Systemic Mycoses
(Dimorphic Fungi)

Dimorphic Fungi

- Histoplasmosis
- Blastomycosis
- Coccidioidomycosis
- Paracoccidioidomycosis
- Sporotrichosis
- Penicilliosis marneffei

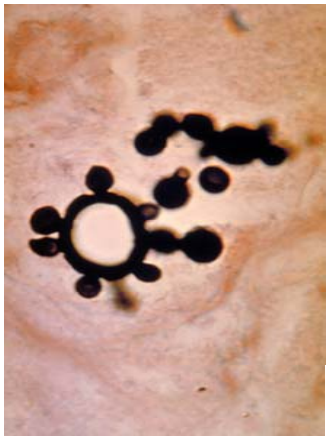
Dimorphic fungi (General Features)

- These infections result from inhalation of the spores of dimorphic fungi that have their mold forms in the soil .
- Within the lungs, the spores differentiate into yeasts or other specialized forms.
- Most lung infections are asymptomatic and self-limited.
- However, in some persons, disseminated disease develops in which the organisms grow in other organs, cause destructive lesions, and may result in death.
- Infected persons do not communicate these diseases to others.

Agent	infection	Dissemination	Drug of choice
Histoplasma capsulatum	Histoplasmosis	*Acute pneumonia (cave disease) *Chronic pneumonia (smoker) *Disseminated (immunocompromised) *Primary cutaneous (lab accidents)	Amphotericin B
Blastomyces dermatitidis	Blastomycosis	Skin and bone Later nervous system and visceral organs	Amphotericin B itraconazole
Coccidioides immitis	Coccidioidomycosis	Skin, bones, joints, subcutaneous tissues, and visceral organs	Amphotericin B
Paracoccidioidoes brasiliensis	Paracoccidioidomycosis	Oro-nasal mucosa latter spleen, liver, intestine and skin	Amphotericin B + sulfas or azoles

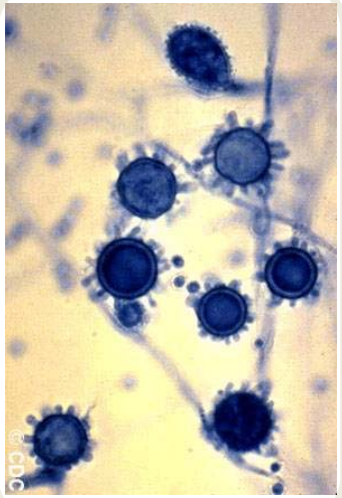
Systemic Mycoses

PARACOCCIDIOIDES

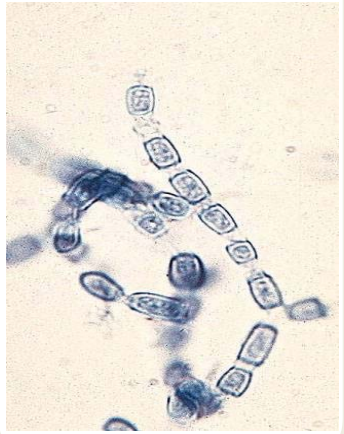


BLASTOMYCES

HISTOPLASMA

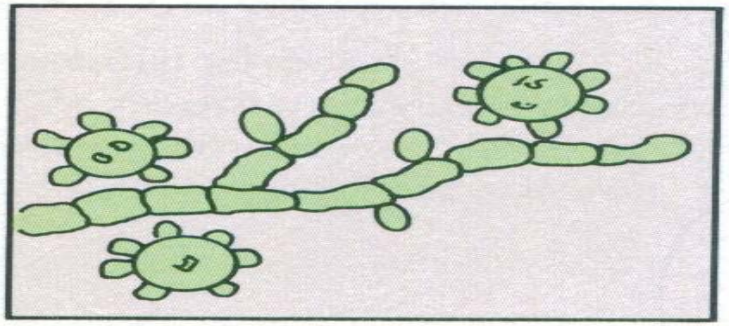


COCCIDIOIDE



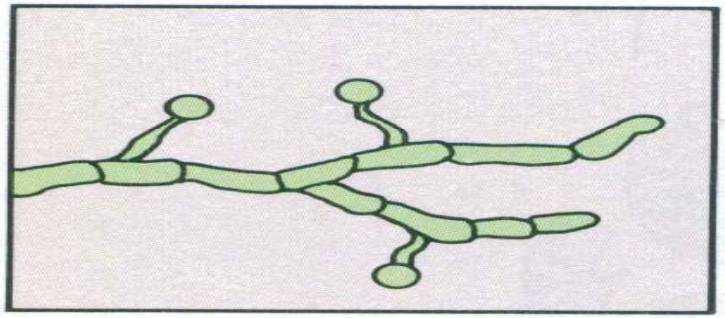
Saprobic phase
(25° C)

Parasitic phase
(37° C)



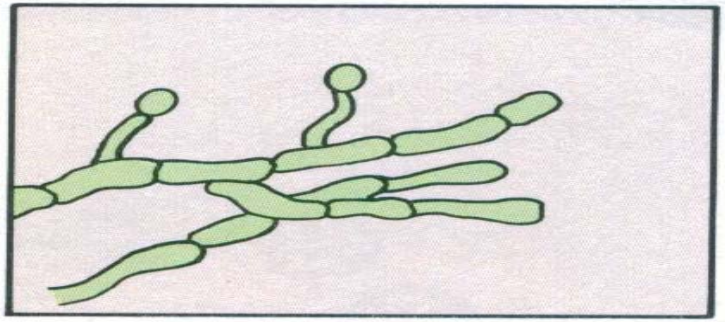
A

A. *Histoplasma capsulatum*



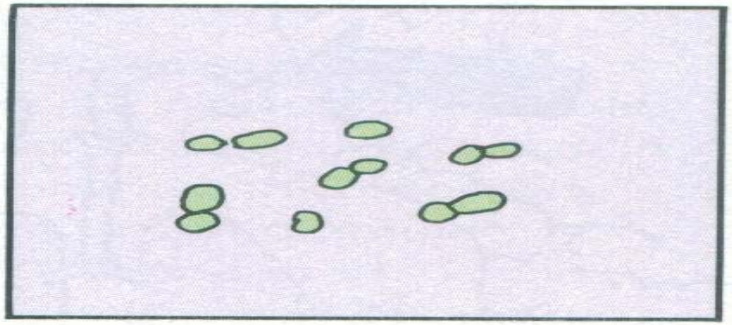
B

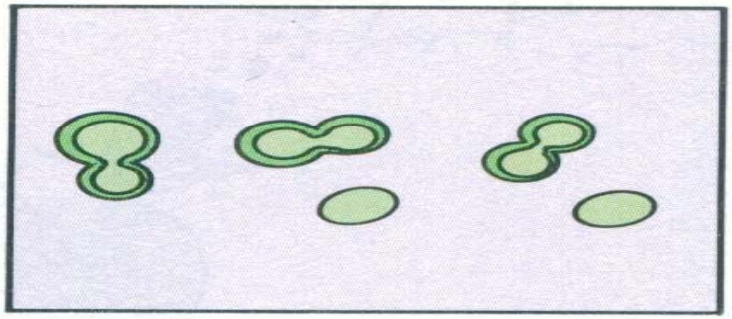
B. Blastomyces dermatitidis

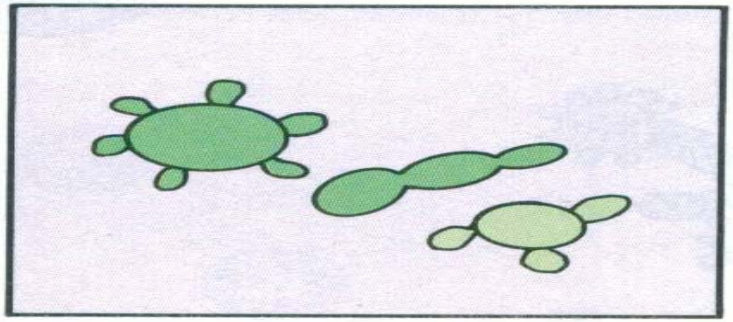


C

C. *Paracoccidioides brasiliensis*







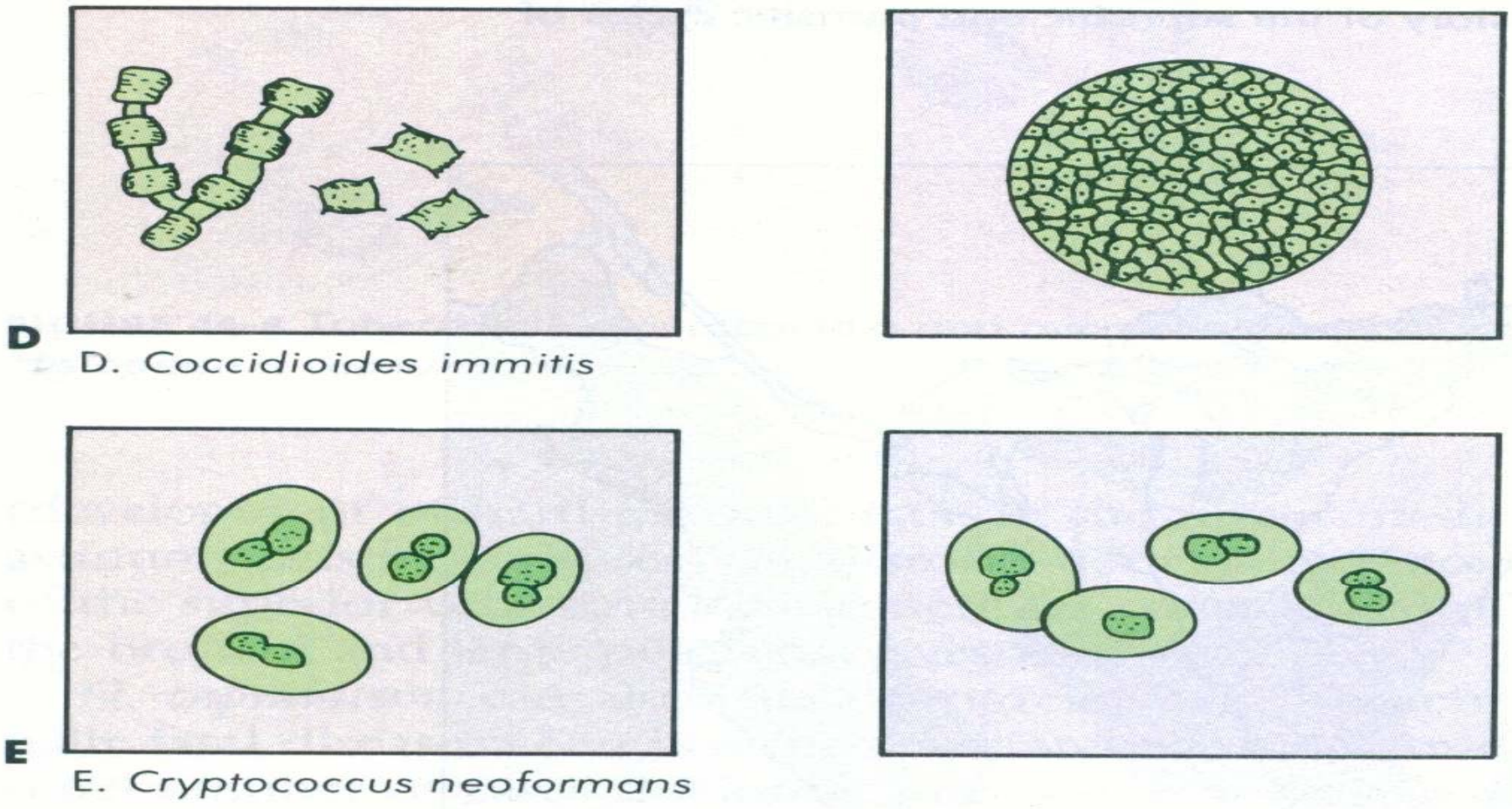


FIGURE 44-1 Schematic illustration of the saprobic and parasitic phases of systemic pathogenic fungi. **A,** *Histoplasma capsulatum,* **B,** *Blastomyces dermatitidis,* and **C,** *Paracoccidioides brasiliensis* exhibit mold-to-yeast transition when infecting susceptible species; **D,** *Coccidioides immitis* exhibits mold-to-spherule transition when it infects susceptible species; **E,** *Cryptococcus neoformans* is an encapsulated yeast at 25° C, 37° C, or in infected tissues.

ECOLOGICAL ASSOCIATIONS

PATHOGEN	HUMAN	SOIL
BLASTOMYCES DERMATITIDIS	1898	1964
CRYPTOCOCCUS NEOFORMANS	1894	1951
HISTOPLASMA CAPSULATUM	1934	1949
COCCIDIOIDES IMMITIS	1900	1932

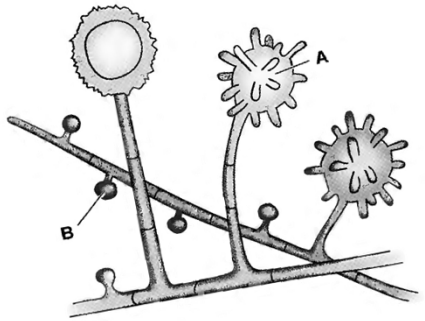
Histoplasmosis

Properties of *Histoplasma*

- *H. capsulatum* is a dimorphic fungus that exists as a mold in soil and as a yeast in tissue.
- It forms two types of asexual spores

(1) tuberculate macroconidia, with typical thick walls and fingerlike projections that are important in laboratory identification,

(2) microconidia, which are smaller, thin, smooth walled spores that, if inhaled, transmit the infection.



Transmission & Epidemiology of *Histoplasma*

- This fungus occurs in many parts of the world.
- In the United States it is endemic in central and eastern states, especially in the Ohio and Mississippi River valleys.
- It grows in soil, particularly if the soil is heavily contaminated with bird droppings, especially from starlings.
- Although the birds are not infected, bats can be infected and can excrete the organism in their guano.

Transmission & Epidemiology of Histoplasma

- In areas of endemic infection, excavation of the soil during construction or exploration of bat-infested caves has resulted in a significant number of infected individuals.
- In several tropical African countries, histoplasmosis is caused by *Histoplasrna duboisii.*
- The clinical picture is different from that

  caused by *H. capsulatum.*

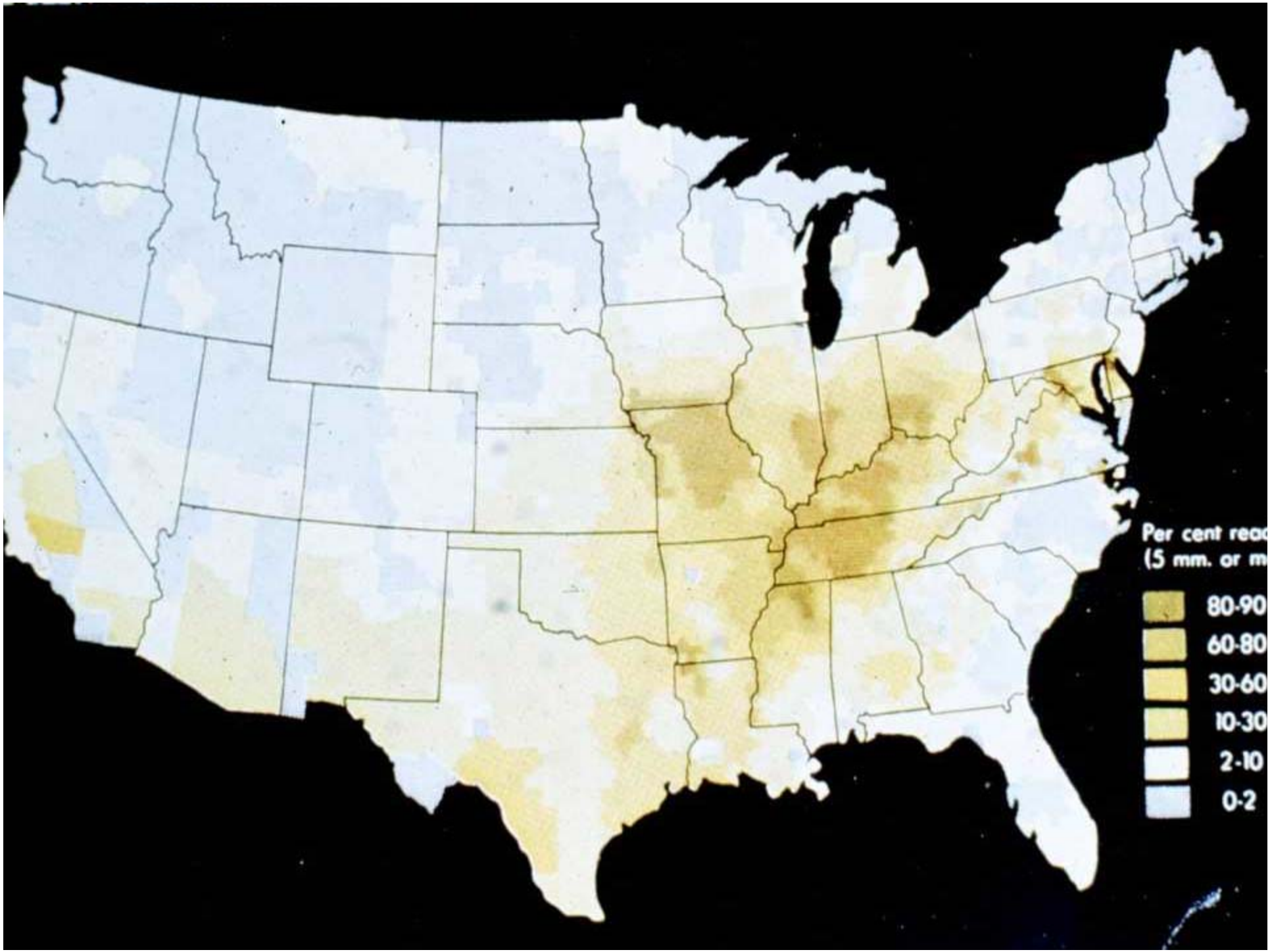
ECOLOGICAL ASSOCIATION

- Blackbird roosts
- Bats
- Bat guano
- Chicken houses

UT OF BOUNDS

BY RECHIN & WILDER

Once his eyes adjusted, Prof. Tudbury realized he had stumbled upon the great bat cave of Louisville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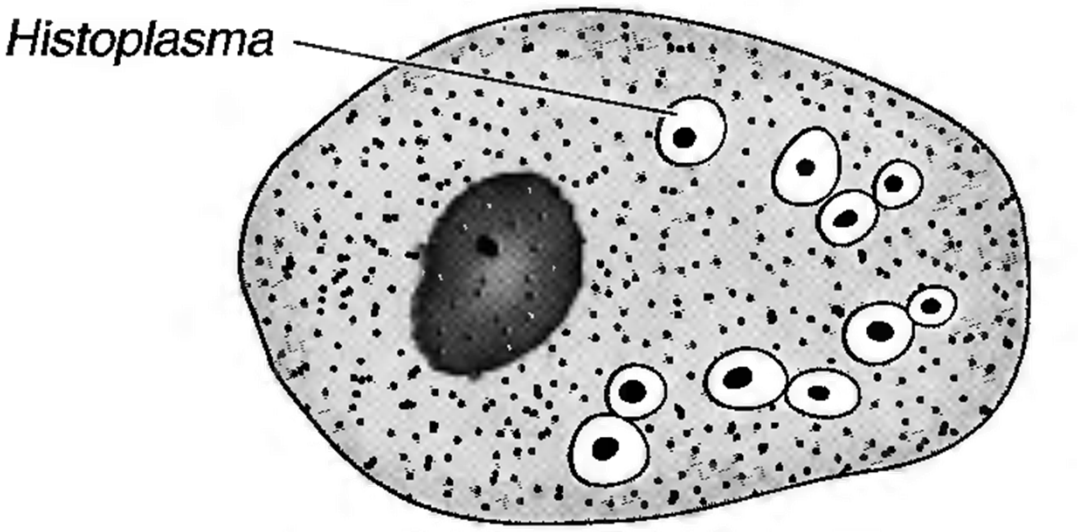
30-60
10-30
2-10
0-2

Pathogenesis & Clinical Findings of *Histoplasma*

- Inhaled spores are engulfed by macrophages and develop into yeast forms.
- In tissues, *H. capsulatum* occurs as an oval budding yeast inside macrophages



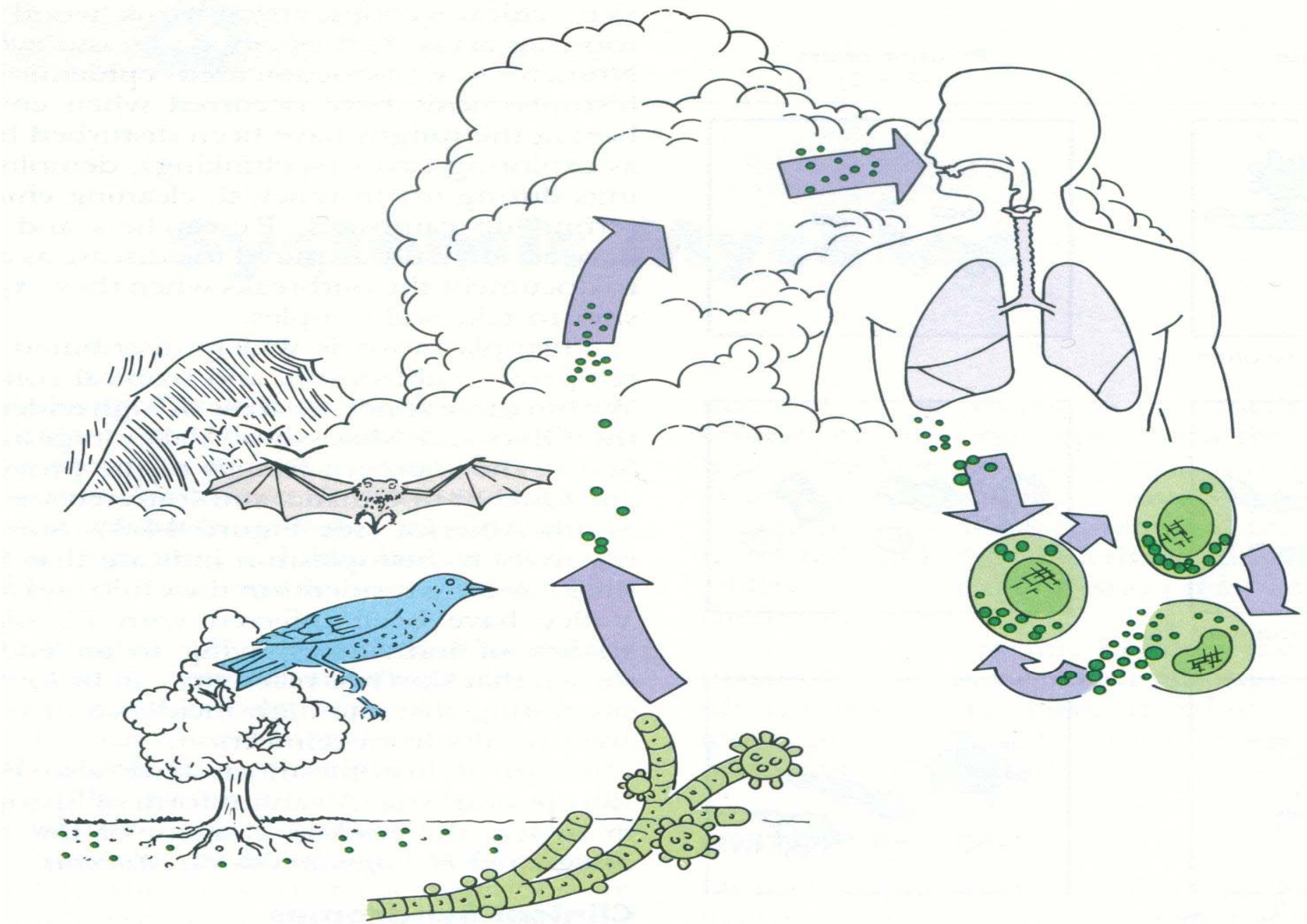


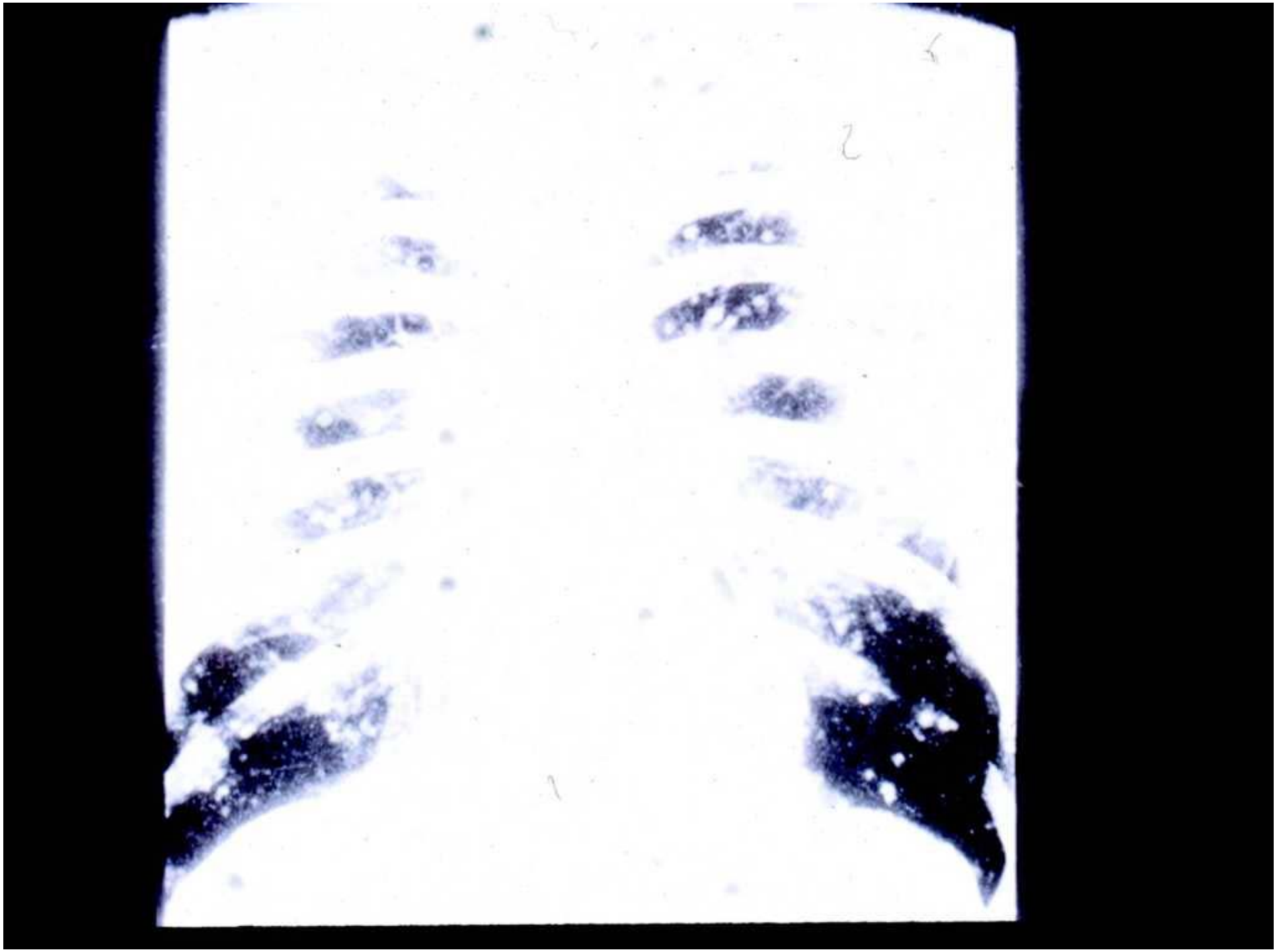
FIGURE 44-2 Schematic illustration of the natural history of the saprobic and parasitic cycles of *Histoplasma capsulatum.*

Pathogenesis & Clinical Findings of *Histoplasma*

- The yeasts survive within the phagolysosome of the macrophage by producing alkaline substances, such as bicarbonate and ammonia, that raise the pH and thereby inactivate the degradative enzymes of the phagolysosome
- The organisms spread widely throughout the body; especially to the liver and spleen, but most infections remain asymptomaric, and the small grantdomatous foci heal by calcification.

Pathogenesis & Clinical Findings of *Histoplasma*

- With intense exposure (e.g. in a chicken house or bat infested cave), pneumonia may become clinically manifest.
- Severe disseminated histoplasmosis develops in a small minority of infected persons, especially infants and individuals with reduced cell-mediated immunity, such as AIDS patients.
- In AIDS patients, ulcerated lesions on the tongue are typical of disseminated histoplasmosis. In immunocompetent people, EN can occur.



Pathogenesis & Clinical Findings of *Histoplasma*

- EN is a sign that cell-mediated immunity is active and the organism will probably be contained.
- A skin test using histoplasmin (a mycelial extract) becomes positive, ie, shows at least 5 mm of induration, within 2-3 weeks after infection and remains positive for many years.
- However, because there are many false-positive reactions (due to cross-reactivity) and many false-negative reactions (in disseminated disease), the skin test is not useful for diagnosis.

Pathogenesis & Clinical Findings of *Histoplasma*

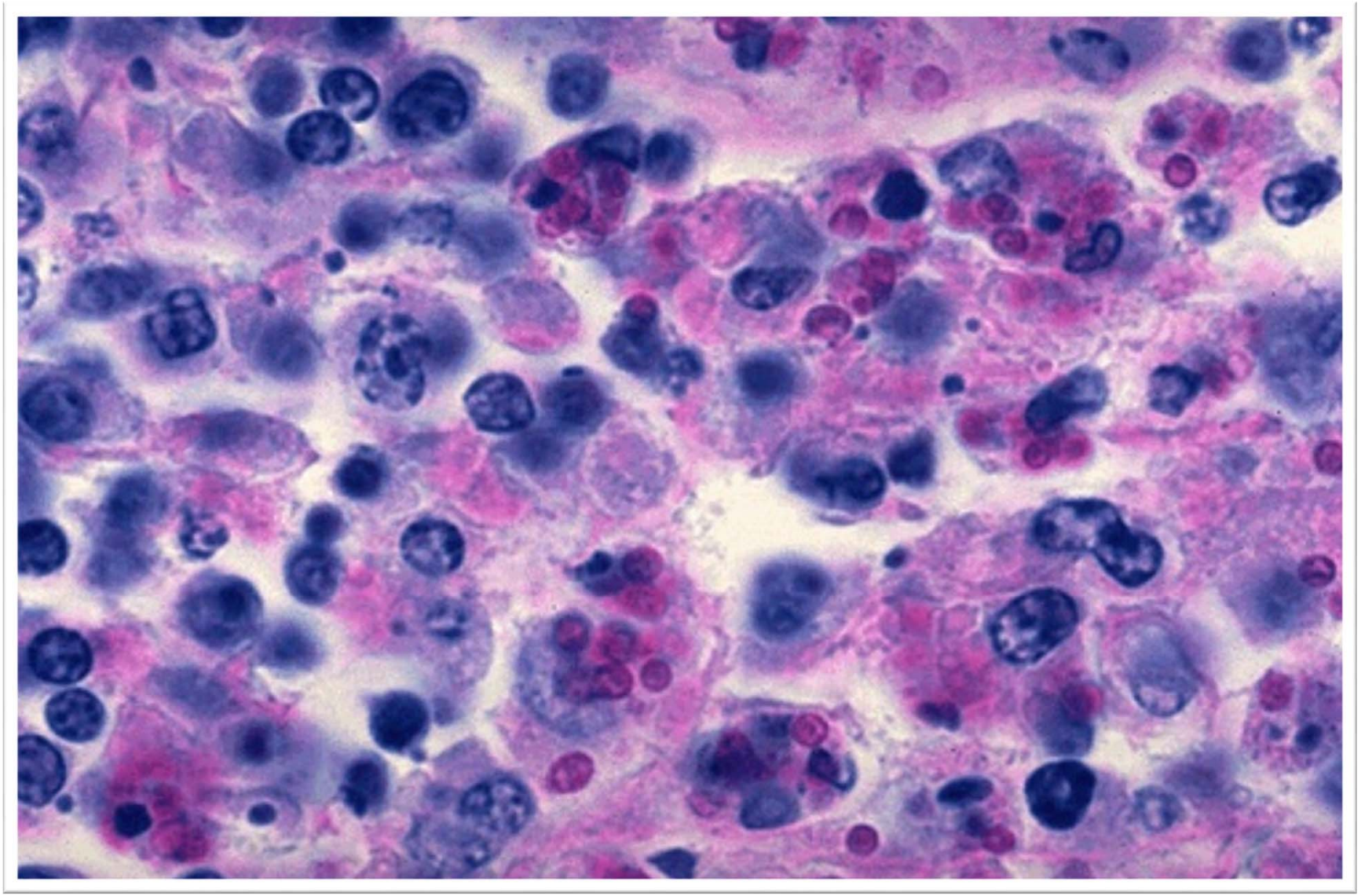
- Furthermore, the skin test can stimulate an antibody response and confuse the serologic tests.
- The skin test is useful for epidemiologic studies, and up to 90% of individuals have positive results in areas of endemic infection.

Laboratory Diagnosis of *Histoplasma*

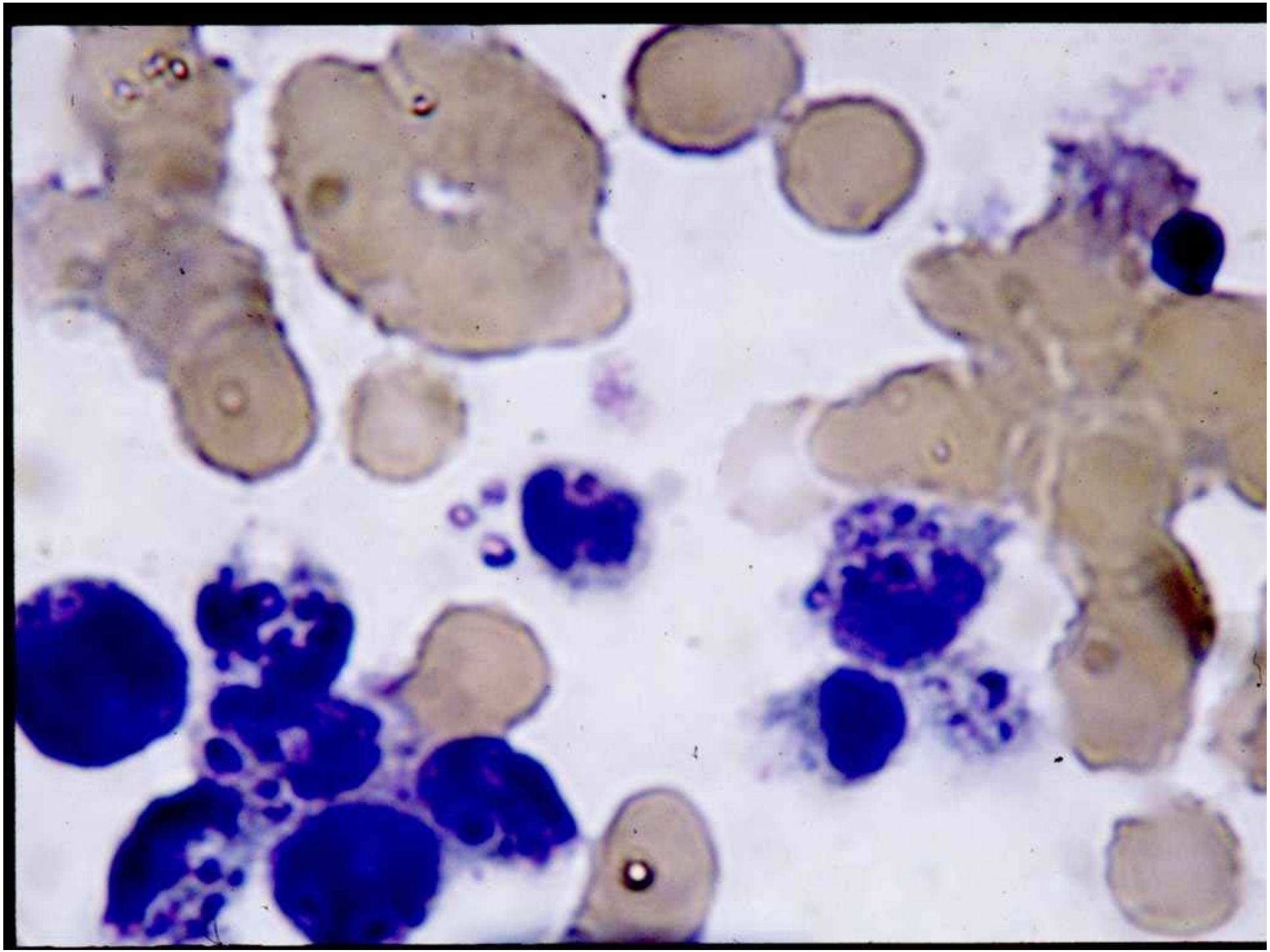
- In tissue biopsy specimens or bone marrow aspirates, oval yeast cells within macrophages are seen microscopically.
- Cultures on Sabouraud's dextrose agar show hyphae with tuberculate macroconidia when grown at low temperature e.g. 25°C and yeasts when grown at 37°C.
- Tests that detect *Histoplasma* antigens by radioimmunoassay and *Histoplasma* RNA with DNA probes are also useful.

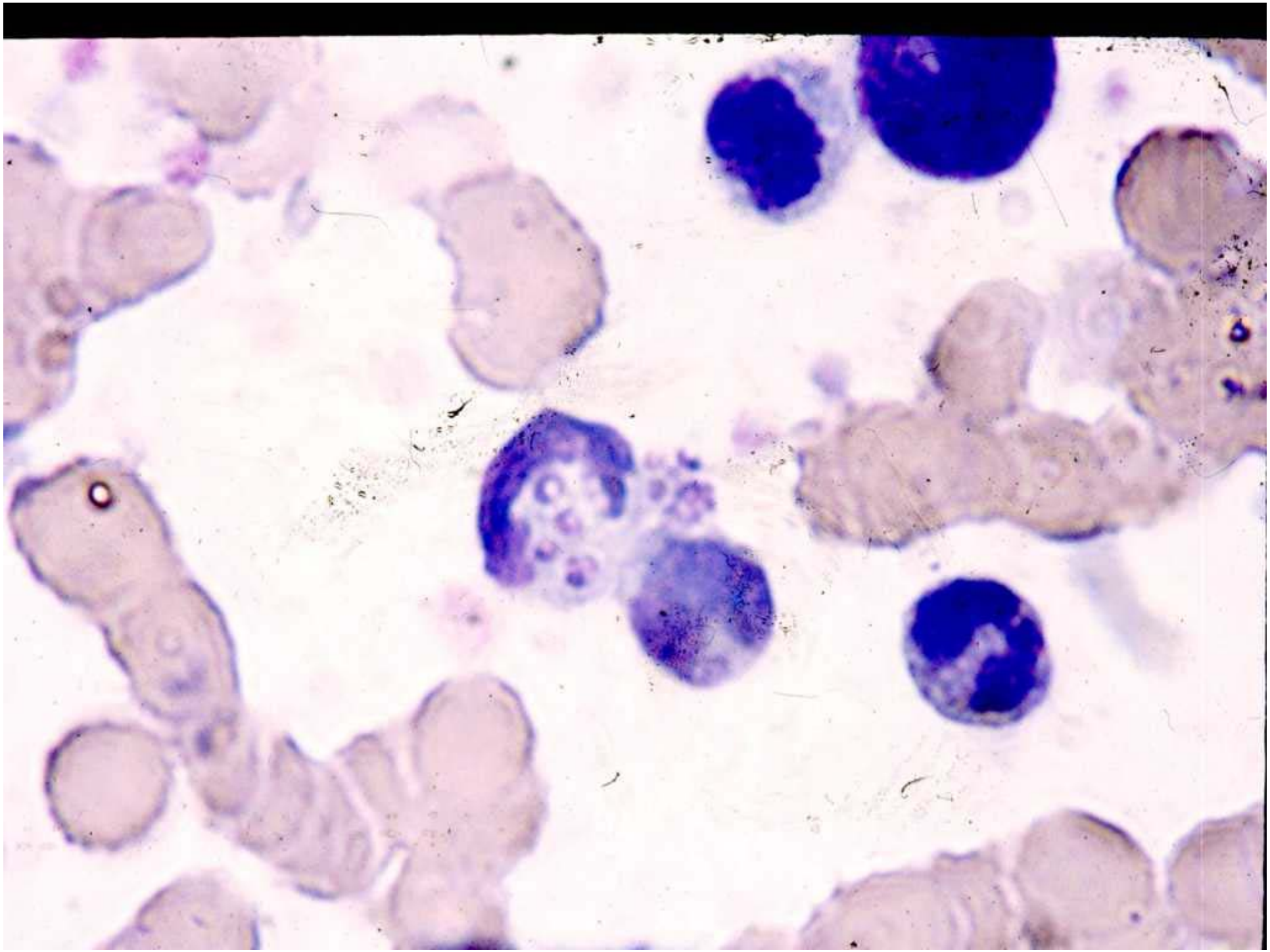
Laboratory Diagnosis of *Histoplasma*

- An antibody titer of 1:32 in the CF test with yeast phase antigens is considered to be diagnostic.
- However, cross-reactions with other fungi, especially *Blastomyces*, occur.
- CF titers fall when the disease becomes inactive and rise in disseminated disease.
- The ID test detects precipitating antibodies (precipitins) by forming two bands, M and H, in an agar-gel diffusion assay.
- The ID test is more specific but less sensitive than the CF test.



PAS stain showing *Histoplasma capsulatum* yeast cells in liver specimen





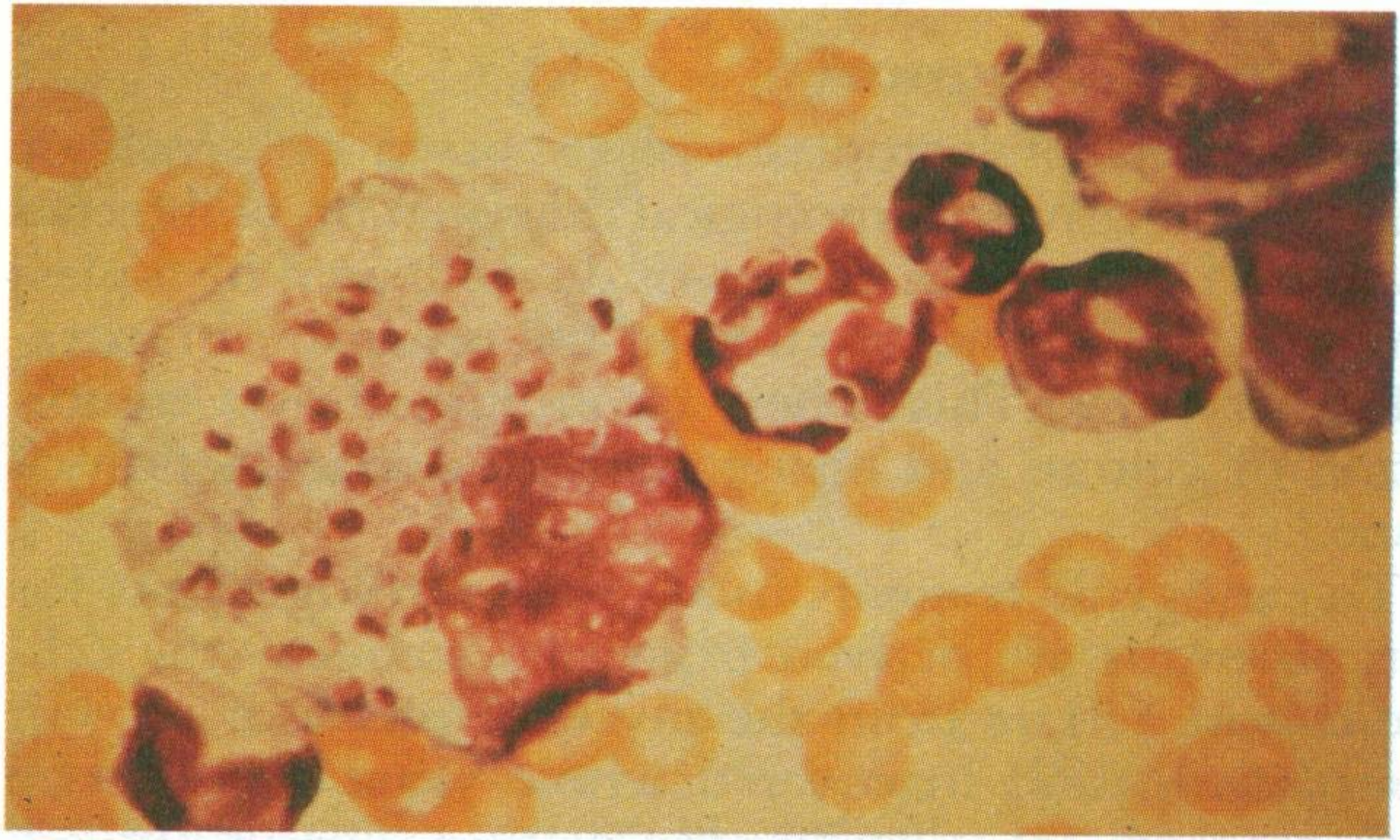
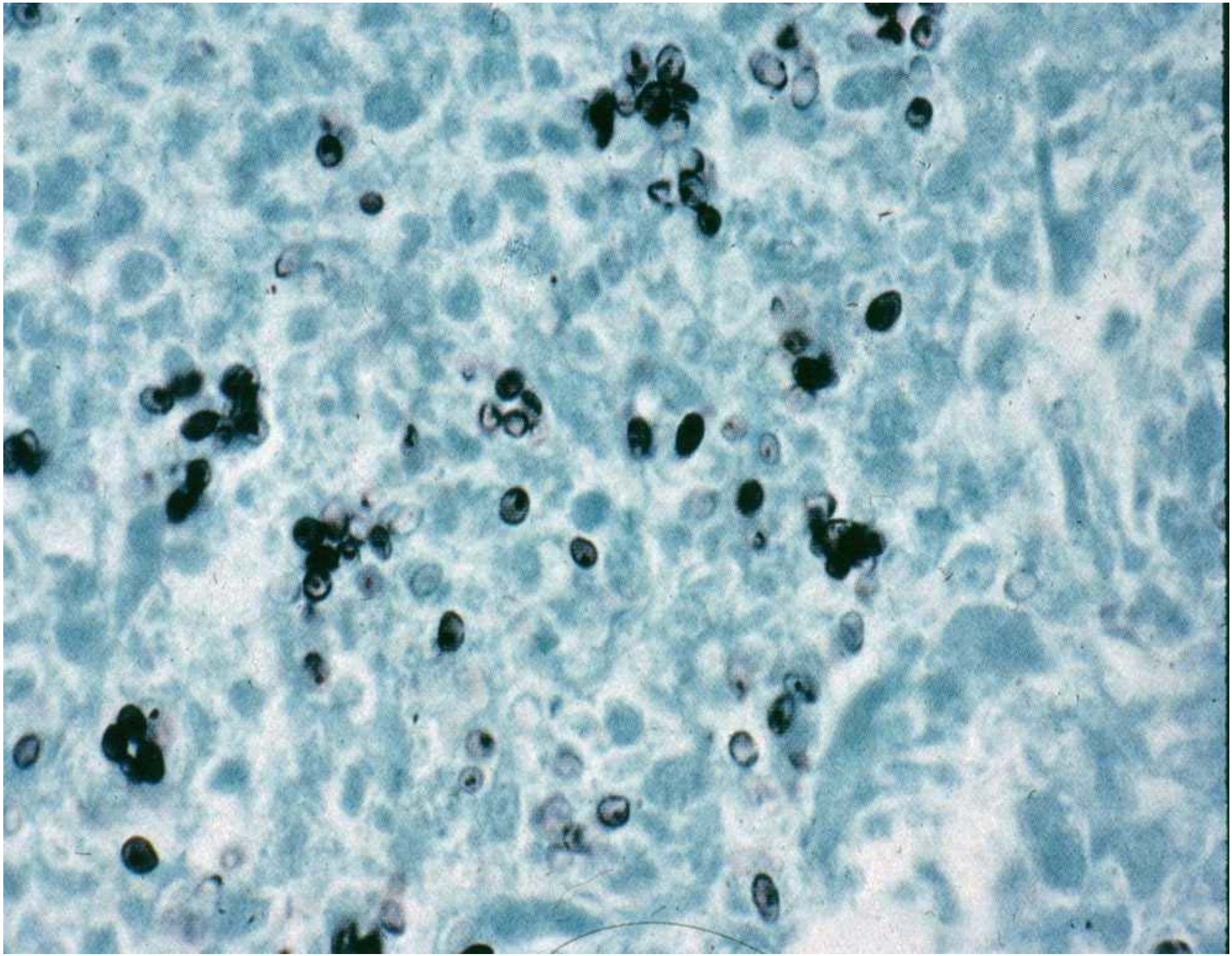
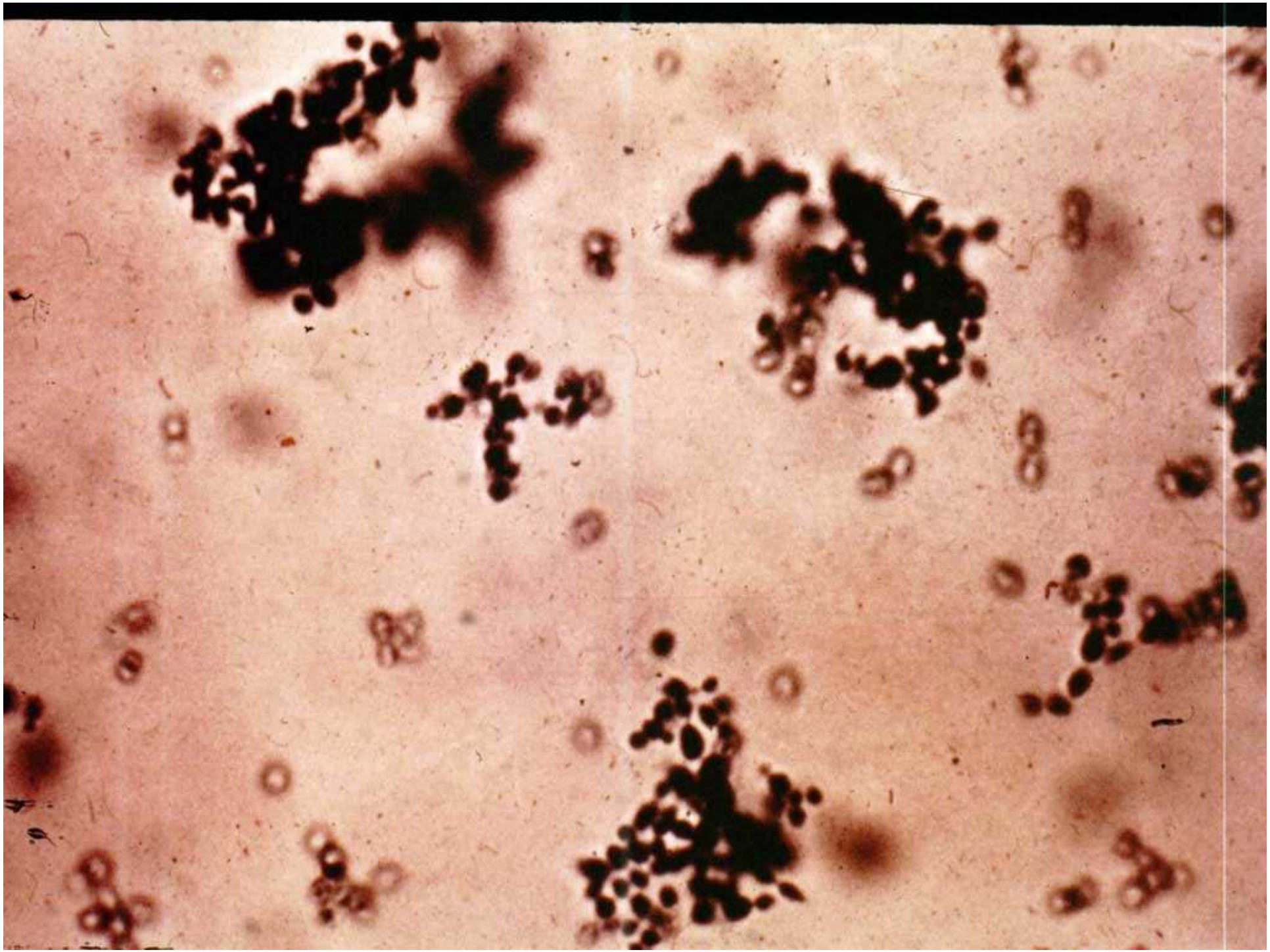


FIGURE 44-5 Yeast cells of *Histoplasma capsulatum* phagocytize by bone marrow mononuclear cells (Giemsa stained section).





Histoplasma capsulatum

Macroconidia and microconidia

Rough-walled macroconidia

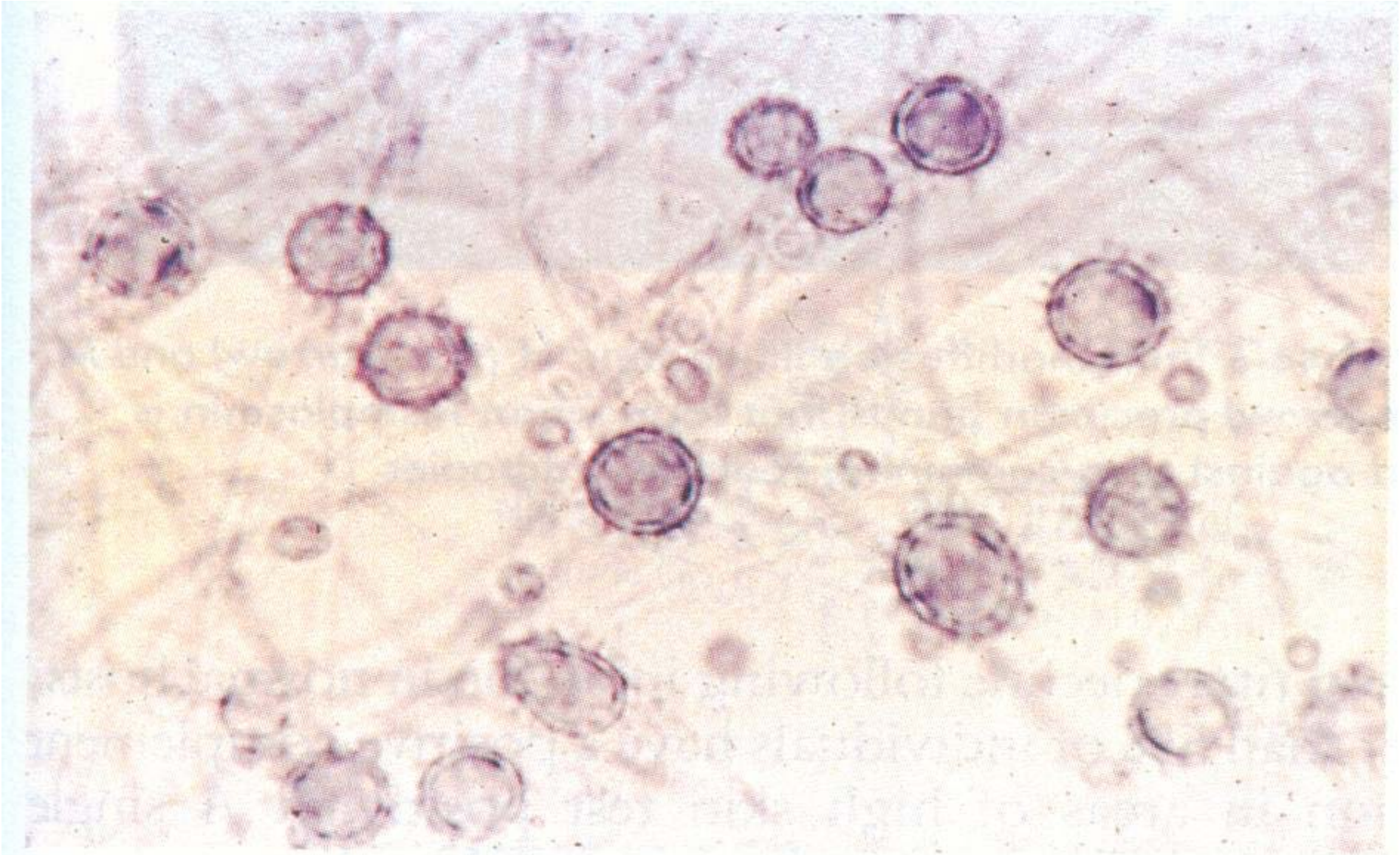
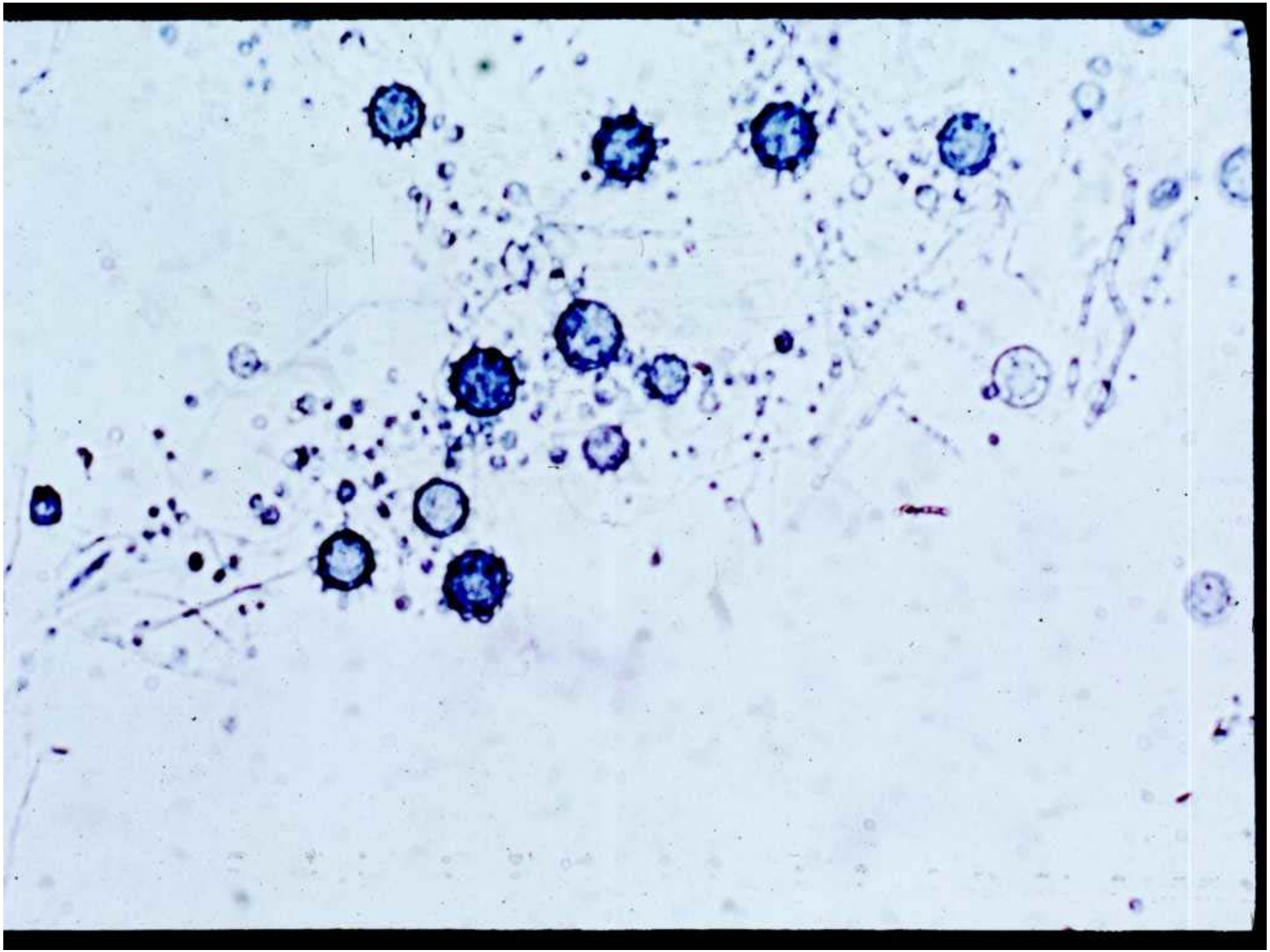
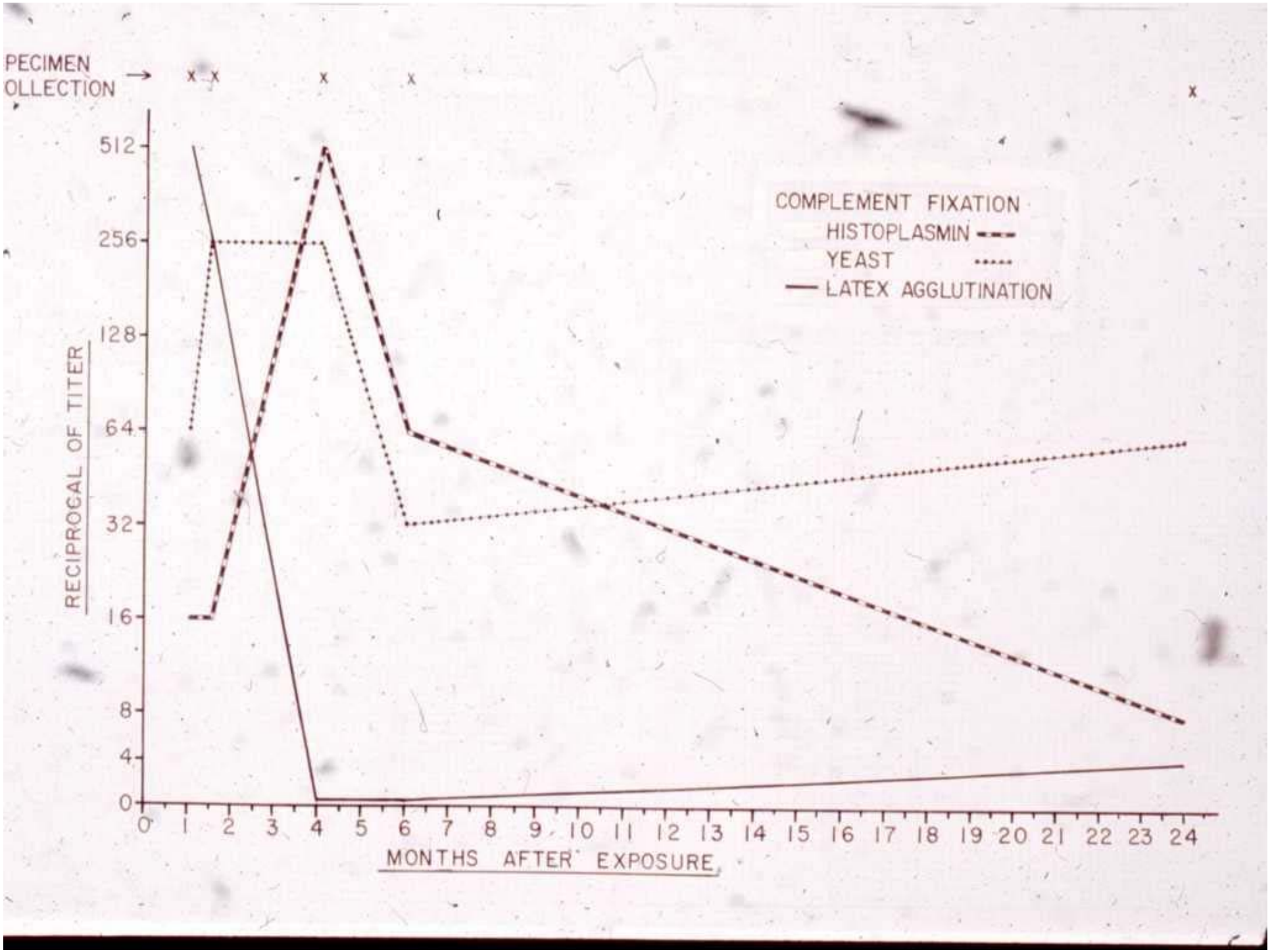


FIGURE 44-4 Tuberculate macroconidia and microconidia of *Histoplasma capsulatum.*

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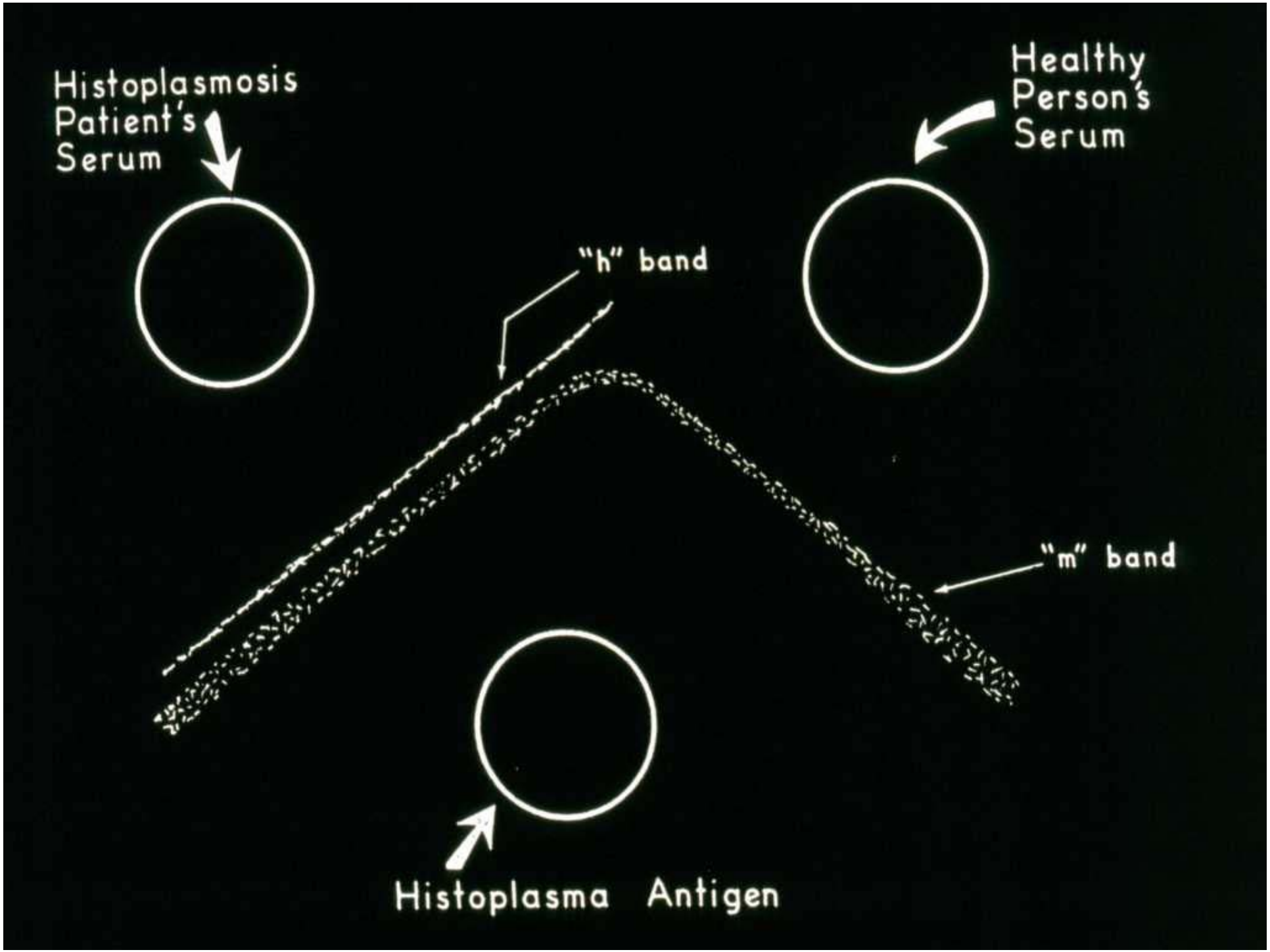
MONTHS AFTER EXPOSURE


Histoplasmosis
Patient's
Serum
Healthy
Person's
Serum
"h" band
"m" band
Histoplasma Antigen

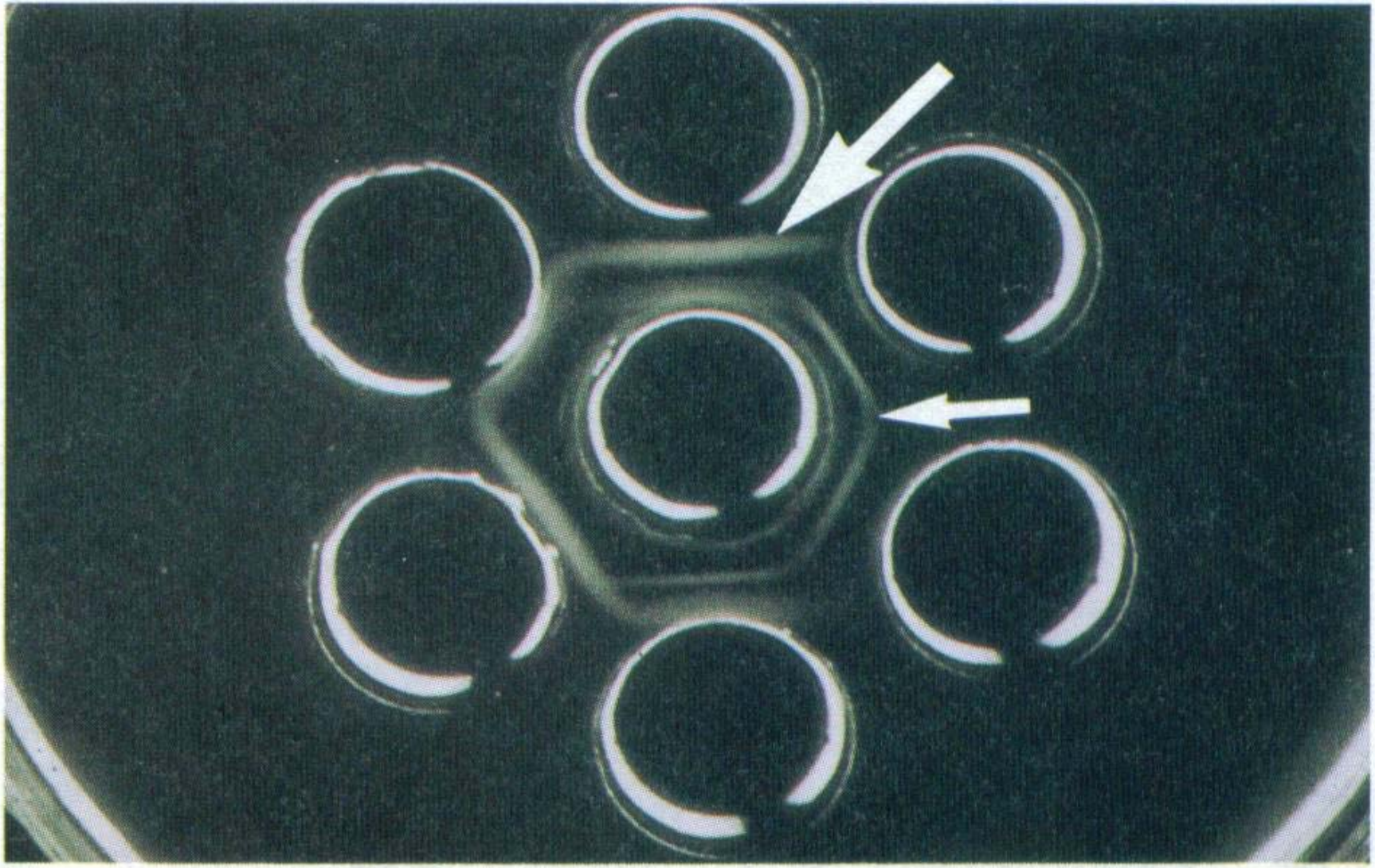


FIGURE 44-6 Immunodiffusion illustrating H *(short arrow)* and M *(long arrow)* precipitin bands that form when histoplasmin is tested against sera containing reactive antibodies.

Treatment & Prevention of *Histoplasma*

- No therapy is needed in asymptomatic or mild primary infections.
- With progressive lung lesions, oral itraconazole is beneficial.
- In disseminated disease, amphotericin B is the treatment of choice.
- In meningitis, fluconazole is often used because it penetrates the spinal fluid well.

Treatment & Prevention of *Histoplasma*

- Oral itraconazole is used to treat pulmonary or disseminated disease, as well as for chronic suppression in patients with AIDS.
- There are no means of prevention except avoiding exposure in areas of endemic infection.