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

Introduction

There are thought to be over 1.5 million species of fungi. Of these, most live on decaying vegetation; others exist in partnerships with algae (lichens) or tree roots (mycorrhizas), or are parasites of plants or insects. Only a few tens of species cause any direct harm to humans, but in forthcoming issues the *Mycologist* will feature a series of articles about some of the principal species of fungi that do cause irritating, and in some cases life-threatening, human infections. In this issue *Candida albicans*, the major serious human pathogen, is introduced.

Candida albicans – a fungal Dr Jekyll and Mr Hyde

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Twenty years ago a clinician could have been excused for being largely ignorant about fungi as disease causing agents. How things have changed! In the league table of serious infections in which microbes enter the bloodstream (septicaemia) and then challenge the functioning of the vital organs, the fungus *Candida albicans* (Robin) Berkhout has risen through the ranks of obscurity to rival some of the most common bacterial septicaemias (Calderone, 2002). It may not be appreciated that there are many more *Candida* infections and *Candida*-related deaths than there are, for example, cases of bacterial meningitis. In fact, there is a small group of *Candida* species that cause disease of which *C. albicans* is the most common and important. It is therefore right to know this yeast as fungal public enemy number one. If a doctor diagnoses a bacterial blood infection, in most cases a number of antibiotics can be used to treat the condition. Unfortunately, fungi share many of the same basic biochemical pathways as humans and so our opportunities to intervene using therapeutic drugs that discriminate between human and fungal target enzymes or biochemical steps are far fewer. Consequently, *Candida* and other fungal septicaemias are perilously difficult to treat, and the treatment is frequently unsuccessful, so that deaths rates may be as much as 30-50% in spite of antifungal treatment.

Mercifully *Candida* septicaemias are still relatively rare, and they are almost non-existent in normal healthy people. Indeed, *Candida* blood infection is often said to be a 'disease of the diseased' since it is only seen when a patient's normal immune system is laid low by some other condition or treatment. For example, a patient undergoing a bone marrow or kidney or heart transplant takes immune-suppressing agents to dampen down immunity to prevent the body rejecting the marrow or organ graft. This opens the door for so-called 'opportunistic' infections like those blood infections caused by *C. albicans*. It should be remembered that amongst healthy people at least 50% carry the organism in the gut, vagina or skin most of the time, and without any signs of infection at all. The organism is clearly adapted to life as a commensal and its transition from a benign Dr Jekyll to an aggressive Mr Hyde is really an unfortunate accident due to the progress and availability of medical treatments for other medical conditions. Therefore, it is medical progress itself that accounts for the meteoric rise in the numbers of *Candida*-associated infections and deaths in recent years.

Although, as mentioned above, serious infections are rare and invariably associated with another influence on normal immunity, these rules do not always apply as strongly to an entirely different form of the disease repertoire caused by *Candida* species – namely 'thrush' or 'yeast infections'. These infections are caused on mucous membranes, most commonly in the vagina or in the mouth (Fig 1). Again, an episode of thrush is often related to some other disturbance of the balance between the infectious capability of the fungus and the constant surveillance of the immune system. Antibiotics that wipe out the competing bacterial microflora, such as gut anaerobes and lactobaccilli, can let the fungus grow unchecked. Despite contrary claims, there is little definitive evidence that taking oral contra-

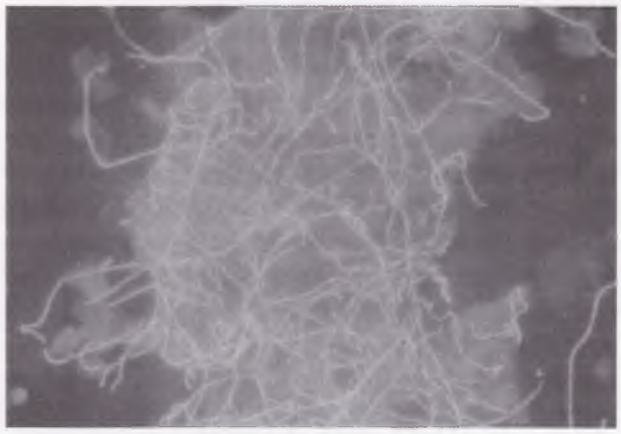

Fig 1. Filamentous hyphae of *C. albicans* adhering closely to diffusely staining epithelial cells of the vaginal epithelium. (Courtesy of Pamela Hunter).

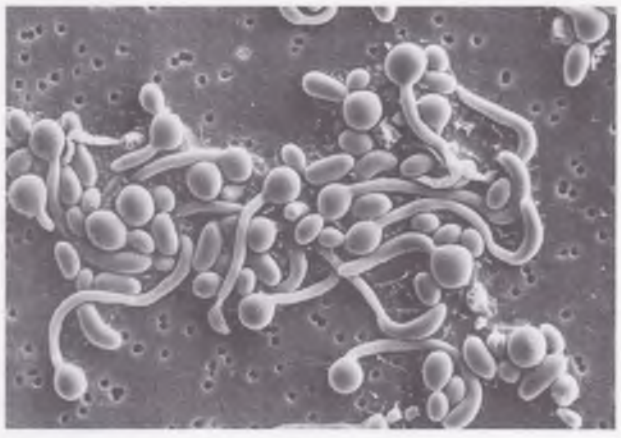

Fig 2. Scanning electron microscope image of *C. albicans* filamentous germ tubes formed from yeast cells.

ceptives, or the condition of diabetes, leads to thrush. AIDS patients very commonly get oral esophageal *Candida* infections although this almost never progresses to a blood infection. The new HAART (highly active anti-retroviral treatment) regimens that include new generation antiviral-protease inhibitors in a cocktail of drugs have been extremely effective in eliminating these oral-pharyngeal infections. It is even possible that the antiviral proteases cross-react and inhibit *C. albicans* proteases, which are implicated in the establishment of *Candida* infections. Fortunately for the majority of people, thrush responds very well to treatment with antifungal drugs such as the azoles. In many western countries some of these azole formulations are available over-the-counter. It is important to note that thrush infections, while painful and often a severe impediment to the quality of life, are never life-threatening. Sadly, some women suffer from recurrent vaginal infections, often associated with the monthly menstrual cycle.

The medical basis of this phenomenon is still not fully understood and although the infection normally responds well to antifungal medication, the psychological and physical effects of regular painful infections are considerable. Preying on this there are many well-meaning but seriously misleading books written by amateur pundits who recommend diets with, often, no provable practical benefits. There is a minor industry of dietary supplements and anti-*Candida* diets that are promoted to those desperate for an alternative to the regular use of prescribed antifungal drugs. Most are unsupported by any credible medical research. It does seem clear that reducing sugar consumption and having a well balanced diet is helpful, but diets that urge the shunning of all yeast products are plainly ludicrous. The basis for this particular idea seems to be the erroneus notion that bakers yeast (*Saccharomyces cerevisiae*) may defy 700 million years of divergent evolution and may be capable of mutating into *Candida*. More likely that a frog could turn into a walrus since, in evolutionary terms, these are closer relatives than the two yeasts!

What about the villain of the piece – the fungus itself? *Candida albicans* is one of many species that have been termed 'dimorphic'. This means that it can grow as either a filamentous mould-like mycelial form or as a budding yeast, similar in shape at least to the harmless yeast used in brewing and baking (Fig 2). Until recently it was thought that the fungus has no sexual form but was locked into a permanent diploid state (with two copies of every gene in each nucleus). But, surprisingly, the genes encoding the mating locus turned up in the *Candida* genome project (http://sequence-www.stanford.edu/group/candida/index.html) and then two groups of reseachers managed to engineer strains that recreated the mating locus of compatible mating partners (Hull *et al.*, 2000; Magee & Magee, 2000). These engineered strains mated successfully but so far the mated strains have not been able to go on to form sexual ascospores. There is also some evidence that mating may occur in nature. This means in the human body since *C. albicans* is a very unusual fungus that is isolated only from humans and other animal sources. The holy grail for the future will be to recreate the ability of this fungus to undergo sexual development and sporulation as this would greatly facilitate the analysis of the *Candida* genes that cause disease.

What of the current state of our understanding of why this fungus causes human infections? This is a huge area of highly active research (Calderone, 2002). Clearly, the situation is very different from that for many bacterial pathogens when the disease is often explainable simply in terms of the effects of a specific toxin. No toxin, no disease. Pathogenic *Candida* species produce no known toxin, but they do have a battery of enzymes such as secreted proteases, lipases and phospholipases, that can

degrade human tissues. *Candida* proteases in particular seem to be an important aspect of virulence. There are also many adhesive molecules, such as mannoproteins on the surface of the cell wall of the fungus that enable the fungus to hang on tenaciously to human epithelia in the gut, vagina, and linings of blood vessels. Finally, the ability of the fungus to form filaments seems to be a part of the repertoire of virulence factors that make this one of the most feared and common fungi that attack human beings. Progress is being made. Techniques have been developed that enable molecular biology to take its part in defining the genes that are required for virulence and the targets for future new generations of antifungal drugs. The need now is to translate our increasing understanding of the biology of this organism into practical benefits such as the development of new treatments.

Nevertheless, it seems certain that for the foreseeable future *C. albicans* will remain a major clinical problem and an important agent of microbial disease.

References

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Book Reviews

***Fusarium*. Paul E. Nelson Memorial Symposium** edited by B. A. Summerell, J. F. Leslie, D. Backhouse, W. L. Bryden. & L. W. Burgess (2001). Pp. 392+xv, illus. (Hardback). ISBN 0-89054-268-6. APS Press, St Paul, USA. Price $59.

Fusarium is a genus of microfungi, many with an ascomycete state and often brightly coloured. It includes important plant pathogens and toxin producers and has attracted enthusiasm and dedication among a large number of professional mycologists and plant pathologists. Paul E. Nelson was among the best known and respected of these enthusiasts, so much so that a Memorial Symposium was held in 1997 following his death the previous year. This volume is based largely on the proceedings of that symposium.

Despite being a proceedings volume, it is clear from a first glance that this book has much more substance than we might expect. It is a collection of 25, mainly short, chapters, each of which is a well prepared review article. Whilst it could not be comprehensive (so keep the older *Fusarium* monographs for reference), the contents are topical and draw particular attention to rapidly developing areas such as systematics, population genetics and biogeography.

The book begins with a tribute to Paul Nelson, which briefly outlines his career and achievements. The rest of the book is divided into five sections, each of three to nine chapters usually with an introduction, sections describing principles or examples, especially on the more topical aspects, a conclusion or summary paragraph and, particularly important, a long list of references. Some chapters on specialised subjects, such as individual pathosystems, deviate from this layout; some of these would have benefitted from a summary. There is a little overlap between chapters but this, and cross-referencing, helps our understanding and emphasises important and topical issues. Reading through, I was not particularly in need of an index, but the absence of one diminishes the book's potential value as a source of reference.

Section I, on Taxonomy, has three chapters discussing, respectively, perithecial species, the anamorph (asexual form) and secondary metabolites. The first of these includes a new key for perithecial species of *Gibberella*. This may be useful provided that perithecia are available as the starting material (often they are not). Chapter 2 mentions how, despite much change and confusion concerning *Fusarium* taxonomy, the situation could have been much worse if the taxonomists had not shown restraint by not rigidly following the taxonomic rules. There is much useful background information on fungal systematics in this section.

Section II contains five short chapters on aspects of *Fusarium* genetics, quite difficult in parts but immensely satisfying. We are now in a position to appreciate, for example, the huge contribution that vegetative compatibility studies (Chapter 6) are making to our understanding of the evolution and distribution of the important plant pathogens in the *F. oxysporum* and *G. fujikuroi* groups (examples of which are the subjects of later chapters).

Section III has four chapters on Ecology, ranging from a study of biogeography, exemplified by the evolution and adaptations of two species occurring in Australia (Chapter 9), to an unexpected but interesting