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THE LIFE CYCLE OF *CRYPTOCOCCUS HOMINIS*

RAMONA L. TODD

Two groups of fungi which include organisms pathogenic for humans have received some attention from medical men in recent years. These groups, the true yeasts and the false yeasts, have been studied only superficially from a standpoint of morphology and taxonomic relationships; hence, the classification and nomenclature, particularly of the false yeasts, has been in a state of confusion. The true yeasts, those which produce ascospores and form no mycelium, are placed in the family Saccharomycetaceae, order Endomycetales, class Ascomycetes. The yeast-like organisms for which no perfect stage has been demonstrated are grouped in one form family (given various names by different authors) of the Fungi Imperfecti. The majority of these false yeasts were originally placed in this group, and further taxonomic work has not been reported. Many of them are human pathogens, such as the organisms causing "Torula" or "yeast" meningitis, and those causing pulmonary or other infections. Benham (1) uses the form family Pseudo-saccharomycetaceae, order Moniliales, to include these forms.

Various generic names have been proposed for the organism causing "yeast" meningitis. Benham (1, 2) suggests that *Cryptococcus* Kützing, 1833, should be adopted as the genus name, and defines it as including: "unicellular fungi consisting of round or ovoid cells, occasionally in chains but never forming a well-defined mycelium. Reproduction by one or more buds; no ascospores. Growth on artificial media in pasty or dry colonies, white or colored." *Torula* Turpin, 1838, was proposed later than the name *Torula* Persoon, 1801, which is used to designate a fungus with short, dark hyphae and catenulate conidia; consequently, *Torula* Turpin is not a valid genus for yeast-like organisms. *Torulopsis* Berlese, 1894, should be a synonym for *Cryptococcus*, but it is regarded as a distinct genus by Dodge (3). Those, as Lodder (4) and Benham (5), who have made comparative studies of representative organisms of each genus have concluded that they are identical. Several other generic names have been suggested, but the above-mentioned terms are the only ones which have come into wide usage. After due consideration of rules of

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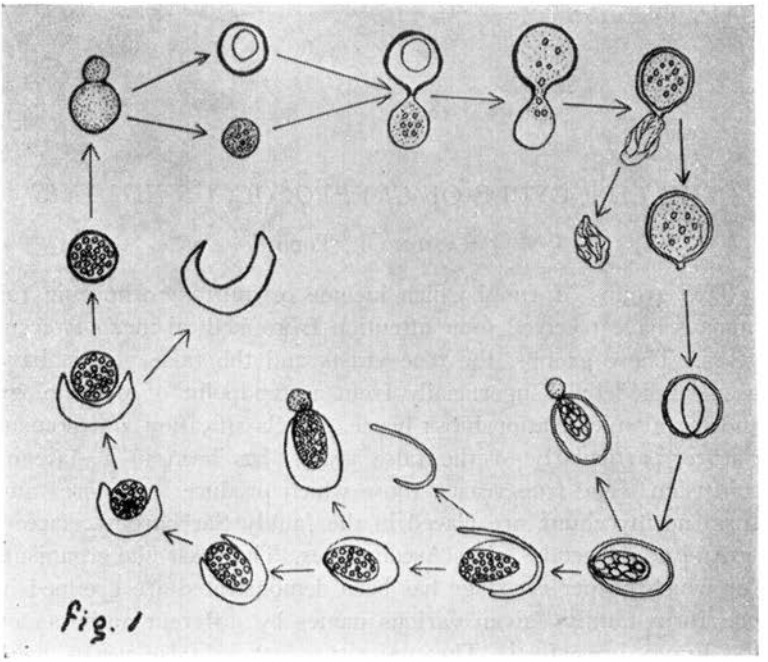

Fig. 1. Diagram of the cycle. Structures approximately x900.

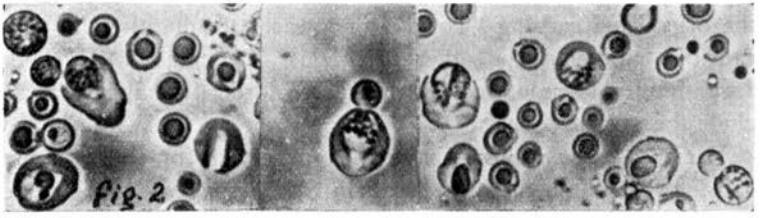

Fig. 2. Photomicrograph from mount under oil. Cells from a culture eight weeks old. Magnification x550.

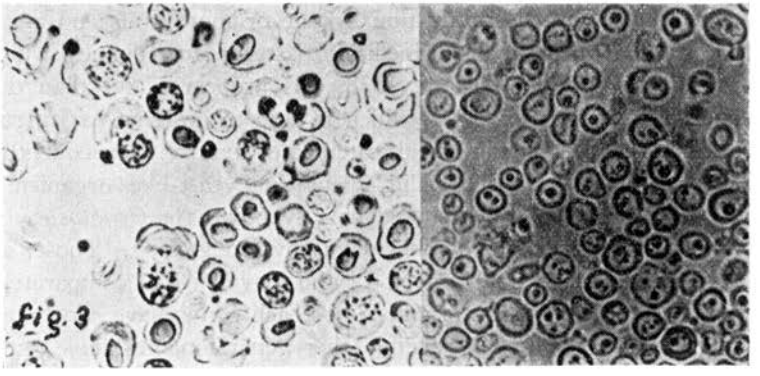

Fig. 3. Photomicrograph of two fields, the left field showing a six weeks' old culture and the right showing a five weeks' old culture. Magnification x550.

priority and usage, it seems advisable to accept *Cryptococcus* Kützing, and to adopt *Crytococcus hominis* Vuillemin, 1901, as suggested by Benham (1), for that species of non-sporulating organism causing "yeast" meningitis. *Torula histolytica* Stoddard and Cutler, 1916, becomes a synonym of this species.

In studying the morphological characters of several strains of organisms isolated from cases of "yeast" meningitis, structures were observed which indicated that a process of endospore formation was taking place. A survey of the literature concerning the species failed to reveal a report of endospore formation in any strain; therefore, a careful study was undertaken to determine the sequence of changes. Ten different strains of the species were found to show these structures. One of these was isolated from the spinal fluid of a patient in the University of Iowa Hospitals; another from a patient in the Minneapolis, Minnesota, General Hospital; one strain was received from Los Angeles, California; one from Madison, Wisconsin; and the others were strains from cases of "yeast" meningitis which have been reported by various workers.

Studies

The organisms were studied in van Tieghem cell cultures, in temporary mounts from cultures on Sabouraud's maltose or dextrose agar slants adjusted to an initial pH 7.0, and by the usual methods of inducing spore formation in the yeasts: plaster blocks, carrot slants, beet slants, and Gorodkowa's medium. The age of the culture and the amount of moisture present proved to be more important than the type of medium or device employed.

On Sabouraud's agar, young cells of these cultures were globose to ovoid, 5 to 10 mu in diameter. Cell walls were single and contents were granular. Mycelium was not found. A capsule surrounding the cell was demonstrable in India ink preparations. The cells reproduced by budding, usually singly. This type of cell continued to occur in a culture until the medium began to dry out, generally for three to six weeks. If a moist condition was maintained, budding of the cells proceeded without interruption for a longer period of time, eight weeks or more; however, depriving young cells of moisture did not induce changes in less than three weeks.

In the old, drying cultures, two types of cells appeared: a fairly thick-walled, spherical cell, 5 to 10 mu in diameter, containing a large globule which stained with Sudan III and with osmic acid; and a thin-walled cell, globose to ovoid, smaller, contents

granular with two to six small globules. Both types of cells budded, and many possessed tube-like projections some of which were as long as 4 mu. In two instances, fusion of one of the thin-walled cells with one of the thicker-walled type was seen to take place by the uniting of these protuberances. This occurred in broth mounts in van Tieghem cells set up from old cultures on Sabouraud's agar. Cells in temporary mounts, as well as the van Tieghem cultures, indicated that the entire contents of the thinner-walled cell passed through the narrow tube into the other cell. Various stages of the fusion process were noted in slide preparations, such as pairs of cells connected by means of tubes and pairs in which the thin-walled cells were collapsed, the globules in the thick-walled cells having disappeared, leaving a homogeneous mass usually oval in shape, lying eccentrically within the cell. In addition, cells were found composed of a central, oval or spherical area filled with granules. In one instance, these granules were seen to coalesce and form a homogeneous mass which later divided up into small globules. This central protoplasmic mass was surrounded by a thick, shell-like layer wth an aperture near one pole. Occasionally, a second layer, much thinner, lay as a cap over the end opposite this aperture. The aperture of the inner layer ranged from a minute opening to complete separation of the structure from the inner oval or spheroid. Many empty husks were seen. The bodies thus freed were nearly always spherical, fairly thick-walled structures, ranged from 7 to 11 mu in diameter, and contained varying numbers of small globules which took fat stains. These freed spheroids germinated by budding, usually singly, and in some instances were found with buds while the outer husks were still attached.

THE CYCLE

These phenomena seem to have been overlooked in previous studies of this organism, although structures have been described which apparently are phases in this sequence of changes. Many authors have reported observing large, thick-walled resting cells. Freeman and Weidman (6) described the young cell with granular contents, and the old cell with a double-contoured wall and a spherical body which almost filled the interior; in cultures several weeks old the central part of such a cell contained two to eight or more larger or smaller spheroids. Stoddard and Cutler (7) described two types of cells which agree in morphology with the thick and the thin-walled cells. They found empty capsules, which

suggested sporulation to them, but no other evidence of such a process was found.

In consideration of the present observations, it seems logical to interpret the process as representing the perfect stage of this species. This phase occurs only in old cultures which have begun to dry out. In such conditions, cells differing morphologically appear, they fuse and the contents of the thin-walled cell pass through the germ tube into the thick-walled cell. The empty donor cell eventually collapses and breaks away from the fertilized cell. The large globule in the recipient cell probably represents stored food, subsequently used to supply nutriment to the zygote. The contents of the fertilized recipient cell coalesce and form an oval, homogenous mass lying eccentrically in the cell and surrounded by a wall; the interior then breaks up into many globules which almost fill the developing spore. The innermost of the two layers seen at this stage is the spore sac; the outermost layer is probably the old wall of the recipient cell. Finally the spore rounds up and is separated from the sac; it buds, giving rise to the globose cells with granular contents.

The activities of the nucleus during this process are not known; consequently, the single, endogenous spore cannot be termed definitely an ascospore or an oospore until cytological studies have been made.

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