

Fungal meningitis pathogen discovers new appetite for human brains

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The nation's ongoing fungal meningitis outbreak has killed 30 and sickened 419 people so far, but the fungus responsible has never wrought such havoc before.

The fungus, *Exserohilum rostratum*, is a plant-eating generalist equipped with a spore-launching mechanism ideal for going airborne, is not an especially picky eater and, although it prefers grasses, will dine on many items—including humans.

But just how a pathogen typically associated with the great outdoors got into the three lots of injectable steroids prepared inside an admittedly filthy laboratory—and why only three lots—remains a puzzling mystery.

The errant fungus has been identified in lab samples from 52 of those affected and was similarly found growing in unopened vials of the steroid alleged to have caused the outbreak, according to the U.S. Centers for Disease Control and Prevention. A third recalled lot is still being tested. But *E. rostratum* is not a household name, even among mycologists.

Glenn Roberts, a retired medical mycologist, says that in his 40 years of experience at the Mayo Clinic in Rochester, Minn., he had seen only one case: a soft-tissue arm wound in an immunocompromised patient. He was shocked when he heard the identity of the pathogen in the epidemic that originated with the New England Compounding Center pharmacy in Framingham, Mass.

"I could hardly believe it because it's just so uncommon," he says.

And yet, outside in the air and on plants, *E. rostratum* is not so uncommon.

In press reports, it has been described as occurring "on grasses," but that is not the full story. The fungus, which seems to prefer tropical and subtropical environments, has turned up on a wide variety of plant species, says Kurt Leonard, an emeritus professor in the Department of Plant Pathology at the University of Minnesota who retired in 2001 from the U.S. Department of Agriculture's Cereal Disease Lab (then the Cereal Rust Lab).

Early in his career, Leonard untangled the taxonomic mess of similar-looking, but only distantly related, fungi with multicellular dark spores that were causing disease in grains such as corn. He named one new genus he had created—*Exserohilum*—for the prominent protuberances called hila (the belly buttons of the fungal and botanical world) on its spores.

The modus operandi of one species in this genus – *E. rostratum* -- was to infect a plant and in some cases precipitate tissue death. Plant defenses—which can include induced cell fortification, cell suicide, toxic chemicals, and defensive enzymes and proteins—typically were sufficient to keep the infection in check, but not strong enough to eliminate it. The payoff came when the plant died—the fungus was first in line to feed on its decaying remains. "I think it's just a general weak pathogen of plants," Leonard says, "something that can infect plants while alive and not really do much damage until the leaf senesces."

Leonard found *E. rostratum* on corn, sorghum and Johnsongrass fairly often, although it was not nearly as common as several more severe corn pathogens. It was an opportunist and would sometimes infect ears and stalks when insects drilled into the plant, creating a convenient landing pad of dying tissue for the fungus.

Most often the fungus shows up on grasses and other monocots—plants often distinguished by flower parts in threes and parallel leaf venation—such as pineapples, bananas and sugarcane, but it has also been found on non-monocots such as grapes and muskmelon.



It's a fungus that is not, apparently, very picky about its food. "It's just a really common fungus in the environment that mostly lives on dead and dying plant tissue," Leonard says. There are many such others, and many of them can also occasionally infect animals or people.

Leonard has observed one other intriguing characteristic of *E. rostratum* in his lab: The fungus can grow from a single spore to a lawn of freshly spore-crowned fungal filaments on a piece of dried leaf in two days flat—faster and more abundantly than any other related species he studied. "This is a fungus very well-adapted to colonizing senescent or dead leaf tissue once conditions are right," Leonard says. "So that would be another reason *E. rostratum* would be a likely candidate for showing up in a messy lab."

But if the fungus is primarily tropical and subtropical, what was it doing in a place like New England?

In the summer the fungus can probably find ideal growing conditions in places in the northern U.S., Leonard explains, or it may be spread northward by winds. The spores have a static electricity-based ejection system designed to launch them into the air with ease. And plentiful lawn clippings provide an ideal place for the fungus to grow.

Roberts says the group of fungi pigmented with melanin (which includes *E. rostratum*)—the same molecule that darkens and protects human skin—seem to be generating more human infections for reasons he does not understand. *E. rostratum*, in addition to causing soft-tissue infections, has also rarely provoked sinus or eye infections, primarily in immunocompromised patients.

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Although the identity of the fungus surprised him, Roberts was not surprised by its ability to capitalize on its situation once inside a patient. After the fungus was injected along with the drug into the epidural space—the space between the dura mater, which encloses the spinal fluid and spinal cord, and the inside walls of the vertebrae—the fungus's filaments were able to penetrate the dura mater, enter the spinal fluid and travel straight to the brain, an environment where the immune system has a very difficult time eliminating or even just controlling infection. "Spinal fluid is a great culture medium—one of the best," he says. "The nutrients are there, and the temperature is certainly right."

Those who suffered the worst infections, he speculates, were probably those in whom the needle accidentally penetrated the dura mater, thereby shortening the fungus's deadly path into the spinal fluid. Then, in some fatal cases, the fungal filaments began to grow in the brain, attracting platelets and white and red blood cells to aggregate around the filaments and form a mass that could block a blood vessel and initiate a stroke. Strokes were not implicated in all the fatalities, however, so the mechanism(s) in those other deaths remains unclear.

The fungus's confinement to just three lots of the drug also remains unexplained. If the facility's water or air supplies in general were contaminated, one would expect all lots to be affected. Perhaps something blew in from a nearby recycling center or some other source on one or a few days and not on others, Roberts speculated.

Another pathway could be the drug itself: Although the water used for making up the final doses was allegedly sterile, the steroid drug ingredient was not. "Using nonsterile components [for injection] in somebody's spine?" Roberts says. "My goodness, that's terrible."

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