above is found here too, as well as the sloping periphery.

The gummatous type develops from the subcutaneous layers of the tissue of the deeper portion of the cutis in the form of small,

slightly elevated, somewhat tender, reddish, deep-seated, soft nodules situated on the characteristic violaceous-red surface of the skin. There is a diffusion of the color with subsequent establishment of new nodules in the vicinity. The nodules enlarge, become soft and gummatous, and then break down to form masses of ulcerative, proliferative materials bordered as in the other two types, and contain numerous abscesses.

The *secondary* cutaneous form consists chiefly of variously formed ulcers which give off a purulent or sanguino-purulent discharge from a soft, granulating floor. Some may develop crusts with raised edges, while some may assume hyperplastic functions with papillomatous characteristics, and usually there may be a metastatic action on the part of the ulcers represented by the formation of new lesions which are surrounded by a dark red or purplish zone. Healing may be spontaneous with indurated scars, as noted in some cases, or infection may persist but may finally succumb to treatment with iodides as was noted in the case reported here.

A study of the ulcers formed in blastomycosis shows them to originate in abscesses which from a clinical point of view can be divided into the superficial and the deep types. Secondary, cutaneous, superficial ulcers arise usually in the subcutaneous tissues as nodules of varying size as shown by Stober ('14), Engelhardt ('24), Ferguson ('28), and Montgomery and Ormsby ('08). These ulcers usually enlarge, rupture, and spread the material over the surface of the skin, setting up new foci, or in some cases they have been found to dry up and disappear.

The deep type of secondary cutaneous blastomycosis (Grschebin, '27, '28), characterized by smaller number and deep-seatedness, is by far the most serious of the two, involving destructive processes of the bone, muscle, and deep tissues and organs. It rarely shows any inflammatory reaction, but can be distinguished by the purulent character of the abscesses as contrasted with the mucoid or mucopurulent nature of the superficial abscesses.

The above types represent the typical forms occurring in a clinic. However, Weidman and Douglas ('21) reported the occurrence of a sarcoma-like tumor on the leg of a patient, which

looked like lupus vulgaris and yielded blastomycetoid bodies on histological sectioning. Then, about six years later, Cleland ('27) reported a case with the formation of a myxomatous-looking tumor mass which also showed typical cells on sectioning. These, however, are rare and until more cases are reported cannot be placed in the definite clinical types.

Under the heading of cutaneous blastomycosis, Castellani has also established principal types of blastomycosis of the cutis from a clinical point of view.

1. *Blastomycosis verrucosa* (Synonym: Blastomycosis, Gilchrist type).

Etiology: *Cryptococcus dermatitidis* Gilchrist and Stokes, 1896 (Synonym: *Cryptococcus gilchristi* Vuillemin).

Castellani here creates the genus *Blastomycoides.*

2. *Blastomycosis ulcerativa profunda sen mutilans* (Synonym: Blastomycosis, Wernicke-Ophüls type or Blastomycosis coccidioides type).

Etiology: *Coccidioides immitis* Rixford and Gilchrist, 1896.

3. *Blastomycosis purulenta profunda* (Synonym: Blastomycosis, Busse type; Blastomycosis subcutanea purulenta).

Etiology: *Cryptococcus hominis* Vuillemin, 1901 (probably covers many species).

4. *Blastomycosis glutealis* (Synonym: Blastomycosis, Kartulis type).

Etiology: mycological investigations not yet completed. The fungi seem to belong to the genera *Monilia* and *Cryptococcus.*

5. *Furunculosis blastomycetica cryptococcica* (Folliculitis decalvans cryptococcica, pro parte, Castellani type). (Synonyms: Furunculosis cryptococcica; Pseudofurunculosis blastomycetica; Furunculosis mycetica; Folliculitis decalvans saccharomycetica; Folliculitis decalvans moniliaca).

Etiology: yeast-like fungi either of genus *Cryptococcus* or *Monilia* (No asci or ascospores according to Castellani).

In addition to the above types, Castellani adds the following, although they are in no way connected with the blastomycosis organism: Blastomycosis epidermica; Intertrigo blastomycetica; Dermatitis blastomycetica interdigitalis.

For clinical purposes in diagnosing skin infections such a classification is good, but for correct determination of the etiological agent, it is essential that each type of involvement be named with the infective agent designated as such. For example, if the organism be a saccharomycete, the disease should be called *saccharomycosis;* if a monilia, then *moniliomycosis;* if an endomycete, then *endomycosis.* Thus, when the organism is correctly diagnosed the amount of time necessary to determine the right sort of curative measure for that type of infection may be taken, and the amount of time necessary for healing reduced.

Systemic Blastomycosis

As mentioned previously, the disease is protean in its clinical manifestations, with the result that practically every organ in the body has been shown to be infected either in the living, by various measures, such as X-ray, or in autopsy material. No vital organ is immune, and this in itself is sufficient to cause a careful physician to give more attention to therapeutic measures. This universal infectivity of the agent was especially shown by such writers as Otis and Evans ('03), Eisendrath and Ormsby ('05), Le Count and Myers ('05), Irons and Graham ('06), Montgomery and Ormsby ('08), Wade and Bell ('16), Garr ('25), Panja ('25), Toepel ('29), and Maner and Hammack ('30). There is, however, a difference in frequency with which the various organs show their susceptibility.

The portion of the anatomy that shows the greatest amount of infection is the skin, either primary or secondary, having about 95 per cent of all cases recorded. This phase of blastomycosis has received the greatest amount of attention principally because it is so prevalent, but also because it is usually a manifestation of a metastasis from the deeper organs, and this helps bring forth the diagnosis of blastomycosis.

The pulmonary system, including the lungs and bronchi, constitutes the second most frequent and the most common systemic form, being present to the extent of approximately 95 per cent in systemic infection in available autopsy records, and about 35 per cent in primary cases. This was shown by such men as Stober ('14), Wade and Bell ('16), Wade ('18), Dennis ('18), Miller ('27), Medlar ('27), and Mazza and Niño ('28). The disease probably is primary in the bronchi and from there spreads to the lungs. If secondary in the lungs, as in systemic disorders, the process may be slow and chronic; if primary, however, the spread may be rapid and fatal.

The kidneys are next in frequency of infection. The genito-urinary involvement is usually secondary by way of metastatic foci through the blood. The disease in these organs manifests itself in the form of nephritis, showing casts and albumen in the urine. The culturability of the organism from samples, however,

cannot be demonstrated unless the kidneys are accompanied by infected bladder or prostates.

The spleen follows next in order, but this organ is usually easily susceptible so that a great amount of infection is to be expected in any systemic disorder of this sort.

The complication of the bones and joints seems next in the amount of infection. This form of the syndrome is very common in systemic disorders, and may even be a primary infection if the diagnosis in the patient here described was correct seven years previous to his entry at the Barnard Skin and Cancer Hospital. This type of the disease may manifest itself in the form of arthritis, osteitis, osteomyelitis, or periostitis, according to Ryerson ('08–'09) and Stober ('14). The process usually results in a suppuration, formation of sequestra, and abscesses which break down intervening cell walls and coalesce, causing great damage.

The liver appears to be a rather frequent subject to the infection, coming next in the order of frequency. This is to be expected in systemic disorders where the blood plays an important part. Metastases through the blood vessels are fairly common, and yeast cells are easily transported to the main organs in this manner.

The pleura too are susceptible to a great extent, and here the proximity to the lungs is a great factor in their infection.

The lymph glands follow along rather closely, as shown by Wanamaker ('28), especially for the cervical lymph glands.

Cerebrospinal involvement, including the brain, meninges, spinal cord, and skull bones, occurs fairly often as a secondary metastatic process in generalized systemic blastomycosis, according to studies made (J. T. Moore, '20, Freeman and Weidman, '23, Greenfield, '24, Wilhelmj, '25, and Gáspár, '29), being found in at least 12 per cent of the cases. When the disease is secondary to a general systemic infection, there may be osteomyelitis of the skull bones with destructive processes. The diagnosis rests not upon any clinical entities which may be present, because the inflammatory reaction simulates many other conditions, but upon the actual laboratory finding of the organism either in the spinal fluid or in sections of the diseased brain tissue.

Wilhelmj ('25) states that in those cases where there is no pathological symptomatology or clinical manifestation on any other part of the body, and when the meninges are infected during the primary stages of the invasion, death may occur without the initial appearance of general metastatic foci, and such a condition he calls primary cerebrospinal blastomycosis. The spine may be involved in the process in a suppurating condition (Parker, '23), but this condition is relatively rare.

Jacobson lists the vertebrae as being next to the brain in susceptibility to attack. This condition has been noted on several occasions. Roentgenographic studies usually reveal an infection of bodies of the vertebrae, and lamina and posterior ligaments may show an involvement which simulates greatly tuberculous Pott's disease.

Prostatic infection in blastomycosis is often noticed (Parmenter and Simpson, '19). Usually it is associated with a genito-urinary complication and involves the urinary bladder (Rhamy, '26). In these cases acute urinary urgency and pyuria are well-defined symptoms.

The heart lesions in blastomycosis are shown first in the pericardium and then in the myocardium in the form of an inflammatory reaction (Hurley, '16).

Pancreatic involvement follows in frequency.

Infection in the peritoneum is the next most common. Jacobson reports finding the disease in the abdominal viscera in the following decreasing order of frequency: kidneys, spleen, liver, lymph glands, pancreas, peritoneum, adrenals, and gastro-intestinal tract. These organs, as pointed out previously, become involved usually through metastasis by way of the blood stream or by direct transmission from tissue to tissue. In this manner, testicular blastomycosis is usually developed. Blanchard, Swartz and Binot ('03), as early as 1903, noted an intraperitoneal involvement.

The eyes may also be involved. The infection here is very painful and often dangerous, leading to blindness with perhaps a complication of the nervous system and the brain. McKee ('26) and Ferguson ('28) noted cases of the eye which were secondary infections due to a metastasis from the pulmonary apparatus.

Laryngeal and tracheal blastomycosis are rare infections. Jacobson records four in America and one in Europe. All the patients were adult males working either with the soil or its products, one being a clerk in a general store (Dennis,' 18, Downing, '18, C. Jackson, '26, and New, '28). The larynx showed a "chronic inflammatory mucosa with a grayish, minutely nodular surface in some portion of the lesion, with a few minute, isolated, yellowish nodules." There was often a reddish, raw portion of the larynx due to the ease with which the superficial layers came off with coughing. The process resembled very closely tuberculosis.

Involvement of the tongue is perhaps a rare occurrence, but cases are not reported in great numbers purely because sputa smears usually show a variety of yeasts and thus no definite etiological significance is attached to those obtained. The first case was reported by Copelli ('13), a second one by New ('17) from the Mayo Clinic. Since that time, however, Mazza and Canevari ('29) reported a case from Argentina, and Niño ('29) reported an infection of the lower lip with the involvement of the tongue. Such an infection usually hinders respiration, inasmuch as a tumor-like growth, as evidenced by Copelli and New, developed which enlarged in the back portion of the tongue and practically filled the entire larynx.

Symptomatology

Blastomycosis when of the primary cutaneous type presents no clinical symptomatology of discomfort or pain except for that expressed because of the lesions. When of the systemic type, however, the condition is very different. There are numerous clinical factors to make a picture which might easily be confused with a number of diseases.

According to numerous investigators, the onset of the disease varies with the person and amount of infection. It may be intense and acute, leading to death in a short time, or insidious and mild, with a prolonged chronic condition, death finally occurring as a result of a secondary complication. There is a typical set of symptoms once the disease is well established. This consists of typical malaise, recurrent chills, loss of weight,

as evidenced in the present case, loss of strength leading to general emaciation, night sweats, although morning sweats may be present too, irregular fever, pain in affected parts, and a rapid pulse.

The disease, as noted before, may be primary in the skin with subsequent spread systemically or it may be systemic with the formation in the later stages of nodular growths on the skin. Unless the patient is well taken care of, systemic infection results, leading ultimately to death.

Differential Diagnosis

The final diagnosis of blastomycosis rests on the finding of the organism either culturally in a lesion of the patient or, if that be unavailable as in systemic disorders, the identification of the fungus in biopsy or autopsy material.

As pointed out previously, the disease is protean in character, with the result that a careful examination must be made to diagnose it blastomycosis, comparing it with the several well-known clinico-pathological entities which it may simulate. The most noteworthy of these complicating diseases are as follows: (a) The dermic lesions described previously, developing necrotic and papillomatous growths or ulcers, resemble very closely epitheliomas, differing only in the rapidity of evolution and the absence of deep induration, verrucas, tuberculosis in its various forms, and syphilis. Its resemblance to sporotrichosis (Lewis, '17) has often been noted, but it differs in being less sluggish. It differs from syphilis only by the softness of the lesions, the reddish-blue ring around the lesion, and by a negative Wassermann, with, of course, the presence of the organism in the blastomycosis infection; (b) The systemic infections of blastomycosis must be distinguished through laboratory methods from a great many complications, particularly coccidioidal granuloma described in a previous paper by the author (M. Moore, '32). The organism of coccidioidal granuloma, *Coccidioides immitis*, reproduces by endosporulation, and the blastomycosis organism, through budding. Furthermore, the lesions in the so-called "California disease" are more rapid in evolution than in blastomycosis; (c) Infection of the glands which is quite rare in blastomycosis often suggests

lymphatic leukemia, Hodgkin's disease, and possibly lymphosarcoma; (d) Gastro-intestinal lesions may often resemble typhoid and in some cases the isolation of the organism is necessary to rule out this disease; (e) Osseous infection quite often resembles tuberculosis, particularly as reported by Ryerson ('08–'09); (f) Pulmonary blastomycosis very often presents the same clinical, histological, and pathological pictures as tuberculosis, as noted by Medlar ('27) and Miller ('27); (g) Infections of the brain often confuse the pathologist or clinician with its similarity to torula (Freeman and Weidman, '23), epidemic meningitis, and even tumors of the spinal cord; (h) Sutejew, Utenkow, and Zeitlin ('29) find that the use of bromides and iodides evidently causes an allergy which in its reactions presents lesions similar to those caused by the infective agent of blastomycosis and is often confused with it, the latter differing in their more rapid evolution.

It would seem, therefore, that the recognition of blastomycosis is not a very easy matter. The really important fact concerned with this work is to find the organism, which usually requires laboratory technique, and to verify its pathogenicity by animal inoculation in order to comply with Koch's postulates.

Predisposing factors.—The infective agent shows no particular preference as to sex, although more cases have been males than females, of the industrial classes, chiefly the workers of the soil and its products, a fact well exemplified in the present case. There is no discrimination as to race or color, all peoples being affected in like fashion. Stober ('14) correlates the type and amount of infection with the habitat and environment of the patient. As far as is known, all ages are susceptible, a similar condition existing for many other fungi which tend to become systemic, such as coccidioidal granuloma.

Treatment.—The successful therapeutic measures in blastomycosis are few and limited. The best treatment or cure for the disease rests of course on the skill of the physician in detecting it at an early stage before it has seized a definite foothold, when it can be kept from becoming systemic. If the disease is definitely located in a particular section, surgery may be used to eliminate it, as suggested by several authors (Wade and Bell, '16, R. H.

Jackson, '26). Cautery has also been used with beneficial results. Hedge ('28) has employed carbon dioxide snow in freezing cutaneous lesions with measurable success. X-ray treatment has also been used frequently, being combined with the administration of iodides. On the whole, primary cutaneous lesions yield fairly readily to iodides and even the application of crystal violet and gentian violet, although their use if at all successful is empirical because dye therapy does not rest on any scientific basis (Spring, '29).

In systemic infections, however, one has to contend with complications. The extent of the infection cannot be determined easily. The only cases to recover from an infection of this sort are those to which special care and attention coupled with a change to a clean, pure atmosphere had been made, with the administration of large amounts of saturated iodide solution, either potassium or sodium, although the former has been used more extensively. The dyes mentioned above have proven worthless to the systemic type of disorder. Several workers have advocated copper sulphate, but many others have found this to be useless. Roentgenotherapy has, as yet, no really therapeutic importance. Stober has applied immuno-therapy in the form of a vaccine of suspended blastomycotic cells, heated to 110° C., but no definite results can be shown.

It would seem, therefore, that therapeusis is greatly in need of investigation.

Immunological reactions.—Immunology in blastomycosis has not reached any definite point as yet. Agglutinins have been reported by some, and negative results by others. Precipitins have also had the same reaction, as well as complement fixation. On the whole, results are indefinite and a good deal more information is needed. The main difficulty seems to be that the toxins of the blastomycosis fungus are difficult to demonstrate. So far, immunology is an open book with only attempts proving nothing written on its pages, and it is to be hoped that more work can be done along this line for the benefit of those who may be inflicted with this syndrome-complex.

Mortality.—The number of deaths resulting from blastomycosis is a factor worthy of note, since systemic disorders due to the

typical blastomycotic organism usually prove fatal. This is so because systemic infections are rarely diagnosed as such until there have been cutaneous outbreaks, with the result that therapeutic measures are given too late for beneficial results. It is difficult to quote figures because there are many cases occurring which have rapid recovery and the physician does not report them. Moreover, true blastomycosis is difficult to diagnose unless smears and cultures are made from the abscesses. In many instances, several attempts are necessary before any fungous growth is obtained, and unless the investigator is well trained in mycological technique and in the recognition of such forms typical of the Gilchrist organism the application of Koch's postulates would be essential, particularly with mice and guinea-pigs.

Report of Case

Clinical History.—M. H. L. (Hospital No. 50095), a white, widowed male, farmer by occupation, 43 years of age entered the Barnard Free Skin and Cancer Hospital, at Saint Louis, Missouri, April 5, 1932, with an ulcerating, proliferating infection of the left hand and forearm, which the patient claims to have had for 5 years.

Family History.—Father died as a result of high blood pressure, hypertension, at age of 56 years. Mother dead due to throat trouble, at age of 30 years. Three brothers and one sister dead due to an infancy cause. Patient has 7 children, all living and well. Wife dead due to double pneumonia at age of 38 years. No history of diabetes, nephritis, syphilis, or cancer in family.

Past History.—Past health has been good; usual childhood diseases. He had pneumonia at 15 years of age, bronchial pneumonia at 18 years of age, and influenza in 1918. He has had no operations other than those to be mentioned in the present illness. Right leg injured 7 years ago.

Personal History.—Patient denied any venereal disease.

Present Illness.—Patient stated that 7 years previously, a limb had fallen on his right lower leg, causing a knot to form. The physician who examined his leg thought he had a periostitis and opened the lesion on the leg. About 2 years later, or 5 years previous to entering the hospital, a mossy, verrucous-like lesion similar to that on the leg appeared on the back of the left hand. Both the lesions on the right lower leg and on the hand continued to spread. The patient went to the Vanderbilt University Hospital, at Nashville, Tennessee, about a year later, at which time the eruption had spread over most of the anterior and lateral sides of the right lower leg with two lesions of the right thigh above the right knee and with involvement with most of the back of the left hand and part of the forearm. He remained in the Vanderbilt Hospital for about 3 months, during which time the lesions on the right leg and arm were curetted and treated with X-ray. At the time of his discharge, the lesions on his right leg had healed, as had most of the hand except that portion near the thumb and the wrist. Another currettement was performed, but the lesion persisted. He received two X-ray treatments each on the leg, arm, and hand. Six years previous to entering the Barnard, he had lesions on the right elbow region;

these lesions healed. About 4 to 6 years before his entry he had lost some weight, but at the present time complains of no recent loss of weight. He gives no history of hemaptysis, night sweats, fever, or frequent colds. About 10 days previous to entry, a reddish lump developed on the flexor surface of the left lower arm near the elbow. This lump is not very tender or painful. He has been applying potash on the ulcerated area of the left hand.

Physical Examination.—Patient is a thin, coöperative, moderately active, white male 43 years of age, who has had the condition herein to be described as blastomycosis of the left arm and hand for approximately 6 years and who had the same condition on the leg for 3 years until it was curetted and X-rayed 4 years previously. The right leg and left arm show scarring which will be described later.

Head.—Normal size and shape.

Eyes.—Eyes react to light and accommodation. Reactions normal.

Ears.—No discharge, apparently normal.

Nose.—Septum intact, no ulcers.

Throat.—Slight redness.

Mouth.—Several teeth missing.

Neck.—No stiffness or rigidity; tonsillar and cervical glands palpable.

Thorax.—Thorax hairy, thin, and symmetrical; expansion fair.

Lungs.—Breath sounds a little harsh and rough over both lungs, principally the right and right apex. Voice sounds normal, but louder on the right than on the left. No persistent or moist râles or râles heard after coughing. Expansion and resonance normal.

Cardiac.—Cardiac sounds a little slow and distant, but of a normal quality. No enlargement or pathological murmur. Blood pressure, 106 systolic and 66 diastolic.

Abdomen.—No masses or tenderness. Inguinal glands a little enlarged.

Genitalia.—Normal male; no discharge or penile sores.

Reflexes.—Superficial—present and active. Babinski negative. Deep—present and active.

Extremities.—Left arm and hand—The lower third of the left forearm, back of the hand and extending 2 or 3 cm. on to the palm, is involved in an atrophic process sharply defined superiorly and inferiorly with some scaling, no telangiectasis. On the external surface of the forearm extending on to adjoining parts of the hand and thumb is an ulcerative process which has been covered with a black crust. Ulcerated area of the left thumb and the flexor surface of the left forearm consists of warty-like and cone-like, multiple abscesses with some elevation of the borders. There is a deep scar on the right elbow region. The anterior, medial, and lateral aspects of the right lower leg are covered with a thin, smooth scar about 12 to 14 inches long and covering two-thirds of the right lower leg. There are two scars just above the right knee, about 4 inches, and 8 × 4 inches in diameter, respectively.

On the flexor surface of the left forearm, just below the elbow, is an abscess which is red in color, oval in shape, semifluctuant, practically non-tender and not hot. Extending up from and about the abscess is a chin of firm lymph nodes. The lymph nodes above the left elbow and epitrochlear region are a little enlarged.

Laboratory Findings.—Urine negative, being pale straw in color and clear. Blood tests showed 4,600,000 red blood cells and 10,200 white blood cells, with 84 per cent hemoglobin. The differential blood count showed 26 lymphocytes, 8 large mononuclears and transitionals, 156 polynuclear neutrophiles, 2 polymorphonuclear eosinophiles, and 2 basophiles. Wassermann negative. Smears from the left hand and

arm showed budding forms of yeast cells on April 7, 1932. Blood, urine, and pus from left hand and lower arm and pus withdrawn from abscess of left arm were inoculated on glucose-glycerine agar on April 8. Spinal puncture on April 12 showed a clear fluid with a normal pressure. Glucose-glycerine agar and blood agar were inoculated with spinal fluid, with no growth occurring.

April 9, 1932.—The patient was started on potassium iodide with dosage up till signs of intoxication, and an ointment saturated with gentian violet was applied locally. This treatment was followed with 10 per cent sodium iodide intravenously for several days when patient showed an improvement.

April 16, 1932.—X-ray of left forearm and wrist, right femur, and right leg showed no abnormal bone changes. The hilar and bronchial structures of both lungs showed considerable thickening, inflammatory in character, but the parenchymatous portion of both lungs appeared free from any active pathology.

July 7, 1932.—Patient showed a very marked improvement, with still some evidence of trouble around the left thumb.

Clinical Diagnosis.—Blastomycosis of left hand and arm.

The agar inoculated from the left arm developed a culture which went through the three stages typical of the organism of blastomycosis: the yeast-like growth; the prickly type of growth; and the cottony type of growth. This culture was used for the studies carried out in this paper.

Animal Inoculation

A suspension of a 10-day-old culture of the organism in sterile saline was inoculated in a mouse, intratesticularly. An orchitis developed and the mouse showed typical malaise, emaciation, loss of appetite, loss of weight, rise in temperature, with death ensuing in three weeks. The internal viscera showed numerous, pin-point lesions at autopsy, which when squeezed exuded a muco-purulent material from which the yeast cells were isolated. This was in accordance with Koch's postulates.

Technique

In order to ascertain the morphological characteristics of the fungus, the organism was suspended in hanging-drop cultures, allowed to grow, and observations made from time to time. For finer detail and structure, several transfers were made to slides on which had been placed a drop of a mixture of glycerine (Merck C. P.) and a 1 per cent solution of crystal violet. The fungus was allowed to remain for a period of one-half to one hour to allow for a clearing of the material and sufficient staining to render satisfactory results. This method proved adequate for the work here described. Another method was used also, whereby material was fixed on a slide smeared with albumin and then stained with

methylene blue and eosine. The first method, however, was sufficient.

DESCRIPTION

A study of the organism in lesions reveals a yeast-like growth of spherical or ovoid, budding and branching cells with no evidence of any filamentous hyphae. These cells, measuring approximately 7–12 μ in diameter and sometimes as much as 20 μ in length, may occur singly, in groups of two's, three's or four's, as individual colonies. On closer examination microscopically, these yeast-like cells (pl. 6, figs. 1–9) show a heavy, reticulated, granular, and in many cases, vacuolated, protoplasm, and a very definite nucleus with emanating streams of cytoplasm. In many cells the nucleus is barely distinguishable, being a mass of cytoplasmic structures, but further study after several subcultures shows up this part of the cell very frequently. Many of the yeasts of this group may show a double-contoured, highly refractile membrane, and this feature is of little diagnostic use unless demonstrated in tissue sections, as by Rewbridge, Dodge, and Ayers ('29) for *Endomyces capsulatus*, and by Moore (McBride and Thompson, '33) for *E. capsulatus* var. *isabellinus*. Thus Wade ('16) ascribes to the fungus structure in tissues: (1) an inner delicate *capsula vera;* and (2) an outer applied *capsula sclerotica*. In any case, the capsule is lost on repeated cultivation on artificial media.

With agar as a substrate, the yeast-like cells elongate (pl. 6, figs. 10–12, 14–17) and on acid media become thin-walled and long with a diameter of 2–2½ μ. These hyphae become intertwined and are composed chiefly of isodiametric cells. On neutral or slightly alkaline media, with protein as the chief source of nitrogen, the hyphae are thicker and shorter, with a diameter of 3–4 μ. This condition is especially true of media with an excess of carbohydrate as found in glycerine agar.

Budding cells are numerous on slightly acid media, being about 5 μ in diameter (pl. 6, figs. 26 and 28).

The hyphae, at first clear, become granular, and at various points along the sides develop numerous small, knob-like projections of the limiting membrane, which enlarge, round out or become pyriform and sessile, measure approximately 5 μ in

diameter, and occur usually near a septum. These are known as conidia and may remain attached, at times to small stems or sterigmata, or may become free and develop in the media by budding (pl. 6, figs. 24, 26, 28–29).

Racquet mycelium (pl. 6, figs. 23–24), a phenomenon characteristic of the fungi of this group and especially of the Trichophytons and various other Ascomycetes, is common here, having the swollen portion 5–6 μ in diameter and the narrow section 3–3½ μ in diameter. Chlamydospores may be found arising in the hyphae or terminal as hypnospores, varying in size and shape from round cells 7–8½ μ in diameter, to elongated, widened cells 5½–7½ μ wide and 12–15 μ long (pl. 6, figs. 22, 25, 27–29, 31, 32, and 37), or they may arise as sessile cells from the hyphae (pl. 6, fig. 36). Round, thick cells with a coarse, granular cytoplasm are particularly evident on cornmeal agar (pl. 6, figs. 26 and 28).

When first examined in a hanging-drop preparation, one may see oil droplets on the hyphae which are strongly suggestive of endospores. These disappear, however, when the organism is stained. In some cases, as in pl. 6, fig. 25, a hollow sphere or vacuole surrounded by a hyaline, gelatinous substance may be present in the filament.

The development in tissue, as has been noted, is chiefly by budding or gemmation. The process begins with the projection of the inner layer of the cell or endosporium, following Hektoen, which pushes the transparent zone and outer membrane in front of it. The bud becomes enlarged and surrounded by the same walls as surround the mother cell, and division takes place by the presence of a cross-wall which is formed by the pinching in of the cell (pl. 6, figs. 1–3, 6–7). On artificial media, on the other hand, proliferation of the fungus is brought about through sexual reproduction which is heterogamous. Two terminal cells may fuse (pl. 6, fig. 19) or two hyphae growing side by side may send out lateral cells which copulate (pl. 6, fig. 18). In either case, a spherical ascus results which may be terminal on a long filament or lateral on a short peduncle (pl. 6, fig. 33) and has a thick capsule (pl. 6, figs. 21 and 33), sometimes surrounded by a sheath as in pl. 6, fig. 35. The latter case, however, is rare and was

observed only three times. There are formed 8 spherical to ovoid, smooth spores which are hyaline when young and held in a gelatinous substance and when older become chamois-colored and granular, and have at maturity a diameter of 2–3 μ, varying on different media (pl. 6, figs. 38 and 33).

This organism therefore agrees with that described by Gilchrist and Stokes as *Blastomyces dermatitidis*, but further observation has here been made on the sexual development.

CULTURAL DESCRIPTIONS

The culture in this case was growing on glucose-glycerine agar, being an inoculum from an abscess on the left arm. All cultures used in the cultural determinations were taken from the above tube and grown at room temperature, approximately 22° C.

Having the two stages so common with yeast-like organisms and characteristic of several members of the Endomycetales, it was thought desirable to transfer the fungus on a wide variety of media and pH range. Possessed with saccharomycetous properties, on the one hand, and filamentous fungous affinities, on the other, the above method of culturing proved to be satisfactory in this work.

The following media used are arranged in the order of decreasing hydrogen-ion concentration.

Raulin's Solution (*pH 4.1*).—Culture shows a thin, smooth suspension of yeast-like cells, budding and branching, varying in size from 4½–5½ μ x 7–8½ μ, with several showing a change to filamentous formation.

Richards' Solution Agar (*Media consisting of Richards' solution with the addition of 1.5 per cent agar. pH 4.4*).—Growth sparse, of fine filaments. Colony 3½ cm. in diameter at end of 30 days. Culture shows long hyphae projecting from edge of growth, 2½–3 μ in diameter, with numerous budding cells. Filaments branching, with cross-walls, numerous chlamydospores, and swellings. Characteristics of the group present. Color of colony isabella to cinnamon, strongly suggestive of chamois, due to the spores and asci which are in abundance.

Czapek's Agar (*pH 4.4*).—Color of colony white, becoming chamois with age. Growth very sparse and cottony, with much

of the mycelium submerged in the agar. Colony 4 cm. in diameter at end of 24 days. Hyphae long and thin, 1½–2 μ in diameter, with swellings approximately 4 x 12 μ, several thick-walled chlamydospores 7½ x 14 μ, and numerous terminal hypnospores. Several 8-spored asci seen, as well as many conidia.

Malt Extract Agar (*pH 5.3*).—Growth slow and cultural characteristics insufficiently different to be taken into discussion.

Sabouraud's Agar (*pH 5.6*).— Growth rapid, profuse, obtaining a diameter of 7½ cm. at end of 30 days. Culturally the colony simulates very much that of *Microsporon audouini* of Ota and Langeron in the presence of several radiating ridges from the round center, the inoculum, and the several concentric rings of growth of decreasing abundance, just outside the ridges. Color of colony white when young and becoming the characteristic chamois when older. Like *M. audouini*, it has racquet mycelium, chains of round cells on a hypha measuring 3½ μ in diameter, numerous chlamydospores 8 x 12 μ, terminal hypnospores 5 x 11 μ, and many conidia, characters found also in the Trichophytons and peculiar to *Endomyces capsulatus*. Unlike *M. audouini*, however, this organism reproduces by the formation of asci which are numerous here, measuring from 10 to 13 μ in diameter, containing 8 spores.

Sabouraud's Broth (*Sabouraud's medium minus the agar. pH 5.6*).—Culture consists of submerged mycelium of large flakes, each measuring approximately 2 cm. in diameter at end of 24 days. Mycelium floating on surface, dry, and chamois colored, with white region, presumably the young hyphal elements. In general, growth is good. Microscopically, the culture shows long, narrow hyphae 2½ μ in diameter, branching and intertwining. Submerged mycelium shows almost no swellings, chlamydospores, terminal hypnospores, nor thick-walled cells, as compared with the great number found in that on the surface. The several that are present, however, show a great reduction in size and form from the exposed, the measurements of which are similar to those on agar.

Potato-dextrose Agar (*pH 5.6*).—Growth profuse and cottony, covering the surface of the agar completely. Diameter of colony

7½ cm. after 24 days. Color cinnamon, with colony showing concentric circles of color alternating with white, and the cinnamon very pronounced, due perhaps to the medium constituents. Hyphae 3 μ in diameter, with numerous, thick-walled cells 7½ μ in diameter, budding cells, swellings 5 x 12 μ, and chlamydospores varying in size from 4–7 x 9–14 μ. Asci numerous, measuring approximately 13 μ in diameter.

Corn-meal Agar (product of Digestive Ferments Co. pH 6.0).—Growth poor, colony being 1½ cm. in diameter at end of 24 days. Color white. Growth around inoculum loose and cottony. Hyphae short, thick-walled, 2½ μ in diameter, with numerous budding cells approximately 7 μ in diameter. Chlamydospores numerous, 7 x 13 μ, terminal hypnospores several, 5 x 12 μ; a few asci seen, 11 μ in diameter. Conidia abundant, 5 μ in diameter.

June-beetle Agar (medium consisting of a 4 per cent extract of June beetles, Lachnosterna fusca, plus 1.5 per cent agar, sterilized at 20 pounds pressure for 20 minutes, with a final pH 6.1).—Growth of loose, flat, cottony mycelium, forming concentric circles of decreasing abundance until a ring of fine filaments surrounds the culture. Colony 5½ cm. in diameter at end of 24 days. Hyphae 2–2½ μ in diameter, with many conidia 5 μ in diameter. Asci 12–13 μ in diameter, thick-walled, enclosed in a sheath. Abundance of racquet mycelium.

June-beetle Dextrose Agar (above medium plus 2 per cent dextrose).—Growth fair, attaining a diameter of 3 cm. at end of 30 days. Colony bright chamois in color, cerebriform, and cottony. Many conidia, 4½–5 μ in diameter. Hyphae 2½–3 μ in diameter and fairly short. Chlamydospores 8 x 16 μ and numerous, as well as terminal hypnospores 5 x 12 μ. Asci round, 12–14 μ in diameter.

Lactose Agar (product of Digestive Ferments Co., lactose broth plus 1.5 per cent agar. pH 6.8).—Growth good, reaching a diameter of 6 cm. at end of 24 days. Colony chamois-color, profuse and cottony, with a region of very fine mycelium surrounding it. Hyphae 3½ μ in diameter with numerous conidia 5 μ in diameter, budding off. Many thick-walled resting cells 7 μ in diameter. Characteristic racquet mycelium, chlamydospores, terminal hypnospores, with properties similar to those on Sabouraud's agar.

Lactose Broth (product of Digestive Ferments Co. pH 6.8).—Growth good, large white flakes being formed in the solution which later become intertwined, forming a mat of mycelium 7 μ in diameter. Hyphae slightly reduced, 3 μ in diameter, 1½ μ in the younger filaments. Preponderance of budding cells 7 μ in diameter, with thick-walled chlamydospores, asci, and terminal hypnospores, but reduced in size as compared with the growth on agar.

Eosine-methylene-blue Agar (agar used as one of a routine, product of Digestive Ferments Co. pH 7.0).—Growth good, with a diameter of 5½ cm. at end of 24 days. Culture compact, due to the hyphae having absorbed the stain from the substrate and turning the mycelium pink. Colony appears powdery with age. Hyphae characteristic, with swellings, 3 μ in diameter. Many conidia, 5 μ in diameter, and hypnospores with several chlamydospores.

Glycerine Agar (nutrient agar as prepared by the Digestive Ferments Co. plus 6 per cent glycerine, Merck C. P. pH 7.1).—Growth fair, having a diameter of 5 cm. at end of 24 days. Culture shows a crinkled, moist region of budding yeast-like cells and a dry filamentous, cottony, chamois-colored region which has changed to the mycelial form characteristic on agar. Filamentous hyphae 3½ μ in diameter, characteristic swellings being present which are slightly larger than those found on lactose agar. Racquet mycelium also present.

Nutrient Agar (product of Digestive Ferments Co. pH 7.2).—Growth rapid, covering a region 7 cm. in diameter at end of 30 days. Colony filamentous, cottony, brown, with concentric rings of growth, the outermost being white. Hyphae 2½ μ in diameter. Growth similar to that on Sabouraud's agar microscopically, with numerous conidia 5 μ in diameter and asci 13 μ in diameter.

Nutrient Broth (pH 7.2).—Culture forms a mat of intertwining mycelium of long hyphae 2–2½ μ in diameter, with swellings, asci, and chlamydospores. Very few conidia. Terminal hypnospores several, but reduced in size, 4 x 9 μ.

Endo's Agar (product of Digestive Ferments Co. pH 7.5).—Growth fair, colony having a diameter of 3½ cm. at end of 30

days. Culture shows radiating ridges from center of inoculum, with growth becoming flat due to the stain in the medium which is absorbed by the hyphae, as in the case of the eosine-methylene-blue agar, giving the mycelium a pink color. Microscopically, the hyphae have a diameter of 2½ μ. Numerous conidia 5 μ in diameter. Culture otherwise similar to that on eosine-methylene-blue agar.

Gelatine (nutrient agar plus 1.5 per cent gelatine).—Slow liquefaction beginning after 30 days.

Culturally, the fungus is very characteristic of the organism of blastomycosis in that it passes through the three typical stages: the moist, yeast-like stage with a flat growth; the prickly culture with the colonies simulating greatly small burrs (coremia); and the final, cottony growth present on agar after extended growth.

Discussion

As stated in the introduction of this paper, it would seem that the syndrome-complex, commonly known as blastomycosis, has an innumerable list of etiological factors, each causing a condition so much like the other that clinicians have grouped them under one head. However, should one encounter any of these in a clinic one would find that therapeutic measures are so vastly different, varying with the organism, that a direct and accurate knowledge of the causative agent in each particular patient is absolutely essential.

In the past, medical men, not particularly trained in mycological taxonomy, were inclined to class together all fungi presenting ascomycetous characters under one name, *Blastomyces*. So great is the confusion to-day that it is necessary to pick out these pathogenic fungi and classify each one separately.

The organism isolated in the first case was termed *Blastomyces dermatitidis* by Gilchrist in 1894 because of its budding properties in the lesion. In a case of dermatitis reported by Gilchrist and Stokes ('96) the organism, which was evidently of the type termed *Blastomyces*, was called an *Oidium*. In a following paper (Gilchrist and Stokes, '98), it was made known that the organism described in the previous paper was called an *Oidium* because it did not ferment glucose, saccharose, or lactose, and although

developing by gemmation or budding in the tissues, human and animal, developed mycelia with the formation of conidia upon artificial media. Ricketts ('01) made an extensive study of the organism, distinguishing it from several of the yeasts but failing to consider several of the yeast-like fungi, and proposed definitely the name *Oidium* for the genus of the Gilchrist fungus. After this work, several terms were applied to the disease. Busse ('94) described his case a short time after Gilchrist reported his and he named the organism *Saccharomyces hominis*. Vuillemin in a later publication assigned the organism to the genus *Cryptococcus* and called it *C. gilchristi*. However, he failed to make a careful study of the organism culturally on artificial media, and a classification which places a great emphasis on the yeast-like appearance of the fungus in lesions is not exactly justifiable. Brumpt ('27) places the organism in the genus *Mycoderma*, calling it *M. dermatitis*. This terminology, however, is synonymous with *Oidium*, and in that case is likewise useless.

For a great number of years, no great work was done to establish definitely the position of Gilchrist's organism, and the name *Blastomyces* as created by him still held sway. The term presents a lot of difficulties. In the first place, the Blastomycetes, according to Buschke, are that group which develops through budding, provided a mycelium is formed on agar, while to the group of Blastomycetes, as Naegeli names budding, would belong the genera *Endomyces*, *Saccharomyces*, *Cryptococcus*, *Monilia*, and *Oidium*. Now the question arises as to what the actual meaning of the word blastomycete is. According to Vuillemin ('01), it does not designate a natural group, a botanical family based on genealogical affinities. There is in existence a genus *Blastomyces*, but these organisms are not budding fungi in the sense of Buschke. They are filamentous fungi whose spore-bearing elements, whether terminal, lateral, or intercalary, can be isolated by disarticulation, following Costantin and Rolland (quoted by Vuillemin). Frank (quoted by Vuillemin) established the Blastomycetes as an order to include such fungi as the beer yeasts whose elements are isolated by budding and not by disarticulation. In this respect, by virtue of the law of priority, it would seem that the name Blastomycetes, as designated by Frank, should remain. However,

if by general agreement the name of a genus could replace that of an order, then, according to the rules of nomenclature, the genus of Costantin and Rolland is legal, and the name as designated here is not legitimate by reason of the lack of distinct characters which have no generic value.

Castellani recently proposed a new classification of yeast-like or budding fungi based on the presence or absence of ascospores, which includes families of both the Ascomycetes and Fungi Imperfecti.

1. Saccharomycetaceae: budding cells, asci, and ascospores, but no mycelium in culture.
2. Endomycetaceae: budding cells, asci, and ascospores, with mycelium in culture.
3. Cryptococcaceae: budding cells (blastospores), no asci and no mycelium in culture.
4. Oosporaceae: budding cells, no asci, but mycelium in culture.

In addition to this family classification, he created a new genus which he calls *Blastomycoides*, to which he assigns three species, and places it in the family Oosporaceae: 1. *Blastomycoides dermatitidis*, synonym *Blastomyces dermatitidis* Gilchrist and Stokes; 2. *Blastomycoides immitis*, synonym *Coccidioides immitis* Rixford and Gilchrist; 3. *Blastomycoides tulanensis* Castellani. He defines the genus *Blastomycoides* as: "Oosporaceae appearing in the lesions as large roundish cells from eight to twenty microns in diameter, or larger, with the protoplasm containing a number of well-marked granules or spherules, and with a membrane showing a well-defined double contour; in dextrose agar cultures a large amount of mycelium is present." He bases further differentiation of the three species on their cultural differences when grown on mannitol, lactose, glucose, and galactose agar.

The second species that he names, *Blastomycoides immitis*, has already been discussed and classified by the author in a previous paper (M. Moore, '32). The author has made no pretext of studying the third species, so that nothing can be said about that. The first species, however, *Blastomycoides dermatitidis*, is altogether misplaced, simply because there are asci present in the mycelium in culture. This of course would refer the genus to the family Endomycetaceae, in which group the writer definitely establishes the organism.

Observations on the growth, development, reproduction, and further evolution of the fungus show that there are budding cells in the lesions, mycelium formed on agar with an intermediate stage showing the change from the yeast-like to the filamentous form. In accordance with this, Mellon ('24, '26, '26a) has recorded the fact that asci do occur particularly "in the so-called secondary colonies of the cultures which also contained 'dauernzellen' and pigmented oidia." The author wishes to affirm Mellon's findings as to the presence of asci, but suggests that these structures are present in the third stage, whereas the second step would consist of the intermediary forms which have an appearance very much like greatly enlarged oidia. Furthermore, it would seem that Mellon's description was indefinite, inasmuch as he refers to an ascus as an ascospore, and oil droplets are suggested by him as being chromatin indicators and forerunners of the future spores. Such factors as these are very important in the taxonomy of this type of fungi and should not be dealt with so promiscuously. Furthermore, Mellon has not paid much attention to the fact that no matter how old the lesion may be the blastomycosis organism found there does not change from its yeast-like, budding growth until it has been transferred to artificial media, where the change is an adaptation to the mode of life it must lead; in other words, the change from active parasitism to one of saprophytism. It is to be understood, however, that a change such as suggested here will not necessarily reduce its viability, at least for the time being.

A study of the evolution of the organism has repeatedly shown, in several hanging-drop cultures, that reproduction is heterogamous, as given in the description, with the final formation in the series of a large eight-spored ascus. Mellon in his papers consistently shows a four-spored ascus. It would seem, therefore, that he either has an organism unlike the one here described for the blastomycosis parasite, or else he has taken for granted as spores the four oil droplets which may and often have been found to occur on a mature eight-spored ascus, as was evidenced by the author on another ascomycete, *Endomyces capsulatus* var. *isabellinus* Moore, which was described in a case in another paper (McBride and Thompson, '33) and also in *Endomyces*

capsulatus Rewbridge, Dodge and Ayers ('29). Furthermore, it is quite possible that Mellon has observed the ascus just previous to the division of the nuclei, in the formation of the eight-spored ascus. This latter statement is only a conjecture on the part of the writer, but in any case the cultural descriptions do not agree with those given by the early investigators and with which the organism here described does agree.

In view of such criteria, it would seem that the organism formerly described as *Blastomyces dermatitidis* Gilchrist 1894, is not strictly a member of that genus, the name of which, on account of its etymological derivation, is essentially a misnomer. Because of its morphological characteristics, *Blastomyces dermatitidis* does not present those affinities entirely but simply as one phase of its life cycle. However, particularly because of its ascomycetous attributes, it should belong to the class Ascomycetes, order Endomycetales, family Endomycetaceae, and because of its similarity in morphology and reproduction (perfect stage) to that of *Endomyces capsulatus* and its variety, it should belong to the genus *Endomyces*. If taxonomic position in this family and genus be dependent on the number of spores in the ascus, it would seem, according to Whitman ('13), that this organism should belong in the genus *Oleina*. However, the genus *Endomyces* contains a number of pathogenic species with eight-spored asci, whereas *Oleina* has no pathogenic species, and until a classification better than the one now in existence be established, *dermatitidis* should be placed with *Endomyces*.

From the above statement it would appear that the organism should now be known as:

Endomyces dermatitidis (Gilchrist 1894), M. Moore, n. comb.

Mycelium in lesions of budding yeast-like cells 7–12 μ in diameter and sometimes as much as 20 μ in length, occurring singly, in groups of two's, three's, or four's. Growth on agar of isodiametric cells 2–2½ μ in diameter on acid media and 3–4 μ in diameter on slightly alkaline media. Hyphae septate, with conidia pyriform or round, pedunculate or sessile, 5 μ in diameter. Racquet mycelium present, 5–6 μ in diameter at swollen portion and 3–3½ μ in diameter at narrow portion. Chlamydospores terminal or lateral or intercalary, 5½–7½ x 12–15 μ, or sometimes

round, 7 μ in diameter. Copulation heterogamous, asci spherical, 8–13 μ in diameter, with 8 spherical to ovoid, smooth, hyaline to light chamois-colored spores 2–3 μ in diameter, at maturity. Colony white in color, becoming cinnamon to brown with age.

Summary

1. The history of blastomycosis is given, with a review of the early work on yeast-like, fungous pathogenicity, and a report of the first case published.

2. The etiology and clinical manifestations represent a number of conditions due to several yeast or yeast-like organisms: *Saccharomyces*, *Oidium*, *Monilia*, *Endomyces*, *Cryptococcus*, and *Coccidioides*, which have been placed in one category to constitute the agents responsible for the syndrome-complex, blastomycosis.

3. The disease is shown to simulate several conditions, in which cases the diagnosis must be arrived at through the isolation of the organism and the application of Koch's postulates.

4. Immunological reactions and therapeutic measures are as yet indefinite as to specific results, although beneficial results have been reported by the use of iodides.

5. A case of blastomycosis of the arm and hand is reported.

6. There is a description of the organism, culturally and morphologically, showing its relationship to the class Ascomycetes.

7. The fungus is definitely established as *Endomyces dermatitidis* of the family Endomycetaceae.

Acknowledgments

The author wishes to express his sincere gratitude to the following: Dr. Carroll W. Dodge, Professor of Botany in the Henry Shaw School of Botany of Washington University, for his interest, criticisms, and helpful suggestions; Dr. George T. Moore, Director of the Missouri Botanical Garden, for the courtesies extended; Dr. Martin F. Engman, Dermatologist to the Washington University Hospitals, for the use of the data with respect to the case reported; and Miss Nell C. Horner, librarian of the Missouri Botanical Garden, for her assistance.

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Explanation of Plate

PLATE 6

All drawings made with camera lucida at a magnification of × 800.

Figs. 1–9. Yeast-like cells.

Figs. 1, 6, 7. On Raulin's solution.

Figs. 2–5, 9. On Sabouraud's agar.

Fig. 8. On glycerine agar.

Figs. 10–12, 14–17. Yeast-like cells showing a change to mycelial formation.

Figs. 10, 12. On potato-dextrose agar.

Figs. 11, 14. On glycerine agar.

Figs. 15–17. On Sabouraud's agar.

Fig. 13. Germinating spores on Richards' solution agar.

Fig. 18. Heterogamous copulation of lateral cells on Sabouraud's agar.

Fig. 19. Heterogamous copulation of terminal cells on Richards' solution agar.

Fig. 20. Copulating branch on corn-meal agar.

Fig. 21. Maturing ascus on Richards' solution agar.

Fig. 22. Terminal hypnospore on Sabouraud's agar.

Fig. 23. Racquet mycelium on June-beetle agar.

Fig. 24. Mycelium showing conidia on Richards' solution agar.

Fig. 25. Mycelium showing round terminal chlamydospores and swollen hypha on nutrient agar.

Figs. 26, 28. Mycelium showing conidia, oidia-like cells, and resting cells on corn-meal agar.

Fig. 27. Chlamydospore on Czapek's agar.

Fig. 29. Mycelium showing conidia on potato-dextrose agar.

Fig. 30. Racquet formation on Czapek's agar.

Fig. 31. Terminal chlamydospore on lactose agar.

Fig. 32. Terminal hypnospore on Endo's agar.

Fig. 33. Maturing lateral ascus on Sabouraud's agar.

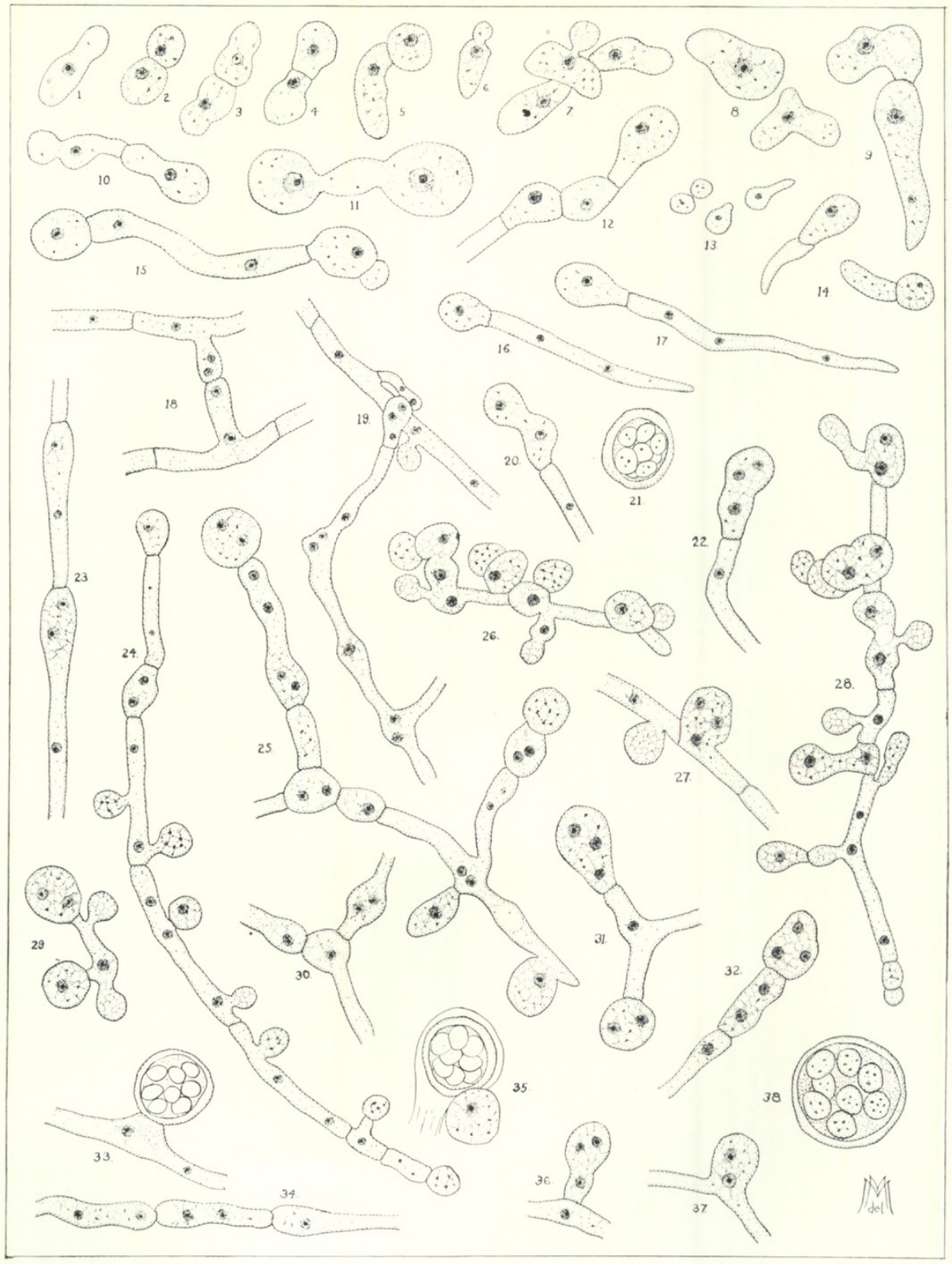
Fig. 34. Racquet mycelium on June-beetle dextrose agar.

Fig. 35. Ascus covered with a third sheath in proximity to a round resting cell, on potato-dextrose agar.

Fig. 36. Lateral chlamydospore on Czapek's agar.

Fig. 37. Resting cell on Sabouraud's agar.

Fig. 38. Mature ascus on potato-dextrose agar.



MOORE—BLASTOMYCOSIS

Explanation of Plate

PLATE 7

Fig. 1. Photograph of hand of patient on day of entry, April 8, 1932, showing lesion involving portion of thumb.

Fig. 2. Photograph taken on April 8, 1932, showing abscess on flexor surface of left lower arm.

Fig. 3. Photograph showing marked improvement after treatment with sodium iodide intravenously.

Fig. 4. Photograph showing almost complete healing.