A KEY TO THE HUMAN MYCOSES

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The following key has been constructed as a guide to the diagnostic characteristics of pathogenic fungi as seen in the human body. It is designed to facilitate recognition of fungus structures as such in tissues and fluids, and to provide a clue to the specific identification of the causative organism in a given mycotic infection. In some instances the microscopic appearance of fungus elements in clinical material is so distinctive as to identify the etiological agent immediately, but usually culture is necessary for a definitive diagnosis. In any case, it is always desirable to supplement direct examination with cultures of the parasite since this will serve either to confirm the original impression or to make possible more specific identification. The descriptions of subcutaneous and systemic fungi in stained tissues are based upon the hematoxylin-eosin stain, except as otherwise stated. The terms "hyaline" and "dark-colored" as applied to the structures refer to their innate coloration, which usually is discernible despite the stain.

It will be noted that some of the fungi (and, therefore, the mycoses) occur more than once in the key. This is because they may vary in appearance depending upon the site of infection, stage of maturity of the microorganism, and other factors. An attempt has been made to utilize all possible pathways to their identification. An additional difficulty is experienced in attempting to identify an organism when it is represented by only a very few elements, either hyphae or spores. In a given population of *Blastomyces dermatitidis*, for example, only a relatively few cells may be budding at one time. If a small number of nonbudding cells is seen, the observer cannot be certain whether he is dealing with this organism or some other, possibly *Coccidioides immitis* in the form of immature spherules or *Geotrichum candidum* as represented by rounded arthrospores. The need for culture becomes acutely apparent in such cases.

A minimum of technical mycological terminology has been incorporated in the key, but certain specialized terms, the omission of which would necessitate repeated lengthy definition, are included.

HOW TO USE THE KEY

The key is completely dichotomous, that is, at each step there are two alternatives, given the same letter, each of which leads to either the name of a mycosis or a letter designating a subsequent pair of choices. In the descriptions, an attempt has been made to emphasize, by means of italics, those characters that most clearly define each fungus or disease. In each instance the name of the disease is preceded, in parentheses, by that of the etiological agent or agents. Hav-

ing arrived at the name of an organism, one should test his judgment by means of a photograph of the fungus or, if available, actual known specimens. Appended are several references to good illustrations of the pathogenic fungi in tissue.

"UNKNOWN" EXAMPLE

An illustrative "unknown" may serve to acquaint users with the function of this key. Figure 1 is a photograph of a representative mycopathological slide, showing fungus cells in a lung section. Starting with A it is seen that the tissue is not hair, so that the choice is A₂, which leads to G. The fungus being uncolored, we proceed to M. Since there are "spores" present in the section, we take M₂,

Figure 1. "Unknown". Fungus cells in lung section. Hematoxylin-eosin stain. $\times 618$.

going to T, where T₂, "hyphae absent", leads to Z. The spores are round, Z₂ (to BB), but not "spherules", therefore BB₂, leading to DD. The organism buds (DD₁), so we go to EE, where "no capsule" takes us to FF. Its cells are large, round, and thick-walled (GG), and double-contoured, with single buds (GG₁), indicating the agent of North American blastomycosis, *Blastomyces dermatitidis*. A careful study of the description of this organism under GG will serve as a check on the accuracy of our finding. The size of the individual cells and the broad septum are good confirmatory details.

DIAGNOSTIC KEY

- A₁. Fungus parasitizing *hairs* exclusively or primarily B.
- A₂. Fungus not parasitizing *hairs* exclusively or primarily G.

- B₁. Hard or gelatinous *nodules*, discrete or continuous, formed on *hair shafts*; *skin not involved*.....C.
- B₂. Hard or gelatinous *nodules not present*; hyaline hyphae (2–4 μ diam) or arthrospores, or both, formed within or on surface of hairs of scalp or beard, *hyphae extending into hair follicle and sometimes onto surrounding skin*.....E.
- C₁. Occurring on *axillary* and sometimes *pubic* hairs; *nodules soft* when moist, yellow, red, or black; fungus consisting of *hyphae* of about the *same diameter as bacteria* (1 μ), largely fragmenting into bacillary elements, and embedded in a *gelatinous matrix* (especially evident when moist); sometimes accompanied by groups of cocci (*Nocardia tenuis*. Not cultivable routinely).....TRICHOMYCOSIS AXILLARIS
- C₂. Occurring on hairs of *scalp, beard, or mustache*; *nodules hard*, either whitish to light brown, or black, consisting of a mass of *closely-septate, coarse hyphae* resembling a mosaic of thick-walled spores, 2–8 μ diam.....D.
- D₁. On *beard and mustache*; *nodules whitish to light brown*; budding cells may be seen in the mycelial mass. This disease has not been reported in the United States (*Trichosporon beigelii*).....WHITE PIEDRA
- D₂. On *scalp*; *nodules black or dark brown*; crushed nodules show asci (spore sacs) containing 2 to 8 single-celled, filiform, slightly curved spores. This disease has not been reported in the United States (*Piedraia hortai*)
BLACK PIEDRA
- E₁. *Hyphae and chains of arthrospores* present in *interior of hair*, usually accompanied by *numerous air bubbles and tunnels*; characteristic *scutula* (raised crusts) often formed in affected area. Hairs usually not fragile, remain long; appear dull white under filtered ultraviolet light (Wood's lamp) (*Trichophyton schoenleini*).....FAVUS
- E₂. *Arthrospores* present with or without hyphae, *within hair shaft or on its surface, either in chains or in a mosaic sheath*. Hairs usually fragile, broken off close to scalp (species of either of the two genera in F)
TINEA CAPITIS
- F₁. Infected *hairs fluoresce bright yellow-green* under Wood's lamp; spores in *mosaic in sheath* around the hair (in early stages of infection some hairs may show ectothrix chains—see later). N.B. Hairs not fluorescing *in situ* may show fluorescent roots when plucked (*Microsporum* sp. Differentiable only by culture).
- F₂. Hairs not fluorescing as before; sometimes appear dull white under Wood's lamp; *spores in chains*, either within shaft (endothrix) or on surface (ectothrix) (*Trichophyton* sp. Differentiable by culture, and to some extent by size of spores and whether endo- or ectothrix).
- G₁. Fungus structures *dark-colored*, olive to brown or black.....H.
- G₂. Fungus structures *hyaline or bright-colored*.....M.

- H₁. Hyphae massed in black or dark-colored *granules* (0.5–2 mm diam); lesions consisting of *tumefactions* which may develop draining sinuses, usually on lower limbs, rarely on hands or other part of body. Granules may appear in the tissues or exudate. I.
 H₂. Hyphae or spores not massed in granules. J.

- I₁. Hyphae of about *same diameter as bacteria* (1 μ), gram-positive (*Actinomyces bovis*, *Nocardia madurae*, *Nocardia asteroides*, other *Nocardia* sp. Culture necessary for specific identification)

ACTINOMYCOTIC MYCETOMA

- I₂. *Hyphae broader*, 2–4 μ diam; large, thick-walled *spores often occur within the granule*, especially near the periphery (*Allescheria boydii*, *Cephalosporium* sp., etc. Culture necessary for specific identification)

MADUROMYCOSIS

- J₁. *Olive-colored hyphae present*, usually accompanied by clumps of dark, budding spores or arthrospores; lesions consisting of *superficial dark brown or black spots* on glabrous skin (*Cladosporium wernecki*, *Cladosporium masoni*. Differentiable only by culture). TINEA NIGRA
 J₂. Hyphae absent or, if present, hyaline; spores dark. K.

- K₁. *Spores alone present*, consisting of thick-walled, dark brown, rounded structures, single or clustered (individual mature cells averaging 6–10 μ diam), that divide by formation of a *broad central septum*; the infection is cutaneous; in advanced cases *cauliflower-like outgrowths* appear above the surface of the surrounding skin (*Phialophora pedrosoi*, *Phialophora compactum*, *Phialophora verrucosa*. Differentiable only by culture)

CHROMOBLASTOMYCOSIS

- K₂. Round to oval spores, brown or black, accompanied by *hyaline hyphae*; spores unicellular, 1.5–5 μ diam, occurring scattered in tissue or in fruiting heads on a hyaline sporophore (spore-bearing hypha). Found usually in external auditory canal (otomycosis) or in bronchi and lungs. L.

- L₁. Hyphae *septate*, about 3–6 μ diam; fruiting heads, if present, typical of the genus (*Aspergillus* sp., and possibly other genera which are usually saprophytic. Culture necessary for specific identification)

ASPERGILLOSIS, etc.

- L₂. Hyphae *nonseptate*, *coarser than above* (from 3–6 μ to 14–18 μ); fruiting head consisting of hollow spherical structure (sporangium) enclosing brown spores. Sporangium frequently ruptured, liberating spores (*Mucor* sp. and possibly related genera. Culture necessary for specific identification)

MUCORMYCOSIS

- M₁. *Hyphae alone present* (sometimes in dense clumps or “granules” which may contain a few spores). N.
 M₂. *Spores or yeast-like cells present*, with or without hyphae. T.

- N₁. *Hyphae of about the same diameter as bacteria* (1 μ).....O.
 N₂. *Hyphae coarser, at least 2-3 μ in diameter*.....P.

O₁. In *superficial skin lesions of axilla, genitocrural region or other intertriginous areas*; usually *greasy-feeling, discolored spots* with well-defined erythematous border; hyphae fragment readily into *bacillary or coccoid elements* (*Nocardia minutissima*. Not cultivable routinely)

ERYTHRASMA

O₂. In *subcutaneous nodules or systemic lesions* that are granulomatous and tend to break down, forming abscesses and discharging through *multiple sinuses*. Hyphae compacted in *granules* or in separate *branching filaments* (*Actinomyces bovis*, *Nocardia asteroides*, and other *Nocardia* species. Culture necessary for specific identification).....ACTINOMYCOSIS OR NOCARDIOSIS (including ACTINOMYCOTIC MYCETOMA)

P₁. Compacted into *granules of various colors*, 0.5-2 mm in diam; in subcutaneous nodules or draining sinuses accompanying *tumefactions*, usually of the lower extremities. Large, thick-walled spores often appear in the granule, especially near the periphery (*Allescheria boydii*, *Cephalosporium* sp., etc. Culture necessary for specific identification)

MADUROMYCOSIS

P₂. Not in such granules.....Q.

Q₁. In lesions of *skin and nails*.....R.

Q₂. Involvement of *external auditory canal, mucosae, central nervous system, lungs or other internal organs*. The causative organisms are all common laboratory contaminants, ordinarily. They may be secondary invaders but are only rarely primary pathogens. In the absence of characteristic spores specific identification must rest upon cultural studies.....S.

R₁*. Hyphae 2-4 μ diam, septate, often (but not always) segmenting to form *chains of square to rectangular arthrospores* (*Trichophyton* sp., *Epidermophyton floccosum*, *Microsporum* sp. Generic and specific identification of causative organism can be made only by culture).....RINGWORM

R₂*. Hyphae slightly wider and more irregular in diameter, septate, not forming regular chains of such spores (*Aspergillus* sp., *Scopulariopsis* sp., and perhaps other such organisms which are ordinarily common laboratory contaminants. In many cases these seem to be secondary invaders)

ASPERGILLOSIS, etc.

* N.B.: In the absence of characteristic spores it is not possible regularly to differentiate between these two groups, nor among the species in each group, without definitive laboratory cultural study. First suspicion should fall upon the ringworm group. Isolation in culture of any of the ringworm organisms is considered proof of its etiological role in a given lesion. Isolation of any of the "saprophytes", such as *Aspergillus*, must be accomplished repeatedly, and to the exclusion of other more probable agents, before it can be suspected as the pathogen.

- S₁. Hyphae about 3–6 μ diam, *septate* (*Aspergillus* sp. and other related organisms which are seldom pathogenic. Culture necessary for specific identification) ASPERGILLOSIS, etc.
- S₂. Hyphae *wider*, may be as narrow as 3–6 μ , but range up to 14–18 μ or more, *nonseptate* (*Mucor* sp. and possibly related genera. Culture necessary for specific identification) MUCORMYCOSIS
- T₁. Hyphae present U.
- T₂. Hyphae absent Z.
- U₁. Spores are *budding, yeast-like cells*, intermingled with the hyphae V.
- U₂. Spores *not budding* (although sometimes appearing to do so, in initiation of germ-tube formation by *Geotrichum candidum*) W.
- V₁. Spores *spherical* or nearly so, 3–8 μ diam, usually in *clusters, thick-walled*, with obscure budding, *apparently unconnected with the hyphae*, which consist largely of *short, straight or sinuous fragments with square-cut ends*, sometimes in chains, with or without branching. Lesions are entirely superficial and usually asymptomatic, consisting of *discolored spots on the skin* (*Malassezia furfur*. Not cultured routinely) TINEA VERSICOLOR
- V₂. Spores predominantly *oval*, 2–4 μ diam, *thin-walled*, with *buds usually quite evident; often connected with hyphae*, which tend to be *rounded at ends*, longer than above, and usually show *branching*. Found in nails, inflammatory lesions of skin and mucosae, or pathologic processes of internal organs (*Candida albicans* and possibly other *Candida* sp. Often present in sputum, gastro-intestinal tract, etc., without causing any symptoms, or may be secondary invaders) CANDIDIASIS (MONILIASIS)
- W₁. Spores *square or rectangular* (arthrospores), formed by *fragmentation of hyphae*. (But arthrospores may become rounded secondarily, especially in *Geotrichum candidum*, whose form in sputum may be predominantly round or oval) X.
- W₂. Spores *oval or round*, 1.5–5 μ diam, sometimes pigmented, *not* formed by fragmentation of hyphae, occurring separately or in *fruiting heads* Y.
- X₁. Involving *skin or nails*. Arthrospores in branching chains continuous with hyphae, which are 2–4 μ diam, *septate and branching* (*Trichophyton* sp., *Epidermophyton floccosum*, *Microsporum* sp. Generic and specific identification made only by culture) RINGWORM
- X₂. Involving *respiratory or intestinal tract*; spores and hyphae (2–4 μ diam) usually found in sputum or pus. Spores oblong or rectangular, with square or rounded ends, and often seen to germinate at a corner; or spherical, 4–10 μ diam. The latter forms may be confused with cells of *Blastomyces dermatitidis* (*Geotrichum candidum*. Often present as secondary invader in lesions of tuberculosis, other fungus infections, etc.) GEOTRICHOSIS
- Y₁. Hyphae *septate*, about 3–6 μ in diam; fruiting heads, if present, typical of the genus. (*Aspergillus* sp., and possibly other genera which are usually

saprophytic. Culture necessary for specific identification)

ASPERGILLOSIS, etc.

- Y₂. Hyphae *nonseptate*, *coarser than above* (from 3–6 μ to 14–18 μ); fruiting head consisting of hollow spherical structure (sporangium) enclosing the spores. Sporangium frequently ruptured, liberating spores (*Mucor* sp. and possibly related genera. Culture necessary for specific identification)

MUCORMYCOSIS

- Z₁. Spores *square or rectangular* (arthrospores), formed by *fragmentation of mycelium*. (But arthrospores may become rounded secondarily, especially in *Geotrichum candidum*, whose form in sputum may be predominantly round or oval) AA.

- Z₂. Spores *round or oval*, not formed by fragmentation of mycelium BB.

- AA₁. Involving *skin or nails*. Arthrospores in branching chains (*Trichophyton* sp., *Epidermophyton floccosum*, *Microsporum* sp. Generic and specific identification only by culture) RINGWORM

- AA₂. Involving *respiratory or intestinal tract*; spores usually found in sputum or pus, oblong or rectangular, with square or rounded ends, often germinating at a corner, or spherical, 4–10 μ diam. The latter forms may be confused with cells of *Blastomyces dermatitidis* (*Geotrichum candidum*. Often present as secondary invader in lesions of tuberculosis, other fungus infections, etc.) GEOTRICHOSIS

- BB₁. Fungus, when mature, consisting of *large spherical structures* ("spherules"), thick-walled, filled with *numerous smaller spores*. The latter, when liberated in the tissues by rupture of the spherule, enlarge, each eventually becoming a spherule in turn. All transitional stages may be found . . . CC.

- BB₂. Not as above DD.

- CC₁. Mature spherule 200–300 μ diam, containing round to ovoid spores 7–9 μ diam, which are in turn filled with granules about 1.5 μ diam. Occur typically in friable polyps of mucosae, usually of naso-pharynx or lacrimal sac, or on skin (*Rhinosporidium seeberi*. Has not been cultured)

RHINOSPORIDIOSIS

- CC₂. Spherules 20–80 μ diam; spores 2–5 μ diam; occurring mainly in internal organs but found also in cutaneous lesions (*Coccidioides immitis*)

COCCIDIOIDOMYCOSIS

- DD₁. *Commonly budding*, at least in some of the forms found; predominantly extracellular; not cigar-shaped EE.

- DD₂. *Buds rare or absent*; predominantly or exclusively *intracellular*, or with some forms *cigar-shaped* HH.

- EE₁. With *thick, colorless, refractile gelatinous capsule* encasing spherical to ovoid, single-budding cells, 5–20 μ diam; the encapsulated organisms fre-

quently coalescing to form large *mucoïd masses*. Tissue reaction often minimal (*Cryptococcus neoformans*)

CRYPTOCOCCOSIS(TORULOSIS)

EE₂. Lacking thick gelatinous capsule; various shapes.....FF.

FF₁. *Small*, oval, usually single-budding, thin-walled cells, 2–5 μ in width. (Usually accompanied by hyphal elements) (*Candida albicans* and possibly other *Candida* sp. Often present in sputum, GI tract, etc., without causing any symptoms, or may be a secondary invader)

CANDIDIASIS(MONILIASIS)

FF₂. *Large*, round to oval, thick-walled cells with single or multiple buds. .GG.

GG₁. "Double-contoured" spherical cells, 8–15 μ diam; *buds*, when present, *single* and often separated from mother cell by a *broad septum*. May be confused with single-budding or nonbudding forms of *Blastomyces brasiliensis*, immature spherules of *Coccidioides immitis*, or rounded arthrospores of *Geotrichum candidum*. Occurs only on the North American continent (*Blastomyces dermatitidis*)

NORTH AMERICAN BLASTOMYCOSIS

GG₂. Round to oval cells, 10–60 μ diam, with single or *commonly multiple buds* ranging from 1–2 μ to 10 μ diam. Single-budding forms may be confused with *Blastomyces dermatitidis*, immature spherules of *Coccidioides immitis*, or rounded arthrospores of *Geotrichum candidum*. Has been found only in South and Central America (*Blastomyces brasiliensis*)

SOUTH AMERICAN BLASTOMYCOSIS

HH₁. Fungus cells small, oval, 1–3 μ diam, *rarely budding, appearing encapsulated* in stained sections (Giemsa, Wright's, H&E); predominantly or exclusively *intracellular* in mononuclear cells or macrophages. Can be confused with the protozoa *Toxoplasma* and *Leishmania* (*Histoplasma capsulatum*).....HISTOPLASMOSIS

HH₂. Fungus cells small, *cigar-shaped* (1.5–2.5 $\times$ 3.0–6.5 μ) or *oval to spherical* (3–6 μ), sometimes found in polymorphonuclear cells or giant cells, where they may appear encapsulated; *rarely seen in human infections*, but develop in large numbers in animals (rats, mice) inoculated with infected material, usually pus from subcutaneous nodules or abscesses which are characteristic of the disease (*Sporotrichum schenckii*).....SPOROTRICHOSIS

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