

► **Molds and maladies**

Though fungi have always plagued human health, they were not recognized until the 19th century; only in the 20th were scientific means to fight back found.

BY MARK S. LESNEY

Fungal diseases have been the common lot of humanity since the dawn of our species. Fortunately, fungal diseases of humans are generally debilitating rather than lethal, discomfiting rather than agonizing, cosmetic rather than crippling. To bacteria and viruses belong the credit or the infamy of the great plagues of the past. That is not to say that fungi cannot be deadly pathogens under certain circumstances. To the immunocompromised and the unlucky, fungi can be killers, although the number of victims is comparatively small. For the rest of humanity, affected in surprisingly large numbers over the course of their lives, the insidious discomfort, disfigurement, and shame of fungal infections provide chronic rather than acute disaster—from athlete's foot to ringworm to genital yeast infection (see box, "Modes of mycoses").

The historical origin and development of the science of mycology played an integral role in the rise of modern medicine. In fact, many historians consider it the cornerstone of germ theory (perhaps surprising to those who think only of bacteria and of Koch and Pasteur in their vision of "microbes and men"). The historical quest for understanding and for therapeutics and preventives of fungal disease continues as a key component in modern pharmaceutical discovery and development.

Past and present

In the ancient world, many diseases caused by fungi were well known but were ascribed to different causes. The Romans, for example, recognized the disease that we call ring-

worm but attributed it to infestation with small insects. They called the infection "tinea", which refers to small insect larvae. This attribution survives in the medical designations of the fungal diseases ringworm (tinea capitis), jock itch (tinea cruris),



Johann Lukas Schönlein (1793–1864), a pioneer researcher of fungal disease.

and athlete's foot (tinea pedis)—each of which is caused by one or more fungal species.

In 1791, M. Plaignaud first reported anecdotally a fungal infection of the sinuses, although it was not until 1885 that Schubert gave a complete clinical description of the disease, showing it to be caused by an *Aspergillus* species.

In 1888, C. Pellizari described the first case of athlete's foot, tinea pedis, which was not recognized in Europe until 1908. The disease, caused by a fungus endemic to Southeast Asia—*Trichophyton rubrum*—

was considered at the time to be rare. It spread through Europe (one might postulate as a revenge for colonialism), and today it is considered the most common fungal disease in the world, estimated to infect, at one time or another, 70% of the human population. (See box, "Over Here!")

The fungal lung disease histoplasmosis was first identified in 1905 in the Panama Canal Zone, although it was not until 1934 that W. A. DeMonbreun of Vanderbilt University determined that it was of fungal origin. The disease was thought to be rare until a massive X-ray program as part of the military draft in the United States in 1940 showed a high incidence of healed-over pulmonary lesions. Modern estimates hold that approximately 20% of the U.S. population is infected by this fungus.

The rise of germ theory

But perhaps more important to the history of medicine than the discovery of this or that particular disease being caused by any one fungus is the role that medical mycology played in the development of the very concept of microbial infectious disease.

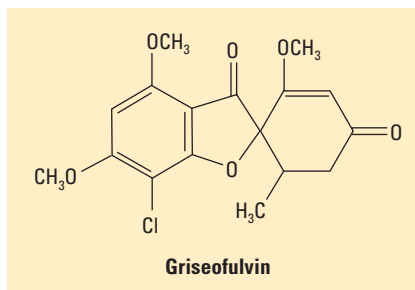
As late as the mid-19th century, most medical practitioners and scientists believed that diseases were caused by poisonous miasmas or imbalanced bodily "humors". The oft-told tale of Pasteur, Koch, Semmelweis, and the other "microbe-hunters" has shown how that attitude changed to the modern belief that a wide variety of microbial agents cause infectious disease.

But surprisingly, the origin of the germ theory of disease traces itself not to these well-known figures but to Agostino Bassi, an Italian lawyer-turned-farmer, who in 1835 was the first to demonstrate that a microorganism, in this case a fungal mold, could cause disease in an animal—the disease was called muscadine, and it affected the economically vital silkworm.

Such research was directed immediately to human fungal disease. For example, in the late 1830s, the fungal agents of tinea infections of the beard and scalp were first described by Robert Remak and Johann Lukas Schönlein. In the early 1840s, David Gruby independently demonstrated that a human scalp disease fungus could be transferred from infected to healthy individuals (including himself!). Unfortunately, this research did little to help the germ theory of disease gain wide acceptance until Louis Pasteur became its chief apostle.

Similar studies of fungal blights in plants would help to establish the notion that microorganisms caused, and did not simply take advantage of, diseases. In 1845, Charles Montagne, a retired French army doctor, advanced a fungal cause for the great Irish potato blight, but it was not until 1853 that his idea was conclusively proven by Anton de Bary, who performed “Koch’s postulates” with the fungus some 30 years before this method was defined.

In 1865, Pasteur took up the study of the same silkworm disease as Bassi, developing methods to prevent the spread of the infection and to detect infected worms. This research, and other investigations into agricultural blights and problems with the fermentation of wine, led Pasteur to develop and promulgate a coherent and



Griseofulvin, the first modern antifungal agent.

widely accepted formulation of the germ theory of disease.

By the 1890s, fungi were recognized as the cause of many skin disorders because of the work of researchers such as Raimond Sabouraud and J. E. Olavide, overcoming the earlier protests of anticontagionists like Alphée Cazenave, who were convinced that microorganisms were artifacts of microscopy, not rational causes of disease.

Modern therapeutics

But knowledge of fungal diseases did not lead to a cure. Not until 1939 was the first modern antifungal agent, griseofulvin—a product of *Penicillium griseofulvum*—discovered, almost inadvertently, during the massive search for penicillin-like antibiotics. It was ignored because of its lack of antibacterial activity until, in 1947, in another of the striking coincidences linking plant

pathology to medical mycology, it was discovered to be an effective antifungal agent in plant disease. Still, not until 1958 was the compound tested in guinea pigs and shown capable of treating infections of *Microsporium canis*. This led to tests that established griseofulvin as a therapeutic agent for human ringworm, which resulted in its commercial development for this disease.

But there was still little effective treatment for the most serious, systemic fungal infections other than attempting to reinvigorate the patient’s immune system to fight them off. It was not until 1956 that the first systemically effective drug for fungal infections, amphotericin B, was isolated from a bacterium, *Streptomyces nodosus*, obtained from the Orinoco River Valley in Venezuela.

Amphotericin B had the drawback of having to be given intravenously. It was not until the 1970s that a systemically effective drug, ketoconazole, was introduced that not only had low toxicity but could be taken orally.

Opportunism knocks

The human body is normally an inimical environment to opportunistic fungi, but when it is immunocompromised, it can become simply food and a place for fungi to live.

Modes of mycoses

One of the most common methods of classifying fungal diseases, which partly reflects their varying degrees of severity, is based on the site of infection. Thus, mycoses are deemed to be superficial, cutaneous, subcutaneous, or systemic (deep), depending on their degree of invasiveness. Superficial and cutaneous fungal infections have been reported since the days of Hippocrates in ancient Greece (though not their fungal origin). Both types of disease involve infections of the hair, skin, and nails. Superficial mycoses include diseases such as black and white piedra (which make nodules on the shafts of hairs), and pityriasis versicolor, an infection of the keratin layer that increases or decreases pigmentation of the skin of the upper body, such as the neck, shoulders, and back. Cutaneous mycoses consist of infections caused by a variety of fungi, including *Candida* species, some of which cause the disease known as thrush in debilitated individuals.

Subcutaneous mycoses can be damaging and disfiguring. These include not only infection of the upper tissue layers but also

infection of bone, tendons, and muscles. There are three general classes: chromoblastomycosis, mycetoma, and sporotrichosis. Some of these infections can develop into systemic illnesses.

Systemic infections are produced by either primary or opportunistic pathogens. Many of the infections are asymptomatic or mild, infecting the sinuses and lungs of large sections of the population in regions where particular fungi are endemic. In infants or immunocompromised individuals, such infections can become systemic, and they can also become lethal as they move into critical organs, including the brain, kidney, spleen, heart, and liver.

In addition to causing infection, fungi can impact human health by triggering allergies and by producing dangerous toxins that can contaminate foodstuffs. One of the most historically significant examples of the latter is the classic medieval epidemics of dancing and the numerous instances of witchcraft hysteria thought to be due to ergotism caused by ingesting toxins in *Claviceps purpurea*-infected rye. Recently, fungal toxins, especially from *Fusarium* species, have been developed as chemical warfare agents.

Because of the stress of frequent wars and malnutrition in the developing world, coupled to an aging population in the developed world and the global specter of AIDS (first diagnosed in the early 1980s), the deadly play of opportunistic fungi has become more common.

Even enhancements in modern medicine have unwittingly increased the likelihood of serious fungal infection. Since the last quarter of the 20th century, the rise of tissue and organ transplants involving immunosuppressive drugs and temporarily debilitating medical treatments has created new homes for opportunistic fungi.

For all these reasons, the quest for more and better antifungal agents goes on, from new treatments for athlete's foot to improved therapeutics for opportunistic fungal infections in AIDS patients.

Fungus amongus

Without doubt, the history of medical

"Over Here!"

According to dermatologists Elizabeth Martin and Boni Elewski, "The first reported case of tinea pedis in the United States occurred in Birmingham, Alabama, in the 1920s. It is thought that World War I troops returning from battle may have transported *T. rubrum* to the United States."

mycology reveals the way in which diverse scientific disciplines can contribute to the understanding of disease and the development of therapeutics. From the investigations of a lawyer-turned-farmer studying silkworm disease in the 19th century, to the multilab genome-sequencing projects being performed today on yeast and *Aspergillus* species, investigations into the nature of the

kingdom Mycota (first separated from plants and bacteria in 1969) have provided information critically relevant to human health, demonstrating clearly the unity of biology that allows biomedicine to flourish as a discipline.

Further reading

Dermatology and Olavide; www.bium.univ-paris5.fr/sfhd/ecrits/olavid2.htm.

Fungi as human pathogens; www.botany.hawaii.edu/faculty/wong/Bot135/LECT09.HTM.

Human mycoses; www.doctorfungus.org/mycoses/human/human_index.htm.

Martin, E. S.; Elewski, B. Tinea pedis; www.emedicine.com/derm/topic470.htm.

MSD fungal disease site; www.mercksharpdohme.com/pro/fungal_disease/info/facts/home.html.

Mycology online; www.mycology.adelaide.edu.au.

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