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EDITORIAL

Fungal Diseases: the Last Frontier?

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Fungal organisms are ubiquitous in the environment, with the average human breath estimated to contain up to 10 fungal spores (Fröhlich-Nowoisky *et al.*, 2009). Fungi are increasingly recognized as an important part of the mammalian microbiome and dysbiosis of the fungal population is associated with a range of diseases (Huffnagle and Noverr, 2013; Luan *et al.*, 2015). A wide variety of these agents can cause infection of crops and other plants, and localized or systemic infectious disease in man, insects (e.g. bees) and wild and domesticated animal species. However, in contrast to bacterial, viral or parasitic pathogens, we know relatively little of the epidemiology of fungal diseases, the pathogenesis and tissue pathology related to fungal infection, and the nature of the immune response to these organisms.

Fungi are generally regarded as opportunist pathogens – causing infection in immunodeficient or immunosuppressed individuals, for example, people with primary immunodeficiency or haematological disease or those undergoing chemotherapy for cancer or being medically immunosuppressed for transplantation surgery or immune-mediated disease. Effective therapies for fungal diseases are few in number and there are recent concerns about the development of resistance to some treatments (Pfaller and Diekema, 2004). For example, multiple resistance to the azole drugs amongst human isolates of *Aspergillus fumigatus* has increased in the UK from 16% of isolates in 2009 to 38% in 2011 (Busca *et al.*, 2015).

Resistance is related to a mutation in the fungal *cyp51A* gene and the increased incidence may relate to more widespread and more longterm use of azole drugs in human medicine (Busca *et al.*, 2015) and in crop production (Fisher *et al.*, 2012). Against this background, the prevalence of fungal infections appears to be increasing in the human population with emergence of new opportunist fungal pathogens (Pfaller and Diekema, 2004; Nucci and Marr, 2005; Richardson and Lass-Flörl, 2008). This increase may partly reflect the availability of new diagnostics (e.g. serological testing and computed tomography), but also the increased performance of procedures such as transplantation (Low and Rotstein, 2011) and the effects of predisposing diseases such as the acquired immunodeficiency syndrome. Similarly, there are increasing examples of emerging fungal infections in wildlife species (e.g. ‘white nose disease’ in bats caused by *Geomyces destructans*; chytridiomycosis of amphibians caused by *Batrachochytrium dendrobatidis*) with the survival of some 39 wildlife species threatened by fungal diseases (Fisher *et al.*, 2012). These changes may reflect human interventions to the natural environment (e.g. land clearance, climate change) or intercontinental dispersal by international animal trade. The emergence of new diseases in new habitats, the increasing prevalence of fungal infections and antifungal drug resistance all set new challenges for science.

Over the past few months, the *Journal of Comparative Pathology* has seen a number of submissions relating to fungal diseases (or diseases caused by fungus-like eukaryotes) of domestic animals and these have been collected together to create this partly themed issue. These include case reports of infection by the oomycote, *Pythium insidiosum*, in the upper respiratory tract of two horses in Brazil (Souto *et al.*, 2016), and co-infection with algae characterized as *Prototheca zopfii* genotype 2 and *Pithomyces chartarum* in a case of equine rhinosinusitis from Germany (Shöniger *et al.*, 2016). Two papers describe feline *Aspergillus* spp. infections. The first documents two diabetic cats from Brazil with pulmonary infection

caused by *Aspergillus* section *Nigri* and proposes that the infection may have been secondary to immunocompromise related to the diabetes mellitus (Viana Leite Filho *et al.*, 2016). The second manuscript uses immunohistochemistry to describe the mucosal immune response to invasive upper respiratory tract infection by either *Aspergillus felis* or *Aspergillus fumigatus* in six cats from Australia (Whitney *et al.*, 2016). Finally, a large review of avian diseases from the USA documents the occurrence of fungal disease in this population (Nemeth *et al.*, 2016). Fungal infections accounted for 33% of all infectious diseases recorded in 528 Psittaciformes and, where identified, the most common causative agents were *Aspergillus* spp. and *Candida* spp. Collectively, these papers provide valuable new information on this challenging group of pathogens and some comparative insights with equivalent human infections.

To complete this thematic issue, we delve into the rich historical archive of the *Journal of Comparative Pathology* and reprint two manuscripts providing early descriptions of fungal disease. The first, by Foulerton, was published in 1898 and provides a fascinating discourse on the nature of granulomata and describes fungal granulomata in birds and animals. The paper discusses the nature of multinucleated giant cells within granulomata and the contemporary proposal by Metchnikoff that these cells are active participants in immune defence, rather than being a stage of cellular degeneracy. This paper also uses the descriptive term ‘kunker’ for the firm, coral-like tissue lesions of fungal disease – and the same terminology is used in the reports of equine pythiosis in this issue.

The second manuscript, from 1908, appears to be an anonymous translation of a paper by Neumann, published originally in the *Revue Vétérinaire* (July 1st, 1908, p. 417) in the same year. This provides a review of avian aspergillosis, first described as early as 1815. The author notes the greater frequency of fungal infection in the respiratory tract of birds compared with mammals and relates this to the avian air sacs providing an environment

conducive to fungal growth. The paper concludes with a recommended therapy, ‘vapour of tar’ that is created by mixing a tablespoon of ‘vegetable tar’ with half a litre of water, after which ‘a piece of red-hot iron is plunged in the mixture and stirred about’. These early, carefully-made descriptions of fungal morphology and tissue pathology are not dissimilar to those in the current manuscripts, although more than a century later, we at least have access to more effective anti-fungal therapies! There is, however, still much to learn about fungal diseases and these infections have rightly been described as the ‘last frontier’ in infectious disease research.

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