BACK TO THE

Cytologic testing of cerebrospinal fluid is simpler and certainly a lot faster than serologic testing to diagnose cryptococcal meningitis

THE BEST way to diagnose cryptococcal meningitis is one you can do yourself—look into a microscope, says an NIH neurologist, who prefers "bedside" cytology to all other CSF tests for this disease. And now that meningeal infection with the fungus *Cryptococcus neoformans* is treatable, it's more important than ever to diagnose it promptly and accurately.

"This is a good technique that's been around for many years," says Dr. Peter G. Bernad, clinical associate in neurology at the National Institute of Neurological and Communicative Disorders and Stroke. "It's widely used for Pap smears and other cancer studies but very few cytologists and pathologists are aware of its application to neurologic diagnosis."

What's gratifying about cytologic testing for cryptococcal meningitis is that "you can see the bug under the microscope with your own eyes," Dr. Bernad told EM. "You don't necessarily need an expensive lab setup nor do you need to send out samples for serology and wait 24 to 48 hours for results."

If a patient displays signs and symptoms of cryptococcal meningitis, Dr. Bernad advises you to order a lumbar puncture, have 3 to 4 ml of cerebrospinal fluid withdrawn, and have the fluid filtered or centrifuged. After the residual cells have been stained by the Papanicolaou method, you simply put them under the nearest available microscope.

"Every hospital has a lab open 24 hours a day," he points out, "and any internist in the emergency room or neurologist on duty can take a look at the CSF cells himself. He can diagnose the disease in five minutes or less and hardly has to leave the patient's bedside."

The Cryptococcus organism is spheroidal and looks like a lymphocyte, only a little larger, according to Dr. Bernad. "If you move the microscope up and down you'll see something that looks like a halo around the organism, giving the impression of a double capsule. Sometimes you'll see a bud forming on one side: this is pathognomonic for a fungus and if you see it with the halo you can readily assume it's Cryptococcus, especially in a patient who is on immunosuppressive drugs. Occasionally the organism will be enclosed in a macrophage. If you see that plus budding, then you're home free in your diagnosis of cryptococcal meningitis."

Cytologic testing proved 100% accurate in a study of seven patients Dr. Bernad and Drs. Wanda M. Szyfelbein, Howard D. Weiss, and E. Pierson Richardson, Jr., did at Massachusetts General Hospital in Boston. In one patient whose clinical picture suggested cryptococcal meningitis, a latex agglutination antigen titer—regarded as 94% accurate—was positive, they report in *Neurology* (Vol. 30, p. 102), but no organism could be seen under the microscope. "The patient was treated for cryptococcal meningitis and got steadily worse," says Dr. Bernad. "Two days later the lab called to say the titer was false—the serologic agents used had been outdated. The patient was discovered by brain biopsy to

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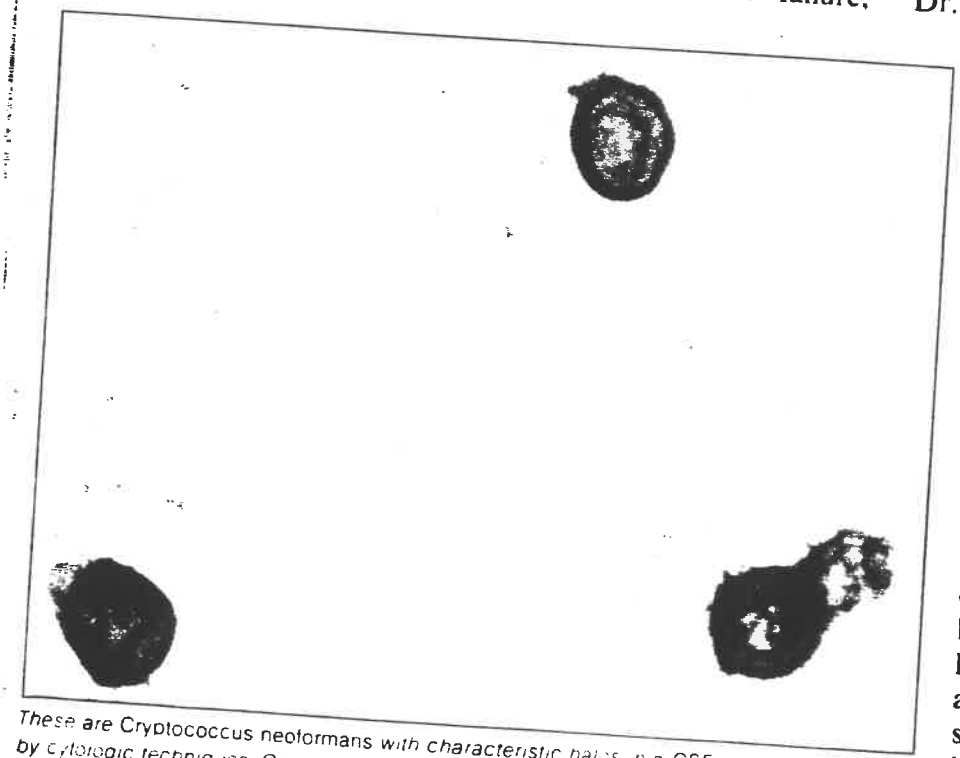
have herpes simplex encephalitis. What we had seen with our own eyes—the absence of an organism—was correct."

The treatment that's gaining acceptability these days is a combination of amphotericin B (*Fungizone*) and 5-fluorocytosine (*Ancobon*). The amphotericin is given intravenously at a dose of 0.3 mg/kg each day for six weeks. "We infuse over a three- to four-hour period," says Dr. Abe M. Macher, a physician in the department of clinical pathology at NIH. "Most reports recommend six hours of infusion, but we've found we can safely infuse the drug in a shorter period."

At the same time, the patient is given oral 5-fluorocytosine, 150 mg/kg a day, in four divided doses for six weeks. "If he can't tolerate the oral drug because he has thrombocytopenia, leukopenia, or renal failure," Dr. Macher adds, "we use the amphotericin B alone at 0.4 to 0.6 mg/kg a day for 10 weeks. We prefer to use the synergistic combination because it subjects the patient to a lower total dose of amphotericin B."

The patient is not considered cured until three criteria have been met. "You do CSF cultures every week during treatment," says Dr. Macher, "and four consecutive cultures should be negative for the organism. Then make sure the CSF glucose—which is very low in meningeal disease—has returned to normal. Finally, the CSF cytology should be negative after therapy. If any of these tests indicate persistent disease, we recommend continuing therapy."

Untreated, cryptococcal meningitis causes progressive neurologic deterioration leading to paralysis, stupor, coma, and death, Dr. Bernad points out. Some patients become hydrocephalic because the fungus blocks their CSF circulation and they have to be kept on shunts for years. "This kind of thing can and should be avoided," he says, "especially since we have such a simple, inexpensive, and accurate technique available to help us." □



These are Cryptococcus neoformans with characteristic halos in a CSF sample prepared by cytologic techniques. One cell is budding, which is pathognomonic for a fungus