did a far greater good when he described a method of massage for the breast which was based on sound anatomic reasons. Massage should not be done indiscriminately; it should only be done on an engorged, tender breast. It is almost criminal to continue the manipulations when inflammation has occurred. Then, too, I think the nipple should be better prepared, not by using hardening solution, such as alum, which I believe tends to promote fissures, but by using an oily preparation, such as cacao butter impregnated with some mild, innocuous antiseptic like boric acid. These two suggestions, Bacon's massage and preparation of the nipple, will go a long way toward preventing such complications as were described by Dr. Manton; massage will often disseminate a local process into a systemic disease. Further, a well applied binder is a useful adjunct. I do not believe that staphylococcic infection of the breast is so infrequent; this presumption is based on the myriads of these germs normally found in the skin. Undoubtedly it is more rare to have a systemic infection originating from a mammary contamination. The question naturally arises if the massage in the early part of the treatment might not have been a factor in the later course of the disease.

Dr. W. P. Manton—I do not believe that general staphylococcic infection is uncommon, but I can not find any record of cases.

THE MORPHOLOGY AND BIOLOGY OF THE PARASITE FROM A CASE OF SYSTEMIC BLASTOMYCOSIS.*

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The observations recorded in this paper were made on the parasites obtained in the tissue and by artificial culture from the case of fatal systemic blastomycosis reported by Ormsby and Miller.[1] We wish here to acknowledge their assistance in the work done and kindness in allowing us to use the material from their case.

In May, 1894, Gilchrist[2] described in tissues from a skin lesion the spherical, double-contoured, budding microörganisms which have since been observed in about thirty-five reported cases. In this case cultures were not made and little was known of the biology or nature of the parasite. In November of the same year Busse[3] reported a case of systemic infection resulting fatally in which a similar parasite was described as the etiologic factor. Cultures were made from this case and the organisms extensively studied by Buschke.[4] In culture the organism grew by budding, and mycelial formations were also seen.

The cases reported have had lesions for the most part confined to the cutaneous surface. A few cases of systemic infection, however, have been observed. The cases have largely occurred in the United States. The largest number have been observed in and about Chicago. The cutaneous lesions have characteristics which show such uniformity that they may be distinguished often by their gross appearance. The microscopic findings are similar in all cases, and the presence of the typical organisms in the tissue, or pus of miliary abscesses, is pathognomonic. The cases of systemic infection, as far as we can determine, which seem to have definite confirmation, are four: First, the case of Busse and Buschke; second, a case reported by Montgomery and Ricketts,[5] and later by Walker and Montgomery;[6] third, one reported by Ophüls and Moffit[7] (San Francisco), identical with those cases which have heretofore been called a protozoan infection, but which was proved by him to grow as a typical fungus in artificial media; and lastly, the case of Ormsby and Miller,[1] in Chicago, from which our material was obtained. All of these systemic cases have resulted fatally.

There is much uniformity in the morphology of the organism, as found in the tissues and purulent exudate, in all these cases, both cutaneous and systemic. They are spherical or oval, double-contoured, with very refractive cell capsule, increase by budding, and, in the Ophüls' case by sporulation, which has not been definitely proved in any other case. No mycelia are found in the tissues or pus. The size varies within wide limits in different cases, parasites from three to thirty microns in diameter being seen. The cultural characteristics of the organisms from different cases show marked variations, in some cases multiplying by budding exclusively, in others growing mycelia principally, and in others abundant aërial hyphæ are produced. Hektoen[8] describes very minute forms which, under proper conditions, develop into the larger form. And, further, some of the organisms, if watched for some time through a number of generations of growth, completely change in their characteristics on artificial media, multiplying at one time by gemmation, and afterward forming mycelia, or vice versa. We may thus say that in its growth and cultures, polymorphism is manifested to a striking degree. Hektoen made a careful study of the parasites from a case of blastomycetic dermatitis.[8] He describes the appearance of the different forms of the organism as seen in the tissues; some with a clear zone surrounding the protoplasm inside the capsule, others in which this is inconspicuous; some with large vacuoles in the protoplasm, others with dense, granular protoplasm without vacuoles. He also describes mulberry-like masses of hyaline bodies in the tissues, both intracellular and extracellular. The cultural forms varied much in size, a small, coccus-like form being described.

Gilchrist[9] makes extensive observation on the morphology and biology of the parasite. The process of budding, as it occurs in the tissue, is accurately followed. The endosporium, or protoplasm, of the bud increases to almost the size of the parent, and then becomes separated. He also notes peculiarly refractive forms which will not take the stain. Other forms in

* Read at the Fifty-fourth Annual Session of the American Medical Association, in the Section on Pathology and Physiology, and approved for publication by the Executive Committee: Drs. L. Hektoen, F. B. Wynn and W. S. Hall.

1. Ormsby, O. S., and Miller, H. M.: Report of a Case of Systemic Blastomycosis with Multiple Cutaneous and Subcutaneous Lesions, Jour. Cutan. Dis., March, 1903.

2. Gilchrist, T. C.: Communication to the American Dermatological Association, May 30, 1894.

3. Busse, Otto: Ueber Parasitare Zelleinschlusse und Ihre Zuchtung, Centralbl. f. Bakt. und Parasitenk, 1894, xvi, 175; also, Ueber Saccharomycosis Hominis, Virchow's Archiv, 1895, cxl, 23; also, Experim. Untersuch. Ueber Saccharomycosis, Virchow's Archiv, 1896, cxliv, 360; also, Die Hefen als Krankheitserreger, Berlin, 1897.

4. Buschke, A.: Ueber Hefenmykosen bei Menschen und Thieren, Volkmann's Samml. Klin. Vortrage, 1898, No. 218; also Ueber Hautblastomykose. Verhandl. der Deutschen Dermatologischen Gesellschaft. Sechster Congress, 1899, 181.

5. Montgomery, F. H., and Ricketts, H. T.: Three Cases of Blastomycetic Infection of the Skin; One Case Limited to "Tumor" of the Lower Lip, Journal Cutan. and Genitourinary Diseases, January, 1901.

6. Walker, J. W., and Montgomery, F. H.: Further Report of a Previously Recorded Case of Blastomycosis of the Skin; Systemic Infection with Blastomyces; Death; Autopsy. The Journal A. M. A., April, 5, 1902.

7. Ophüls, W., and Moffit, H. C.: A New Pathogenic Mould, Phila. Med. Jour., June 30, 1900.

8. Hektoen, L.: The Organism in a Case of Blastomycetic Dermatitis, Jour. Exper. Med., vol. iv, 1899.

9. Gilchrist, T. C., and Stokes, W. R.: A Case of Pseudo-Lupus Vulgaris Caused by a Blastomyces, Jour. Exper. Med., vol. iii, No. 1, 1898.

which the protoplasm has contracted into a half-moon shape are described. The adult forms in cultures show in the protoplasm fine, deeply-staining granules, larger refractive granules, and often one or more vacuoles.

Ricketts[10] has collected and tabulated observations concerning the morphologic, biologic and cultural characteristics of the organisms from a number of cases (seventeen), from which table he concludes that there are three more or less distinct groups of organisms having common generic characteristics. Montgomery[11] gives a very careful description of the clinical, pathologic and bacteriologic features from thirteen recorded cases.

DESCRIPTION OF CASE.

The clinical history and discussion of the present case have already been reported by Ormsby and Miller,[1] accompanied by a brief description of the microscopic and gross pathology of the tissues affected, and also a short study of the cultural characteristics of the organism by the present observers. The history indicated that the primary infection was located in the pulmonary tissue, followed by the cutaneous and subcutaneous lesions. Practically all the cutaneous lesions were of such a nature as to indicate the hemal origin of the infection, the superficial tissues being affected only after the process progressed from the deeper tissues. One lesion only, on the hand, had the characteristics described in the lesions of blastomycetic dermatitis of local origin. Of the internal organs, the lungs were most extensively involved; grayish nodules of varying size, and in enormous numbers, being distinguished in all parts of the tissue of both lungs. The pleuræ were extensively affected, and adhesions and whitish nodules of varying size were present in all portions. The lesions in the spleen were almost as extensive as in the lung. The nodules composed of typical organisms were found also in the liver, kidneys, pancreas, trachea and larynx. (This is apparently the first case in which involvement of a mucous membrane proper has been described.) The teased specimens in hanging drop from the different organs gave abundant opportunity for studying the living parasites as they occurred in the lesions. The stained sections from the lung tissue, especially, show parasites in immense numbers.

MICROSCOPIC APPEARANCE OF TISSUES.

Lung.—The slight degree of inflammatory reaction is noteworthy, the lesions being composed almost entirely of the parasites. There is some newly-formed connective tissue containing small round cells, polynuclear leucocytes and many mast cells, the protoplasmic granules of which stain red with polychrome methylene blue. There is some coagulation necrosis, areas of caseation appearing mostly at the center of the nodules. In the areas where the parasites are very abundant the elastic tissue has entirely disappeared, as indicated by staining with orcein. The epithelial cells which are remaining in the lung are largely detached, and are remarkable for the amount of brownish pigment granules which they contain. Similar deposits of pigment are found in many other cells, especially the polynuclear leucocytes of the blood.

The giant cells in the lung tissue are remarkable for their number and size. They vary from twenty microns to many times that diameter. They all contain parasites in different stages of development, and the larger ones are crowded with them, the cell nuclei being few and indistinct, while in the smaller giant cells the cell nuclei are numerous and prominent. The peripheral arrangement of the nuclei seen in the tubercular process is not followed, but many of the nuclei are near the center of the cell body.

Spleen.—The splenic tissue is riddled by the growth of the typical organisms, showing grossly as yellowish-white areas and nodules. Microscopically, the parasites are seen scattered widely throughout the tissue, but not in such large masses as in the lung tissue. The splenic pulp contains much brown pigment.

The lesions of the kidney, liver and pancreas are smaller and less numerous, often escaping naked eye examination. The immense numbers of parasites and small amount of newly-formed connective tissue are the principal characteristics of these lesions. In and about them are always seen typical mast cells.

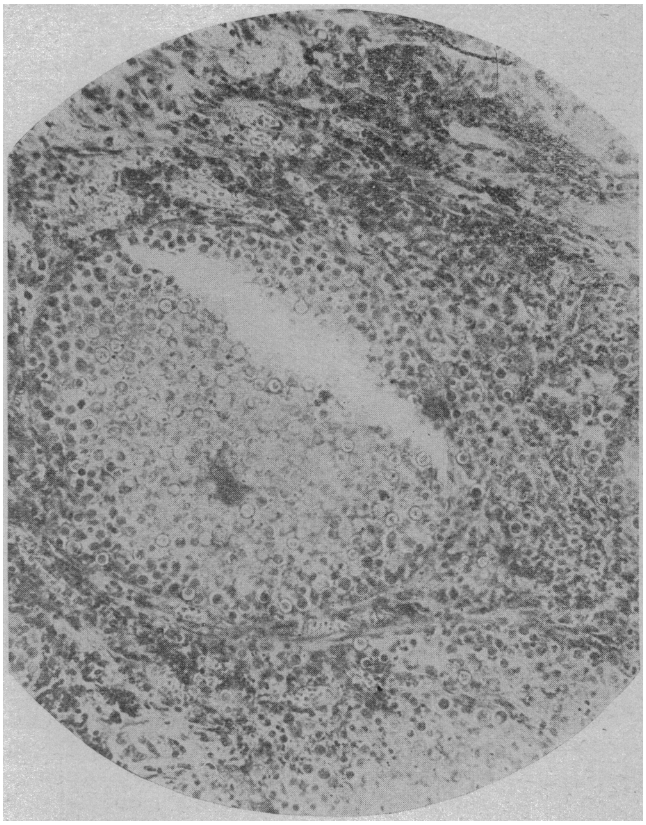

Fig. 1.—Nodule of blastomycetes in lung tissue. Center showing old, poorly-staining organisms, and periphery showing young, deeply-staining organisms.

Lymph Nodes.—The peribronchial lymph nodes were markedly enlarged, and contained large amounts of black pigment, apparently carbon. On microscopic examination we were unable to demonstrate the presence of any parasite in the tissues; however, in one section parasites were seen in the blood stream of one of the vessels.

MORPHOLOGY OF PARASITES IN THE TISSUES.

The stained sections of lung tissue offer excellent opportunity for a study of the parasites in different stages of their development. There are seen large, rounded masses of parasites under the microscope (Fig. 1), at the center of which the organisms are all of large size, take very little stain, show few buds, and many contain large vacuoles, occupying almost the entire cell. These are evidently old cells which are degenerating and disintegrating, as indicated by the granular detritus

10. Ricketts, H. T.: Oidiomycosis (Blastomycosis) of the Skin and Its Fungi, Jour. Med. Research, vol. vi, No. 3.

11. Montgomery, F. H.: A Brief Summary of the Clinical, Pathologic and Bacteriologic Features of Cutaneous Blastomycosis, The Journal A. M. A., 1902.

among them. At the periphery of these areas the organisms differ much from those at the center. The cells are of various sizes, have deeply-staining protoplasm and are undergoing cell division actively. These areas, therefore, give excellent opportunity for the study of the life history of the parasite in the tissue.

The most satisfactory stain which we have found for studying the structure of the yeast-like organism is the polychrome methylene blue stain, applied according to Unna's method. Other stains used are hematoxylin and eosin, methylene blue and eosin, Gram's stain, Van Giesen's method, carbol fuchsin and orcein.

The typical parasites are of various sizes, measuring from five to fifteen microns in diameter. They all have a definite, refractive capsule, which takes most stains sparingly, usually less than one micron in thickness. The capsule stains best by methylene blue and eosin. Within the capsule the structure has so many variations as to be almost picturesque in the variety of forms seen. Many of the cells have a wide, clear zone within the capsule and surrounding the protoplasm.

In the natural order of growth of any organism, one expects to find a certain definite order of development, and it has been our effort by careful study of the various

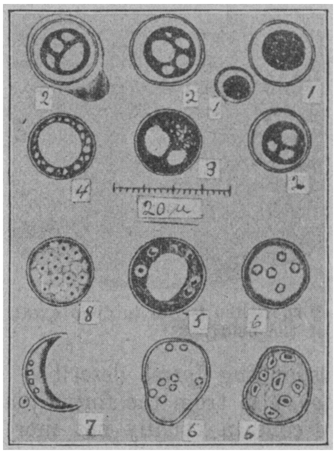

Fig. 2.—Diagrammatic representations of adult forms of parasite showing different stages of development. (Made from drawings.) 1. Young forms, dense protoplasm, wide clear zone. 2. Protoplasm vacuolated; one enclosed by tissue cell. 3. Protoplasm fills capsule. 4. Contains one large vacuole. 5 and 6. Contain spore-like bodies. 7. Collapsed form; one extracellular spore-like body. 8. No vacuole; protoplasm transformed into spore-like bodies.

forms to determine the characteristics of the cells at the different stages of their development. We see, then (Fig. 2), in all forms a capsule protoplasm of varying structure and staining properties; in many the clear space between the capsule and protoplasm, and many contain one or more vacuoles of various sizes. Budding forms are numerous, and cells of almost all types of structure are seen undergoing this form of multiplication; but the budding process is most active in cells of a certain type—those in which the protoplasm is dense, deeply staining and relatively small in amount, being surrounded by a wide, clear zone. These are of medium or small size generally, and are evidently relatively young and actively growing forms. We can distinguish, then, the following types:

1. Cells which are small in size, from five to ten microns usually, having a relatively small mass of deeply-staining protoplasm, surrounded by a wide, clear zone inside the capsule. The mass of chromatic substance is spherical, except in those which are undergoing the budding process, is centrally or excentrally located, is finely granular or homogeneous, but very deeply stained. Many of these are budding.

2. Forms similar to the first, but slightly larger on an average, the deeply staining protoplasm being more coarsely granular and containing clear, rounded spaces, which are evidently vacuoles, of varying size and number. The protoplasm occupies a larger area in the cell, the clear zone being narrower than in the preceding form. Many of these are undergoing the budding process.

3. Forms similar in size to the preceding, protoplasm staining well, granules large, a few large vacuoles being present, all of the space occupied by the protoplasm, the clear zone being obliterated or inconspicuous.

The preceding forms are found especially at the periphery of the circular masses of parasites described in the lung tissue, and are evidently younger and growing forms, actively dividing.

4. Large cells in which the protoplasm fills the capsule and contains a single, very large, spherical vacuole, centrally or peripherally located. The protoplasm thus appears as a ring of granular material, does not take a deep stain, and some small, circular, hyaline areas are seen in it. These forms are seen mostly at the center of the masses of parasites.

5. Large forms with very large central vacuole, a thin layer of protoplasm which has undergone division into spore-like bodies, which have the appearance shown in the figure. These bodies are about one micron in diameter, appear to have a central clear space surrounded by a ring of chromatic substance of irregular thickness, the chromatic substance often being accumulated at one portion of the ring, at other times appearing as two masses on opposite sides of the ring. These spore-like bodies are seen to be only at the periphery of the cell capsule. These forms of cells are found only at the center of the masses of parasites.

6. Similar cells in every respect, except that they are collapsed, the fluid contents of the vacuole having been evacuated. These forms are evidently derived from those described in paragraph No. 5. Very few of those cells with refractive contents have undergone any such change.

7. Another distinctive form appears in which the protoplasm contains no large vacuole whatever, but as they develop the protoplasm divides into from ten to fifteen small hyaline bodies, in many of which is seen a central densely staining body. Similar bodies to these are also seen outside the capsule.

Other variations in the structure of the cells may be seen—some with refractive contents which does not take the stains; others are seen in small numbers in which the protoplasm is completely obscured by a mass of brown pigment. The presence of these forms is possibly an explanation of the origin of the pigment granules described in the tissue cells, and in the leucocytes of the blood. With polychrome methylene blue stain a great many of the organisms contain in their protoplasm basophilic granules staining red. These have been described by Gilchrist and others. There is a remarkable variation in the affinity which different organisms have for the stains, cells lying side by side, and apparently of the same structure, show an entirely different reaction to the stain. Several observers have described adventitious capsules. We have not observed a similar condition, but often individual parasites are seen within the protoplasm of the tissue cells, which is stretched about it and so attentuated as to resemble a capsule.

SPORE FORMATION.

Multiplication of the organism by budding is the usual method within living tissue, and by budding and mycelial and conidial formation in the culture, but the production of endospores and propagation by their development is still a matter of doubt. In the case under consideration the findings in the tissue seemed to indicate the presence of spore formation, and we will endeavor to describe this process here (Fig. 3). These forms occur for the most part in the centers of the masses of parasites where all the organisms are of advanced age, and many are disintegrating. Most of the cells in question contain large central vacuoles, the protoplasm being pushed to the periphery, appearing as a ring just within the capsule. This ring of protoplasm has undergone division into bodies which are small (about one micron in diameter), and are composed of an outer ring of chromatic material and a hyaline center (Fig. 4). These bodies have already been described in a preceding paragraph. These spore-like bodies are seen by careful focusing to be situated at the periphery and not at the center of the cells, the center being occupied by a large vacuole. They number from eight to twelve in a capsule. Exactly identical forms are seen as ex-

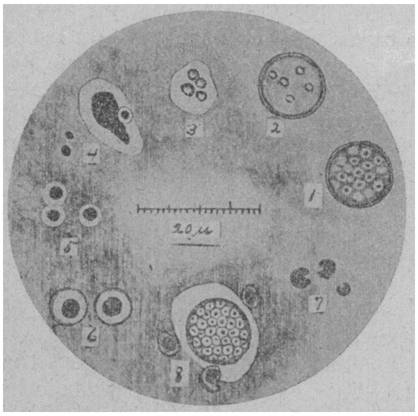

Fig. 3.—Sporulating forms and developing spores. 1 and 2. Adult forms containing spores. 3 and 4. Extracellular spore bodies; one at 4 is situated in protoplasm of tissue cell. 5 and 6. Developing spores. 7. Crescentic forms of developing spores. 8. Organism from guinea-pig's kidney, sporulating.

tracellular bodies, and other larger forms which have a crescentic shape and have evidently been formed by the development of these ring-like bodies, the chromatic substance increasing on one side and the hyaline center becoming eccentric, thus producing the appearance of a crescent. Further, there are found in these old capsules just described other small forms having a solid chromatic center surrounded by a hyaline area, and similar to the bodies appearing in the cells which we will now describe.

There are certain cells which we have already mentioned which do not contain vacuoles, at least have no large central vacuole. In their later stages the protoplasm of these forms breaks up into small rounded hyaline bodies, many of which are seen to have a densely stained spherical center. Bodies exactly resembling these are seen outside the cells, and others, which are larger, one to three microns in diameter, and having about them the hyaline zone, but no distinct capsule as seen in the adult form. Some of these forms have been noted within tissue cells, and these tissue cells with their contained spore bodies are probably the beginning of the giant cells. As soon as these developing spores reach a size of about four or five microns a capsule is seen surrounding the clear zone. It was noticed that the parasites which are in the younger and smaller giant cells are mostly the smaller forms, while the older and larger giant cells contain older developmental forms of the parasites. It seems probable that the large rounded masses of parasites described in the pulmonary tissue are the result of further development of the giant cells.

The sporulating forms described here differ radically in the number of spore bodies formed within one capsule

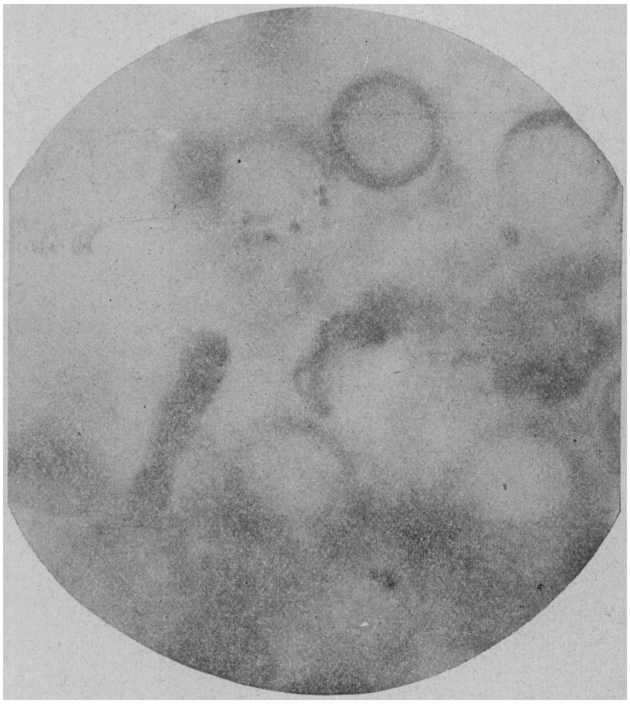

Fig. 4.—Showing spore-like bodies in disintegrating capsule (just above the center of the field).

from the corresponding forms described by Ophüls in his systemic case, also from the forms pictured by Gilchrist.[12] They contain usually not more than twelve or fifteen, while Ophüls describes one hundred or more in each cell. However, we have noted in one of the

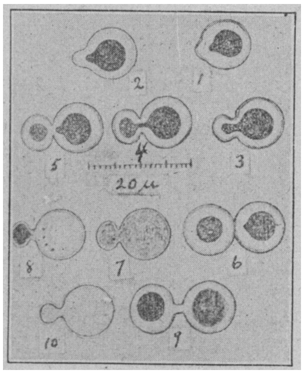

Fig. 5.—Budding forms. 1 to 6. Series showing progressive changes in process of gemmation. 7 to 10. Unusual forms. 8. Organism, budding and apparently sporulating simultaneously.

guinea-pigs experimented on forms containing a very large number of spore-like bodies.

We have, then, two forms of cells producing spore-like bodies, one with a large central vacuole and one without, the bodies produced in these two forms being different in appearance, as already described. In no case

12. Gilchrist, T. C.: Blastomycetic Dermatitis in the Negro, Brit. Med. Jour., Oct. 25, 1902.

have ruptured forms been observed in the tissues, the spores apparently being liberated by the disintegration of the parent organism. There is a possibility of confusing some of the extracellular developing spores with certain products of tissue cell degeneration.

We have not absolutely observed the development of these spore-like bodies into adult organisms, but the appearance of the different forms which we have seen in the tissues leads us to believe that this is really the case.

THE BUDDING PROCESS.

The process of budding, as observed in the tissue sections, is almost entirely confined to the younger forms, those having deeply staining protoplasm and a wide, clear zone within the capsule. However, it is seen in other forms. A few cells are seen undergoing gemmation and apparently sporulation simultaneously. The different stages in the budding process are represented by a series of drawings in Figure 5.

CHANGES IN THE BLOOD.

In the case of Busse,[3] where there was a fatal systemic

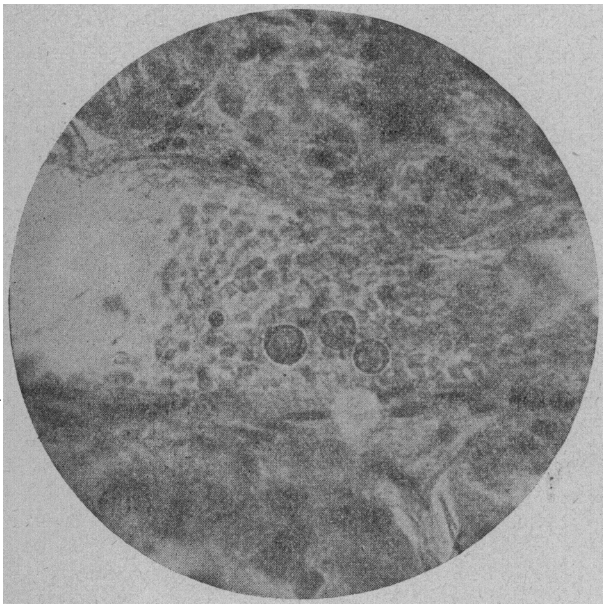

Fig. 6.—Three adult parasites seen in the blood stream of a vein of the kidney.

infection, cultures of the parasite were made from the blood during life. In Gilchrist's case,[12] which he regarded as a beginning systemic invasion, examination of the blood by culture failed to reveal their presence. In the case under consideration, we have observed in the blood stream of vessels of the kidney (Fig. 6), also in other places, adult parasites mingled with the blood cells. On examination of sections of a postmortem clot from the heart practically all of the leucocytes were seen to contain large, brownish pigment granules of uniform size, from three to ten in a cell.

TEASED TISSUE IN HANGING-DROP CULTURE.

In the teased specimens of fresh tissue from the affected organs large numbers of blastomycetes were observed. They were not all of uniform size and structure. They varied from five to fifteen microns in diameter. The contents of the cell were often nuclear in appearance. Sometimes there were only granules present. Frequently the granular contents were lobular in appearance. raspberry-like; again, they would assume a circular form about a large vacuole.

The cell wall is refractive and perfectly spherical. There is frequently one point where the capsule appears very thin, a point at which the protoplasm is often seen to protrude in the budding process. This is not always the point through which the growth takes place, for budding cells have been observed to produce mycelia from a point at sufficient distance from the point of attachment of the daughter cell to subtend an angle of twenty degrees. At the point where the mycelium appeared the capsule appeared to be perfectly firm.

Cell Development.—When hanging-drop cultures were first made, the cells varied considerably in size, but in a few days they had all reached a uniform size. As far as could be observed, no new budding processes took place after the cells had been placed in artificial media. Buds already existing grew to full-sized organisms. Some time later there appeared a few very large organisms (twenty to thirty microns in diameter) that changed their form from round to oblong. None of these large forms developed mycelia. In old mounts the cell contents of most of the organisms developed oil-like globules that varied from one to seven microns in diameter. In ten

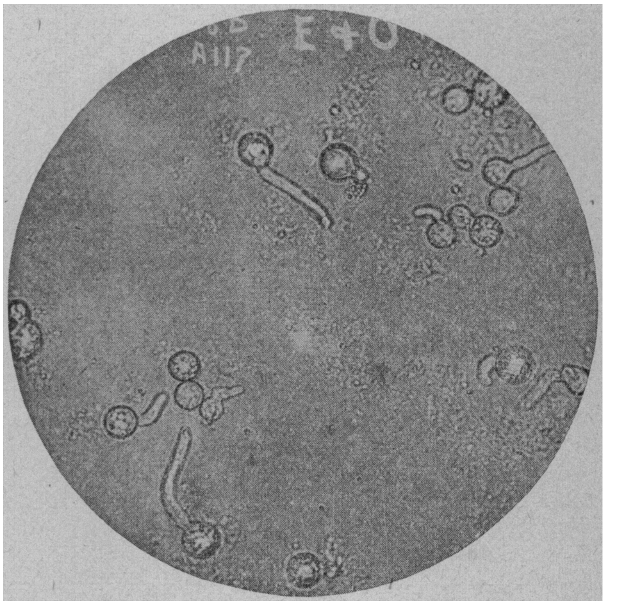

Fig. 7.—Blastomycetes. Teased cells from spleen beginning development in artificial media.

days some of them became so large that one globule occupied most of the cell. Some granule-like bodies manifested a very marked brownian movement. The formation of the fat-like globules seemed to be a process of degeneration, for the cells most exposed and those supplied with the poorest pabulum developed the largest globules.

Formation of Mycelia.—Thirty hours after hanging-drop cultures were made with bouillon for nutriment the cell started out small processes (Fig. 7). In the next twenty hours they grew sixty microns in length. The mycelia were homogeneous and possessed a very thin cell wall. Where the media was adequate, its growth seemed unlimited; but where there was but little media they grew slowly and developed a firmer wall. Protoplasmic granules and pinkish vacuoles formed in the processes. Soon these granules became smaller and more dense. Then they manifested a very active brownian movement. After the mycelia were several days old, there appeared a subdivision of the mycelia into cells or segments of varying length (ten to one hundred microns).

These segments near the focus of growth continued to develop, assuming a spherical form.

After a hanging-drop culture in glycerin bouillon had developed for about a month there appeared an end cell that budded. In a few days there were four cells. These, as in several other places, developed until there were a dozen or more in a cluster.

Fortunately, one hanging-drop culture had but six microörganisms present, thus giving excellent opportunity to observe them individually. One of the budding forms started a mycelium. The process originated from a point near the attachment of the daughter cell. Shortly after the mycelia divide into segments, many of them sending out processes (Fig. 8). There were no more than one process from a given segment. The granules that formed in the mycelia showed a more marked brownian movement than particles in the surrounding fluid. It was as marked as the motility of the pigment in the malarial parasite. This movement lasted for more than two months. It was observed also in the mother cell. As the plant became older there appeared an extra development of some of the individual cells in the thread.

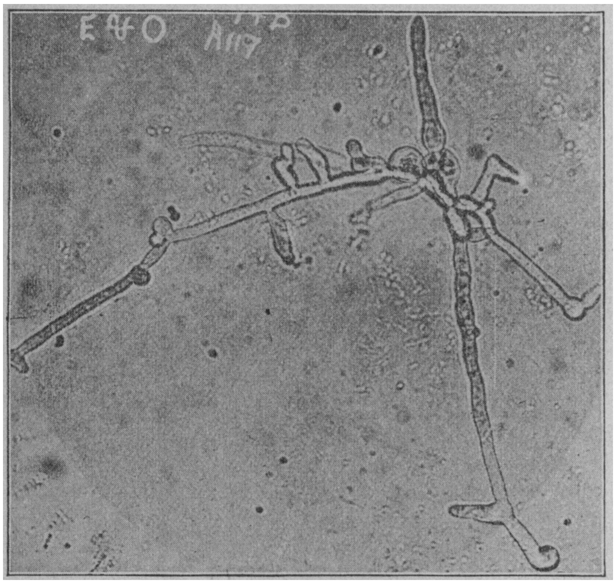

Fig. 8.—Blastomycetes. Dividing cell after ten days' growth in hanging-drop culture.

They took on a spherical form, and produced a protoplasm similar to the protoplasm of the cells in the teased specimen.

CULTURAL CHARACTERISTICS.

Petri Dish.—Six to nine days elapsed after a culture was made before any macroscopic signs of development appeared. Then a white area composed of radiating threads might be seen about the center of growth. If the cultures are observed with a microscope, these threads may be seen a few days earlier. One or more mycelia may be seen growing from a point as early as the third day. These soon subdivide, others are given off nearer its point of origin; these grow out in radiating lines, subdividing as they grow. The growth may be very rapid, the mycelia increasing two millimeters in length in a day. The rapidity of the growth did not seem to depend on the temperature so much as it did on the amount of moisture in the atmosphere. The most rapid growth was manifested when the Petri dishes were kept so there was considerable moisture condensed on the inner surface of the covers. In the Petri dish the most rapid growth was manifested in gelatin. It is interesting to note that in all media for some days no aërial hyphæ were produced. Instead, the growth spread beneath the surface in all directions. Later, however, the white aërial hyphæ appeared near the center of the growth.

Bouillon Culture.—Blastomycetes developed in plain, saccharin, glucose, lactose and glycerin bouillon. It is the most rapid and luxuriant in the glycerin bouillon. It grows most readily and rapidly on the surface and clings to the side of the tube very closely. It forms a mycelial growth on the surface of the bouillon so firm that it will prevent the bouillon flowing when the tube is inverted. If the tube is shaken a little after the growth develops, it is forced away from its position on the side and has the appearance of cotton. It never has developed the powder-puff appearance in bouillon. It is quite perfect in agar-agar, however. The teased membrane from the surface of the bouillon showed numerous conidia, three to six microns in diameter. There were also large conidia invariably filled with spore-like bodies. A little pressure between cover slips would liberate the contents of these bodies. Then all the appearances of the cells from teased tissues were observed. These large forms varied in size from seven to fifteen microns. Their arrangement in the teased materials suggested that they grew individually rather than in clusters of conidia.

Agar-Agar.—As has been mentioned, the early growth is quite completely beneath the surface. The growth is silvery white and forms a powder-puff-appearing hemisphere. It sometimes remains entirely beneath the surface and does not wrinkle. Again, it may wrinkle the surface. Sometimes eminences are thus formed from which beard-like tufts of aërial hyphæ are given off. As the culture advances in age it becomes slightly brown. The illustration will show the forms of growth as they appeared under the microscope. Conidia filled with spore-like bodies were also observed. The hyphæ varied much in diameter. There were some very fine forms measuring less than one micron.

Gelatin.—The gelatin plate grew very rapidly and did not wrinkle. No liquefaction was observed. The stab culture grew most rapidly at the surface. No liquefaction was observed in stab culture until after a month, when it was noted that the entire gelatin had gradually liquefied. At the end of three months it is perfectly fluid.

Litmus Milk.—The growth is rapid and abundant. The media changed to a deeper blue.

Potato.—The growth was as rapid as on plain agar. It was white and appeared like froth as the potato dried.

Loeffler's Blood Serum.—The growth was abundant, and did not seem to be more rapid than on glycerin agar. The color was not any different than what might be imparted by the media. There was no liquefaction.

Motility.—The motility of the protoplasmic granules was observed, but there was no motility of the entire microörganism.

Oxygen Requirements.—The cultures grown anaërobically by the Novy method showed no signs of growth in a month; but when removed from the hydrogen developed growth in seven days. A microscopic examination of material from the surface of the culture when taken from the jar showed no growth and no unusual forms.

Gas.—Although growth took place quite readily in the fermentation tube, no gas was produced, though grown in lactose, glucose and saccharose media.

By-Products.—No alcohol was developed in bouillon above mentioned. No carbon dioxid was produced in quantities that could be detected. There was no nitrite or indol produced.

Destruction by Heat.—Growths in which there were aërial hyphæ grew readily after being exposed to 100 degrees C. for five minutes; while, if the hyphæ were submerged in bouillon before submitting to the heat, they were destroyed in less than five minutes at 54 degrees, centigrade.

Destruction by Antiseptics.—The microörganism is destroyed when exposed as follows: Five per cent. carbolic acid, for one minute; 2 per cent. commercial formalin, one minute; 1/1,000 bichlorid, for one minute. When exposed to 2 per cent. hydrochloric acid, specific gravity 1,320, for fifteen minutes, it not only was not destroyed, but it seemed to grow more rapidly.

Animal Experiments.—Of five guinea-pigs that were successfully inoculated, four developed ulcers at the point of inoculation. One developed simply a nodule. The ulcers were oblong, having the long axis parallel with the long axis of the body. In the center of a typical ulcer there is a dry, bloody scab. If this is raised it bleeds readily, while there may also be seen many pin-head-size gray foci. They suggest the miliary pustules characteristic of the human skin lesion. Around the central portion is a raised slightly indurated area from which the hair has fallen. The third day after inoculation one animal developed a subcutaneous abscess from which a bloody fluid was evacuated in which blastomycetes were observed. Two weeks after inoculation a ridge was noticed from the ulcer along the sternum to the clavicle, suggesting an enlarged lymphatic. The animals died a month after inoculation, all within a few days of each other. Although an epidemic was suspected it could not be proven bacteriologically, as blastomycetes were found near the seat of inoculation, while from the liver and spleen a pure culture of blastomycetes was grown in one instance. Cultures taken from the internal organs of the other animals did not develop any growth. However, had a larger number of cultures been made undoubtedly a positive result would have been more often obtained, for two-thirds of the successful cultures in the one case were negative. The lesions observed were numerous. Infarcts appeared in the lungs, kidneys, spleen, and in one case seven small, round hemorrhagic infarcts were observed in the stomach wall. Pin-point foci were seen in the liver and spleen. An ulcer was noted in the upper intestine. There was also quite an inflammatory condition in the axilla and groin, but no general glandular enlargement could be seen. One guinea-pig inoculated with material from agar-agar died in two months and manifested similar lesions to the above. Two rabbits were inoculated with teased tissue. Both lost in flesh, one more rapidly than the other. One is living; the other was killed five months later. No lesions were observed except numerous subcapsular scars in the kidneys. The microscopic study proved that they were a healing infarct. Two mice were inoculated with a culture after four months of artificial cultivation. They are alive after three weeks.

The microscopic study of the organs of the animals unfortunately has not been completed; nevertheless, quite a complete study was made of those of the guinea-pig dying of systemic infection. The same kind of lesions were noted as in the human. One observation is especially worthy of mention, namely, many large cells, apparently sporulating forms, as mentioned by Gilchrist,[12] were observed in the kidney sections.

There has also been a case of accidental infection following this case. The microörganism has been isolated in pure culture. It has also been observed in sections.

Experiments were undertaken to determine the effect of the x-ray on cultures of blastomycetes. They were exposed in Petri dishes with covers of oiled paper for periods from ten to thirty minutes in length every third day for two weeks. No visible effect was produced.

An ordinary sixteen-plate static machine was used with an x-ray tube of low tension. The distance of the tube from the cultures was two inches.

Cultures prepared in a similar manner were exposed to the influence of the light of an actinic ray apparatus. In these specimens, the growth of the organisms entirely ceased. However, a certain amount of heat was developed in the exposures, and it is impossible to determine whether the effect was due to the heat or to the influence of the actinic ray.

During these experiments, a very interesting observation was made. The paper covers of the Petri dishes were oiled, some with paraffin, others with cedar oil, to make them more transparent. In the case of those which were exposed to the x-ray, those cultures which were under the paraffin paper grew with their usual activity, while the growth of those under paper prepared with cedar oil was absolutely inhibited, and by culture experiments from those plates it was determined that the life of the parasites was destroyed. In a later experiment in which cultures were employed which had been growing for nine days, and in which the colonies had reached a considerable size, their further growth was entirely prevented by the cedar oil paper, while they continued to develop at a rapid rate in the control plate. In this case the cultures were exposed simply to the influence of the cedar oil, no other agents being used which might effect their growth. Subcultures from these plates made after an exposure of seven days to the effect of the cedar oil paper showed that the organisms were not yet destroyed, although absolutely inhibited. This observation may possibly prove to be of some value in the treatment of blastomycetic infections.

SUMMARY.

1. This case is one of systemic blastomycetic infection and belongs to a class of which but a very few instances have been reported.

2. Parasites were demonstrated in the blood postmortem and dissemination evidently took place through this medium.

3. The lymph glands are remarkably free from infection.

4. In the lesions the parasites were found in immense numbers, and the inflammatory reaction in the tissues were of a remarkably slight degree.

5. The leucocytes of the blood and certain tissue cells contained large quantities of round pigment granules.

6. Parasites grow in the tissue only by budding, the forms appearing from five to fifteen microns in diameter; in artificial culture by segmented mycelia, lateral conidia, and in very old cultures a few budding forms.

7. There is a definite order of development of the parasite in the tissue, the younger forms having a densely staining protoplasm undergoing active cell division by gemmation; the older forms not deeply staining and not actively dividing, and containing spore-like bodies.

8. From the findings in the tissue it seems evident that sporulation occurs, five to fifteen spores developing in each cell where they are seen.

9. Organisms derived from teased tissues have been observed in hanging drop to produce mycelia within a few hours after they were removed from the tissue.

10. The effect of exposure to the x-rays was negative.

11. The effect of the actinic ray is doubtful because the element of heat was not eliminated.

12. The cultures covered with cedar oil paper died within one month. Those exposed for one week were completely inhibited from growth, but were not dead.

13. The organism fulfills the laws of Koch, guinea-pigs being more susceptible than rabbits.

14. The organism grows readily on all forms of artificial media used.

15. In gelatin liquefaction was produced after one month.

ANOPHTHALMOS.

REPORT OF A CASE.*

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The case of anophthalmos which I am about to report is not detailed for the purpose of deriving great clinical benefit from its consideration, but purely on account of its scientific bearing, and the possibility of throwing some light on the intrauterine disturbances that may cause the development of monstrosities.

Cases of anophthalmos are indeed rare, and cases of pseudoanophthalmos or microophthalmos are seldom enough seen to warrant us in presenting them to this scientific body. Aside from the complete absence of the eyeballs, other congenital deformities associated in this case are worthy of consideration. Then, too, the possibility of the influence of consanguinity in their causation makes it doubly interesting.

This case was brought to my knowledge in the following manner:

Sept. 7, 1894, I was summoned to a neighboring town to see a child about two months of age, which apparently had something wrong with its eyes. At a casual glance it seemed to be asleep, and aside from a tendency to anemia appeared to be fairly well nourished. On a more careful examination, however, anomalous conditions were brought to view. When I opened the lids I was astonished to find that there was not the faintest resemblance to an eyeball in either socket. The lids, palpebral muscles and orbits were perfectly formed. The lids were depressed exactly as in a case of enucleation of the eyeballs. The palpebral conjunction extended backward and made a complete sac. The most careful examination could not reveal anything that would indicate the presence of an eyeball, either large or small, nor did it appear that any retinal fibers had developed. I examined the child on several occasions during a year, but was unable to get any response to light stimulation. She slept during the day, but remained awake all night. This circumstance, however, is not uncommon with healthy children who have normal eyes. This girl lived until she was 3 years old and then died from enterocolitis. It was impossible to secure an autopsy. Therefore, any minute details or microscopic pathology can not be given.

There are those in the profession (and among them Fuchs) who deny *in toto* the possibility of an absolute anophthalmos, because in several cases eyes as small as a millet seed have been discovered by postmortem examination where anophthalmos was supposed to have existed. Of course, in this case in the absence of postmortem evidences we can not absolutely and conclusively prove our case. But from rational reasoning such an occurrence would seem possible. We have congenital deformities of all parts of the body, and there is no reason why failure in the development of the primitive ocular vesicle should not occur from some interference of nutrition. A few years ago the reports of the Royal London Ophthalmological Hospital gave ten cases.

During the course of the examination of this girl I found that she was deformed in various ways. The right external ear was smaller than the left. The meatus and internal ear were normally developed on each side. The hearing was abnormally acute, as is usually the case with the blind. Before she was a year old she could hear and recognize her father's footsteps long before any one else in the house, and would manifest her delight by clapping her hands.

The hands were flexed on the forearm at birth and the little and ring fingers of both hands were webbed as far as the second joint. By daily massage, however, the flexor tendons were relaxed and the hands and fingers could be fully extended and used normally.

At the lower third of both legs the bones were deformed and jogged, and large exostoses thrown out the same as in a case of fracture that had not been set. The tibia and fibula were involved alike. There was evidently an attempt at intrauterine amputation or arrested development of the extremities. At the time of examination, however, the bones were fully united and firm. Both feet were abnormally small. There were but four toes on each foot, and all the toes were webbed. In addition to this, both feet were inverted. There was marked varus, or equinovarus. Aside from these described deformities the child seemed normally developed. Mentally she was very precocious.

When such a train of congenital deformities occurs in the same child the profession as well as the laity are apt to attempt a solution of the difficulty. By the laity the condition is ascribed to one of two possible occurrences, namely, that the mother was scared by some animal or thing (in which event the child resembles the object that scared the mother), or it was produced by the near relationship of the parents. In this case the opinion of the laity may be set aside as far as the question of fright is concerned, for the mother had no remembrance of any such occurrence, and beside, the child bore no resemblance to a monster. On the other hand, however, the question of consanguinity enters largely into the case. The father and mother were first cousins. For those who recognize the possibility of deformities occurring in children whose parents are closely related, it opens a wide field for discussion and speculation. For my part I could never trace any physiologic or pathologic connection between deformities and consanguinity.

If we consider closely the nature of the deformities in this case we can easily see that whatever the cause of the uterine disturbance it affected the different parts of the fetus at practically the same time—that is, between the sixth and eighth week of gestation. It is true that the primitive ocular vesicle makes its appearance at the third or fourth week, but at the eighth the lens capsule is just beginning to form and the eye is just in the active point of development. At almost the same time the extremities begin to develop. At the fourth week we have the projection of the upper and lower limbs, but at the eighth week the thigh and leg can be distinguished. Up to this period the fingers and toes are webbed. Thus we have the absence of the eyeballs, which develop before the eighth week, and the webbed condition of the fingers

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