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I'VE GOT YOU UNDER MY SKIN – THE MOULDS OF MAN

There are thought to be over 1.5 million species of fungi. Of these, most live on decaying vegetation, in partnership with algae (lichens) or tree roots (mycorrhizas) or are parasites of plants or insects. Only a few tens of species cause us any direct harm but *Mycologist* is featuring a series of articles about the main species that do cause irritating, and in some cases life-threatening human infections. In this issue *Coccidioides immitis* is discussed.

Coccidioidomycosis: flying conidia and severed heads

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Some of the participants at the 2001 world model airplane championship contest in Lost Hills, California, took home more than suntans and souvenirs. One participant from the UK and one from Finland became very ill with a flu-like pulmonary disease. They had been infected with *Coccidioides immitis*, a fungus endemic to the Californian deserts and a few other similar sites in the New World. Their illness, coccidioidomycosis (also known colloquially and historically as Valley Fever, San Joaquin Valley Fever and Gilchrist's Disease) is a mycosis with a rich and remarkable history.

Biology of *Coccidioides immitis*

The textbook basic details of coccidioidomycosis are easy to describe. *C. immitis* Rixford & Gilchrist is a soil fungus that thrives mainly in regions of the Lower Sonoran Life Zone in the Americas – areas characterized by low rainfall and desert scrub vegetation – which are found in a belt that runs from Central California, southeast through Arizona and Texas, into Central America and some parts of South America. The hyphae of *C. immitis* do not form specialized spore-bearing structures; instead, they break apart at their cross-walls (septa) to form partially jointed conidia (arthroconidia). Unlike most arthroconidial fungi, which turn every cell chamber of the hyphal strand into a conidium, *C. immitis* forms an arthroconidium from every *other* cell (Fig 1). When dust containing *C. immitis* is disturbed, the conidia form an aerosol that is easily inhaled. These are the 'flying conidia' of the title of this article. If visiting the Californian desert, don't kick up the dust!

In the lungs, inhaled *C. immitis* conidia have three possible fates. In the first, they will be engulfed and destroyed by the local white cells – pulmonary macrophages – which act as policemen to remove unwanted microscopic visitors. Secondly, the conidia can evade the macrophages and start to grow. When this happens the fungi develop a totally different growth form, known as the spherule (Fig 2). The conidium swells to form a large cell and as it does so, new, small pre-spherules form within it. Once the mother spherule has grown to its full size, it bursts open, releasing hundreds of individual round cells, each capable of developing into a new spherule. In this form, the fungus can invade lung tissues and set up an infection, with lots of host immune cells swamping the infected site in an effort to remove the fungus.

It takes at least a week or as long as a month after inhalation of the conidia for the infection to begin. The patient experiences a respiratory illness, with

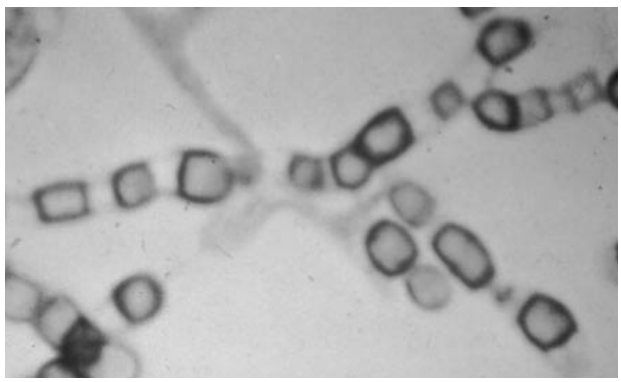

Fig 1 *Coccidioides immitis* alternating arthroconidia formed from hyphae; the form of the fungus found in soil.

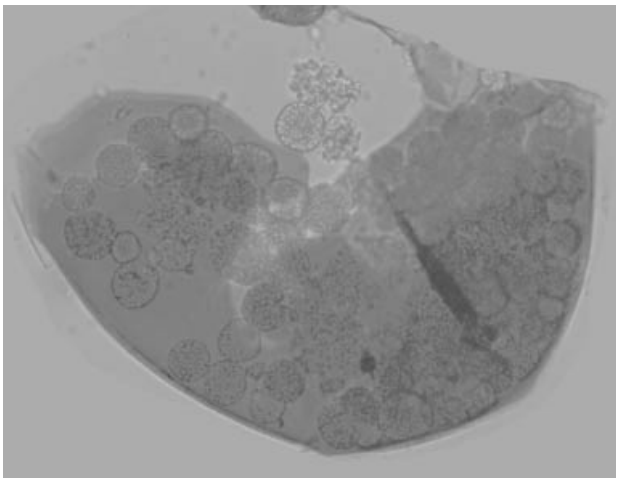

Fig 2 A rupturing spherule of *Coccidioides immitis*. The fungus converts to this endosporulating growth form when it invades human tissues.

symptoms which range from a mild illness not unlike a cold to a severe lung infection with fever and chest pain; this is what happened to the two model aviators who caught coccidioidomycosis at their competition. Because the most common consequences of inhaling *C. immitis* conidia are no illness or a mild respiratory illness, the majority of people who inhale the fungus are not aware that they have done so. However, a simple skin test with *C. immitis* antigen can prove that people have been exposed to the fungus; that is why we know that most people who inhale the conidia suffer no ill effects.

It is the third possible consequence of inhaling the flying conidia that is the worst. The infection spreads beyond the lungs: the fungi get into the bloodstream. The circulation carries the fungal spherules all over the body. They feel particularly at home in the skin and the membranes surrounding the brain and set up progressive infection in these sites. Disseminated coccidioidomycosis, particularly coccidioidal meningitis, is a killer disease. It is a particular problem in individuals with lowered immunity and has ended the lives of many people with AIDS who live in or have visited one of the endemic zones for *C. immitis*. But you do not have to be sick already to suffer disseminated coccidioidomycosis. Microbiology laboratory staff have died of it (never sniff a plate with a woolly, grey mould growth!) and *C. immitis* is the only fungus ever studied seriously as a candidate for germ warfare. For non-Americans, it is not only visitors to Lower Sonoran Life Zones who are at risk of coccidioidomycosis: the fungus is constantly being transferred by aeroplane from its normal habitat in places such as Edwards Air Force Base to US air bases in England and Germany. A few cases are seen every year in Europe.

History and the severed head

Coccidioidomycosis is one of those unusual diseases where the history of the first two patients is known in minute detail: indeed, it is still possible to view part of the very first victim! He was Domingo Escurra. In 1889, when he was a 33-year-old cavalryman serving in Northern Argentina, he noticed what he thought was a spider bite on his right cheek. The lesion worsened, becoming warty, and further similar excrescences developed, not just on his face, but in his groins and the skin of his trunk. He tried treating himself with tobacco and by cutting off the lesions with his knife, but he ultimately sought medical help. He was treated with nitric acid, mercury compounds and potassium iodide, all without effect.

Escurra came under the care of a young physician called Alejandro Posadas, who examined biopsies of his diseased tissues under the microscope. Posadas was therefore the first person ever to see *C. immitis* spherules. He called them 'psorospermiae', or 'sporangia', and christened what he was sure was a new protozoan with the name *Psorospermia*.

Escurra died in 1898; his head was preserved in formalin and was rediscovered in 1948 in Buenos Aires at the University School of Medicine. The head has remained there ever since, in the Institute of Parasitology. In 2000 it had a week's display in the Buenos Aires Hilton hotel, the venue for that year's Congress of the International Society for Human and Animal Mycology, so that many contemporary medical mycologists had the rare chance to see a piece of history more than 100 years old (Fig 3).

A contemporary of Escurra who emigrated in 1886 to the San Joaquin Valley in California was Joas Furtado-Silveira. His fate was to become known as the second coccidioidomycosis patient. Like Escurro, he first developed persistent sores on his head and neck. Silveira was studied over a long period by the physicians Rixford (at what is now Stanford Medical School) and Gilchrist (of Johns Hopkins Medical School in Baltimore). It was Rixford & Gilchrist who coined the name *Coccidioides* for the organism they saw in biopsies of Silveira's sores. They recognised it as the same organism described by Posadas, but they studied it and described it thoroughly and formally, so their choice of name is the one with precedence. However, they always thought it was a protozoan, and regarded the grey mould that appeared every time they tried to culture the organism as a contaminant!

Poor Silveira underwent a series of appalling and mostly ineffectual treatments at the hands of his enthusiastic physicians. These included excruciatingly

painful injections into the lesions of methyl violet, iodine, and bromine, all to no avail. He was treated with mercury salves, phenol and potassium permanganate. His lesions were variously scraped, cut out and cauterized. When he died he had lost both his eyes, his nose and part of an ear.

History and the flying conidia

By the end of the 1930s, coccidioidomycosis was well understood. The endemic zone for the fungus had been largely defined, the risk of the flying conidia was understood, and the skin test to detect persons who had suffered subclinical coccidioidomycosis was in use. It had become recognised that races differ in their vulnerability to systemic spread after inhalation of the fungus particles, with Asiatic races (above all Filipinos) the most vulnerable, followed by blacks, then whites, with the Amerindian tribes native to the endemic areas least likely to develop disseminated disease. (Recent data indicate that blacks are 10-20 times more vulnerable to dissemination than whites, and Filipinos are 175 times more vulnerable.)

Despite the growing knowledge of the risks of coccidioidomycosis, the outbreak of World War II led to the building of many airfields in southwest California, with an inevitable consequent rise in the incidence of the fungal disease. Many of the personnel in the airfields were black, whereas few blacks had previously lived or worked in the desert areas. Urgent efforts were made to develop effective vaccines for coccidioidomycosis, but clinical trials with a spherule vaccine that looked effective in animal studies did not start until the 1970s. To this day we still do not have an effective vaccine for routine use.

When the Vietnam war ended in 1975, the US undertook almost an action replay of its World War II scenario. Of the huge numbers of Vietnamese refugees who were placed in camps throughout the USA, many were initially assigned to Camp Pendleton, located unequivocally in the California endemic area for coccdioidomycosis. At the peak of the refugee influx, Camp Pendleton held 18,000 Vietnamese in tents where the surrounding dust provided an ample source of flying conidia. Not surprisingly, many of these highly susceptible people developed the disease after they had moved elsewhere in the USA.

Treatment and outlook

Most people who inhale *C. immitis* conidia and do not suffer disseminated infection are immune to further disease, although occasional recurrences

Fig 3 The preserved head of Domingo Escurra, the first patient documented with coccidioidomycosis, photographed in 2000 during the Congress of the International Society for Human and Animal Mycology in Buenos Aires.

(reactivations?) have been known. The availability of amphotericin B, a broad-spectrum antifungal agent, has revolutionized treatment of coccidioidomycosis since the 1960s, and the advent of other, safer agents such as triazole antifungals since the 1980s has undoubtedly saved lives and eradicated disfiguring lesions in many people who would otherwise have suffered the consequences of their infection. HIV-infected individuals are particularly susceptible to coccidioidomycosis, so the disease incidence rose markedly through the 1980s and 1990s until the advent of successful anti-retroviral agents impacted on all the collateral infections associated with AIDS.

Coccioidomycosis still remains difficult to treat successfully, and patients with disseminated disease have to continue daily courses of antifungal drugs for the rest of their lives.

The impact of molecular biology: a postscript

John Taylor at the University of California, Berkeley, studies the classification of fungi by molecular phylogeny – the analysis of DNA sequences for classification purposes. He became interested in *C. immitis* when there was a large outbreak of coccidioidomycosis in California in 1994. He began to

develop methods for typing individual strains of *C. immitis* based on the sequences of certain DNA regions known as microsatellites. His group's study of isolates of the fungus from California, Texas, Mexico, and Central and South America began to show unambiguously that there were two major types of strains. One was clustered in California and the US Southwest; the other was found in Texas and in Central and South America. Taylor's data suggest that *C. immitis* found in South America were transported there by southerly migrations of Amerindians from Texas – migrations that are well known to anthropologists. Taylor's research has gone on to show that his two clusters of *C. immitis* undoubtedly represent two well demarcated species of fungi. As of January 2002, we can now talk formally of two species of *Coccidioides* causing the same human disease. The Californian species is *C. immitis*: the new, second species has been christened *C. posadasii* (Fisher *et al*. (2002)), after the Argentinian physician who first saw the fungus.

These findings make it highly likely that Escurra and Silveira, the first two victims of coccidioidomycosis to receive medical attention, were infected with different species of the causative fungus: Escurra with *C. posadasii* and Silveira with *C. immitis*. Will somebody seek to extract the fungal DNA that is undoubtedly still obtainable from Escurra's preserved head to confirm his infection as caused by the fungus now named after his doctor?

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Report of the 8th International Fungal Biology Conference, Guanojuato, Mexico: December 2002

The IFBC, (originally named the International Spore Symposium) met in the beautiful city of Guanojuato to the north of Mexico City on 1-5 December 2002. This meeting encompasses current advances in broad swathes of mycological topics including aspects of growth and differentiation, plant and animal disease, biocontrol, sexual and asexual development and genomics. An extremely high quality of symposia and workshops by international leaders in the field was presented, supported by a wide variety of posters and informal discussions in a relaxed environment. A feature of the meeting was the many recordings of movies of growing fungi, in many cases showing how the distribution of organelles or regulating proteins influenced the dynamic behaviour of fungal cells.

The British Mycological Society was well represented through invited symposium talks by Nic Read, Nic Talbot, Sarah Gurr, Lorna Casselton, Gordon Beakes and Neil Gow – the latter two also serving on the International Steering Committee for the meeting.

Amongst the large number of high quality presentations it was extremely difficult to isolate specific talks as conference highlights. However, from a personal perspective the quality of the work by Nic Read, Robbie Robertson and Anne Straube (representing the Gero Steinberg lab), showing the dynamics of hyphae and growth and *Ustilago* differentiation was extremenly impressive. Regine Kahman gave the keynote address on development and pathogenesis in *Ustilago* and her elegant overview of this maize pathogen was supported by a series of other fascinating talks on this organism. Another exciting vignette for me was the wonderful recent work by Greg Jedd who has established the molecular genetics of Woronin body function in fungi which was presented in the first poster session. This report could be extended by describing many exciting advances, but it may be better to simply record the overwhelming impression that experimental mycology is alive and well and taking its place at the forefront of cell and molecular biology. We all look forward to the next meeting in Nancy, France in 2005.

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