INTRODUCTION TO

THE HISTORY OF MEDICAL AND VETERINARY MYCOLOGY

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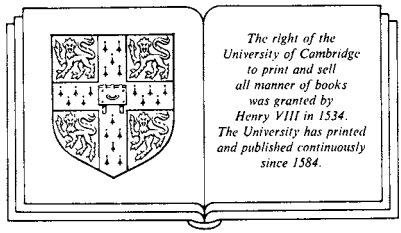

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Introduction

Medical and veterinary mycology (or 'mycopathology' as it is sometimes not very happily designated) is, essentially, the study of infectious disease in man and higher animals caused by fungi but, traditionally, it also includes diseases caused by actinomycetes (because these filamentous bacteria were at one time frequently classified as fungi) and allergic conditions induced by fungi and actinomycetes. During the past twenty-five years the foundations of medical and veterinary mycology have been completed and although in future knowledge of recognized mycoses will deepen, the relative importance of different mycoses will vary, and additional mycoses will be described, such developments should do little to disturb the relationship of this field to human and veterinary medicine in general. This would, therefore, appear to be an appropriate moment at which to pause and survey the history of a speciality which involved the collaboration of clinicians and pathologists with non-medically trained mycologists, microbiologists, and biochemists[1] (see Notes on the Text, pp. 171–80) before satisfactory progress could be made in the solution of many medical and veterinary problems.

That some larger fungi are poisonous (or hallucinogenic) for man has been on record for two thousand years but during the last few decades the recognition that many microfungi produce toxins (*mycotoxins*) in animal feed and human food which induce widespread and sometimes fatal disease in farm animals and man has resulted in the emergence of a major new branch of mycology (see Chapter 8. Cross-references without pagination may be elucidated via the Subject Index). Fungal infections of man, which are usually less-spectacular than poisonings, have been less frequently documented.

Possibly the earliest record of a mycotic infection is that in the Indian Atharva Veda [*c.* 2000–1000 BC] of mycetoma of the foot which was differentiated from filarial elephantitis of the foot and described under the name 'padavalmika' (foot-ant-hill), a forerunner of '*Fourmilière des vers*'

(ant-hill of worms) used for the same condition by a French missionary at Ponticherry in 1714.[2]

Two mycoses familiar today – thrush[3] in infants and favus – were noted in the Greek and Roman classics. In the Hippocratic writings [5th century BC] thrush was included among references to aphthae and Aulus Cornelius Celsus [1st century AD] in *De re medicina* (Book vi (2)), following the nomenclature of Hippocrates, dealt with thrush under ulcers where he wrote:

> ...the most dangerous of these ulcers which the Greeks call aphthae, certainly in children; in them they often cause death, but there is not the same danger for men and women. These ulcers begin from the gums; next they invade the palate and the whole of the mouth, then they pass downwards to the ulva and throat, and if these are involved it is not easy for the child to recover. But the disease is even worse in a suckling, there is less possibility of its conquest by any remedy...[4]

In Book v of the same work Celsus drew attention to the boggy inflammatory lesions of some ringworm infections – the condition known ever since as 'the kerion of Celsus' – and in Book vi described favus:

> ...the condition is called porrigo, when between the hairs something like small scales rise up and become detached from the scalp: and at times they are moist, much more often dry. Sometimes this happens without ulceration, sometimes there is localized ulceration, and from this comes sometimes a foul odour, sometimes none. This generally occurs on the scalp, more seldom the beard, occasionally even on the eyebrow.[5]

In the centuries which followed the term 'porrigo' was used to cover various skin disorders and the Latin 'tinea'[6] was applied in a generic sense to ringworm (from a fanciful resemblance of the signs of the disease to the depredations of the clothes moth (*Tineola biselliella*)) which was recorded with increasing frequency.

There are records of the Tudors granting licences under the signet for loyal sufferers from ringworm to remain covered in the king's presence and on other ceremonial occasions and Samuel Pepys in his diary for 17 June 1665 recorded thrush as one of the terminal symptoms of Admiral Sir John Lawson. During the last decade of the seventeenth century the English antiquary John Aubry compared fairy rings and ringworm:

> As to the green circles on the downes, vulgarly called faiery circles (dances), I presume they are generated from the breathing out of a fertile subterranean vapour. (The ring-worme on a man's flesh is circular. Excogitate a paralolisme between the cordial heat and ye subterranean heat, to elucidate the phaenomenon.)[7]

A pertinent comparison in spite of his incorrect explanation tinged with the doctrine of humours.

About the same time Sir William Dampier, when voyaging round the world, wrote in his journal after a visit to the Phillipines in 1686:

> The *Mindanao* People are much troubled with a sort of Leprosie, the same as we observed in *Guam*. This Distemper runs with a dry scurf all over their Bodies, and causeth great itching in those that have it, making them frequently scratch and scrub themselves, which raiseth the outer Skin in small whitish flakes, like the scales of little Fish, when they are raised on end by a Knife. This makes their skin extraordinary rough...[8]

The same disease was subsequently observed in Polynesia and became known as 'Tokelau Itch' or 'Tokelau Disease', after the islands where the disorder was prevalent, but it was not until 1879 that one of the pioneers of tropical medicine, Patrick Manson, then Medical Officer to the Imperial Maritime Customs at Amoy, China, elucidated its aetiology. Manson noted the presence of mycelium in the skin scales and by experimental inoculation of one of his Chinese assistants showed the fungus to be the cause of the disease which he called 'tinea imbricata', because the skin scales appeared to be like overlapping tiles. Finally, in 1896, the French worker Raphael Blanchard named the fungus *Trichophyton concentricum* after the concentric patterns it caused on infected skin.

Tinea has been illustrated by a number of the old masters. In Murrillo's [1617–82] painting in the Hermandad de la Santa Carida, Seville, of St Elizabeth of Hungary washing the head of a child with another standing by her side scratching himself both children appear to be suffering from favus (Fig. 1)[9] as does the boy being considered for admission to the Amsterdam Leprosy House in the painting by Ferdinand Bol [1616–90] in the Rijksmuseum. Since Biblical times favus and leprosy have been confused and some of the clinical dermatology in *Leviticus* 13 could possibly be interpreted as an attempt at the differential diagnosis of these two conditions.[10]

During the eighteenth century and early years of the nineteenth a number of mycoses of higher animals were reported. On 12 May 1748, Henry Baker communicated to the Royal Society of London a letter he had recently received from the Norwich naturalist William Arderon describing observations on a fatal distemper that was certainly 'salmon disease' (saprolegniosis) affecting a roach (*Leuciscus rutilus*) in captivity. '...after this Fish has been a little while confined, the finny Part of its Tail begins to drop off Piece by Piece; and when the finny Part is all gone, a sort of

Fig. 1. 'St Elizabeth of Hungary caring for the sick' by Murillo. (Hospital Santa Caridad, Seville).

Mortification seizes upon the Tail itself, and gradually creeps along until it reaches the Intestines, at which time the Fish immediately dies'; so wrote Arderon who also described the 'fine fibrillous Substance' which grew out from the mortified tissues (Fig. 2). The same condition, but in a goldfish (*Cyprinus auratus*) was reported by J. Hughes Bennett to the Royal Society of Edinburgh in 1842 (Bennett, 1844). Records of avian aspergillosis began in 1749 with the observation on the moulding of incubating eggs by the versatile René de Réaumur (inventor of the eighty-degree thermometer scale) in *The art of hatching and bringing up of domestic fowls of all kinds*..., the description of a 'mould or blue mucor' in the thoracic air sac of a Scaup duck (*Aythya marila*) by Montagu (1813), and a similar condition in a jay (*Garrulus glandarius*) by Mayer (1815) followed. Subsequently, the English anatomist Richard Owen when dissecting a

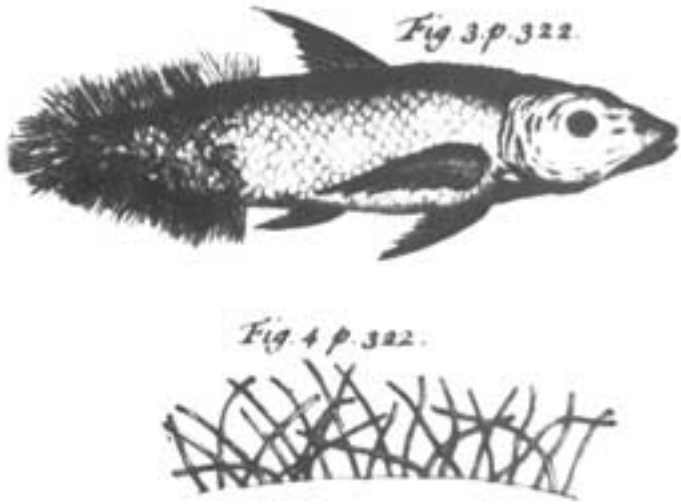

Fig. 2. Saprolegniosis in a roach. (W. Arderon, 1748).

flamingo (*Phaenicopteris ruber*) found 'a green vegetable mould or *mucor*' in the lungs, recognized the parasitic relationship, and concluded 'that internal parasites are not derived exclusively from the animal kingdom' and 'that there are *Entophyta* as well as *Entozoa*' (Owen, 1832). Concurrently, James Kerr, a retired veterinary surgeon of the First Bengal Light Cavalry, described in the *Veterinarian* for 1829 a disease of horses of unknown cause characterized by ulceration of the angle of the lip, face, scrotum, and legs under the name of 'bausette' (or 'bursattee' of which there are a dozen variant spellings). During the next 45 years there were additional communications on the disease to the same journal from veterinary officers of cavalry and artillery regiments stationed in India and others speculating on the cause of the condition, the occurrence of which was associated with water and wet weather. One notable contribution was that in 1874 by F. F. Collins who concluded 'that an active foreign agent is in existence to produce appearance so peculiar, and I do not know of an agent capable of producing such peculiarities other than that of a parasitic origin, and that parasite I conceive to be of vegetable organization...'[11]. From 1886 bursattee was recognized in the United States as 'leeches', 'Florida horse leech' (because of the belief that leeches were responsible), and 'swamp cancer' and in 1895 P.A. Fish of the Division of Animal Pathology of the US Bureau of Animal Industry in addition to an interesting historical review of the condition illustrated

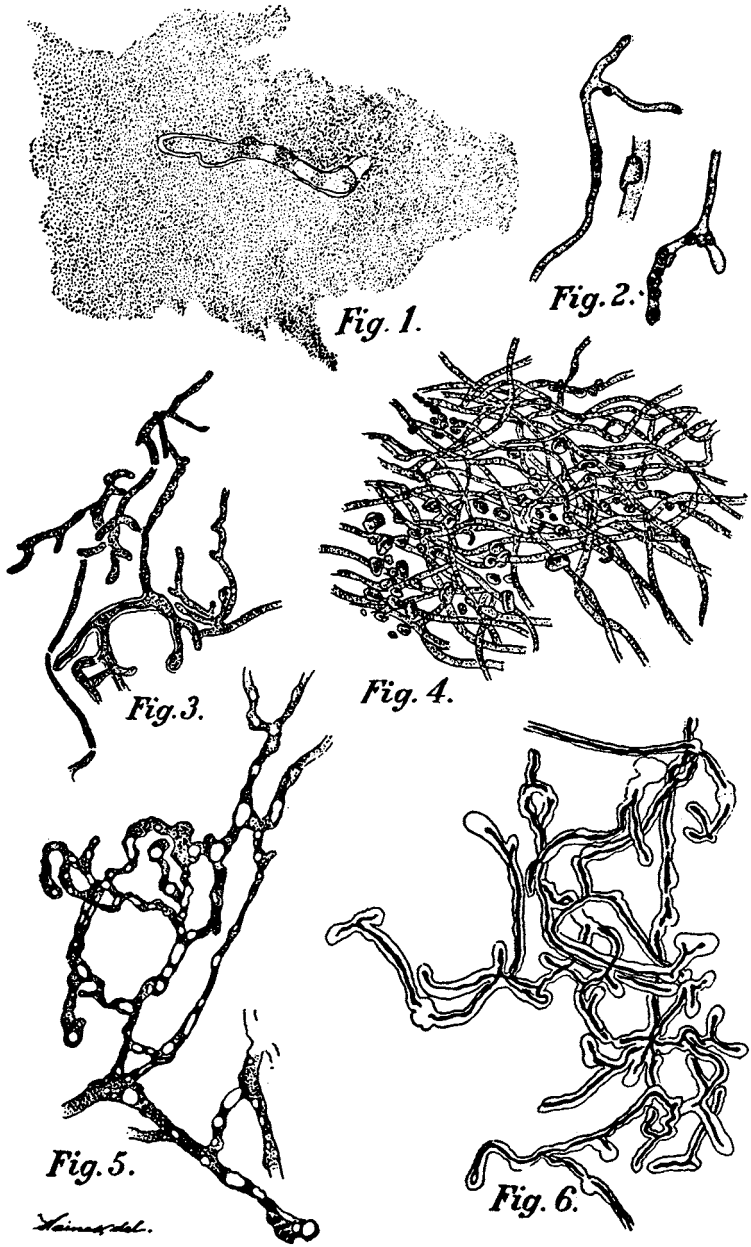

Fig. 3. Fungus from the lip of a horse affected by hyphomycosis. (Fish, 1895).

elements of an unidentified fungus in preparations from infected lips (Fig. 3). The next major studies were made by Haan & Hoogamer (1903) in the Dutch East Indies who named the disease 'Hyphomycosis destruens equi' and Witkamp (1924) called the pathogen by the illegitimate name 'Hyphomyces equi'. Subsequently Bridges & Emmons (1961) suggested that the pathogen was a phycomycete which Austwick & Copland (1974), on the basis of cultures from four cases of 'swamp cancer' in Papua New Guinea concluded was a species of *Pythium*.

The concept of pathogenicity

No real progress in the understanding of mycotic disease could be made until the concept of pathogenicity had been established and that took some two hundred years. Robert Hooke, the young versatile Curator of Experiments of the Royal Society of London, in his *Micrographia*, 1665, illustrated rose rust (*Phragmidium mucronatum*), the Frenchman Isaac Bénedict Prévost (in 1807) offered experimental proof that bunt of wheat was caused by *Tilletia tritici*, and in 1835 an Italian lawyer turned farmer, Agostino Bassi, demonstrated that the muscardine disease of silkworms was caused by a fungus (subsequently named in his honour *Beauveria bassiana*). In spite of these findings, the pathogenicity of fungi to plants and animals was not generally accepted until after the mid-nineteenth century. This was in large measure due to the question of pathogenicity becoming associated with spontaneous generation and heterogenesis (the origination of new organisms from living cells of a different species) which also proved to be intractable problems. The story of their elucidation has often been told – never better than by Bulloch (1938) in his history of bacteriology – so that only the briefest summary is necessary here. As late as 1642, Jean Baptiste von Helmont [1577–1644] believed that adult mice originated spontaneously from bran and old rags. Francisco Redi [1626–98] in 1668 demonstrated that maggots in rotten meat originated from eggs laid by flies and not *de novo* as hitherto supposed. Subsequently, the fundamental researches of the Abbot Lazzaro Spallanzani [1729–99] in Italy during the seventeen-sixties, Franz Schulz [1815–74] and Theodore Schwann [1810–82] in Germany, and finally those of Pasteur [1822–95] in France in the early eighteen-sixties and concurrently John Tyndall [1820–93] and William Roberts [1830–99] in England provided irrefutable evidence that neither spontaneous generation nor heterogenesis of micro-organisms occurs although some proponents of the latter, such as H. C. Bastian

[1837–1915], remained unconvinced and carried the heresy over into the twentieth century (in *The origin of life*, 1913).

The beginning of medical mycology as a distinct branch of medicine can be precisely dated as 1842 to 1844, the years during which David Gruby in Paris published a series of six short, but outstanding, papers in which he showed, very convincingly, that four types of ringworm and also thrush were mycotic in origin (see Chapter 2).

The reception of Gruby's findings varied from enthusiastic acceptance to disbelief (see Chapter 4). Bacterial infections being as yet unrecognized, a fungal origin for cholera and other bacterial diseases was widely claimed but after Koch's classical work on anthrax in 1876 and his demonstrations of the true nature of tuberculosis and cholera during 1882–83, the major importance of bacteria as agents of disease in man and animals became established and pathogenic fungi suffered eclipse. Study of ringworm did continue and this was given a major impetus by the researches of the French dermatologist Raimond Sabouraud which began in the early eighteen-nineties and culminated in the publication of his important monograph, *Les Teignes*, 1910. Another complicating factor before the introduction of pure culture techniques by Koch and others[12] was the phenomenon of pleomorphism (in its original connotation of the existence of sexual and asexual states of one fungus) and the life cycles of fungi in which some workers included both diverse mycelial species and yeasts – and even bacteria. This led to the fantasies of Ernst Hallier (see Chapter 4), assistant professor of botany at Jena, whose claims were finally authoritatively discredited by his fellow countryman the eminent mycologist Anton de Bary. In the late eighteen-seventies medical mycology received a major addition resulting from investigations by German workers on actinomycosis in cattle and in man; the bacteriologist Bollinger coining the designation 'lumpy jaw' (1871) for the cattle disease while his botanical colleague Harz introduced the binomial *Actinomyces bovis* (1877) for the pathogen. Bollinger and Harz had before them both actinomycosis (lumpy jaw) and actinobacillosis (wooden tongue) of cattle caused by the bacterium *Actinobacillus lignieresii*. These two conditions, which have been much confused, were first clearly distinguished by Lignières & Spitz (1902) but the genus *Actinobacillus* was not proposed until 1910, by Brumpt.

At the turn of the century, protozoologists made what eventually proved to be even more important additions to mycopathology. In 1892, Alejandro Posadas, an undergraduate student of Robert Wernicke in Buenos Aires, first described the 'protozoon' believed to be responsible for 'mycosis fungoides' (Fig. 4) and four years later the same organism was inde-

Fig. 4. Specimen at the Faculty of Medicine, University of Buenos Aires from Posadas and Wernicke's original case of coccidioidomycosis. (Niño, 1950).

pendently described in California where it was named *Coccidioides immitis* by Rixford & Gilchrist (1896) after consultation with the eminent protozoologist C. W. Stiles. Eight years later Ophuls & Moffitt (1900) recognized that the protozoan was the pathogenic phase of a mycelial fungus. In 1906, the American S. T. Darling when stationed at the Ancon Hospital, Panama Canal Zone, described *Histoplasma capsulatum* (Fig. 5) but in this case it was twenty-eight years before the fungal nature of the pathogen was demonstrated independently and almost simultaneously by De-Monbreun (1934) and Hansmann & Schencken (1934) in the United States. Subsequent studies on these two widespread systemic mycoses probably did more to establish the relevance and importance of medical and veterinary mycology than any other investigations (see Chapter 5).

It is an acceptable generalization that up to the First World War the fungi causing mycoses in man and animals were studied by medical men and veterinarians who were self-taught mycologists and not by specialists in the study of fungi whose rare excursions into the medical field were notably unsuccessful. As a result, much that was published on these pathogenic fungi was not in line with mycological practice and this led mycologists to regard these pathogens as a special group, 'medical fungi', of dubious relationships. Although a few non-medically trained mycologists in France and elsewhere took up the study of medical fungi,

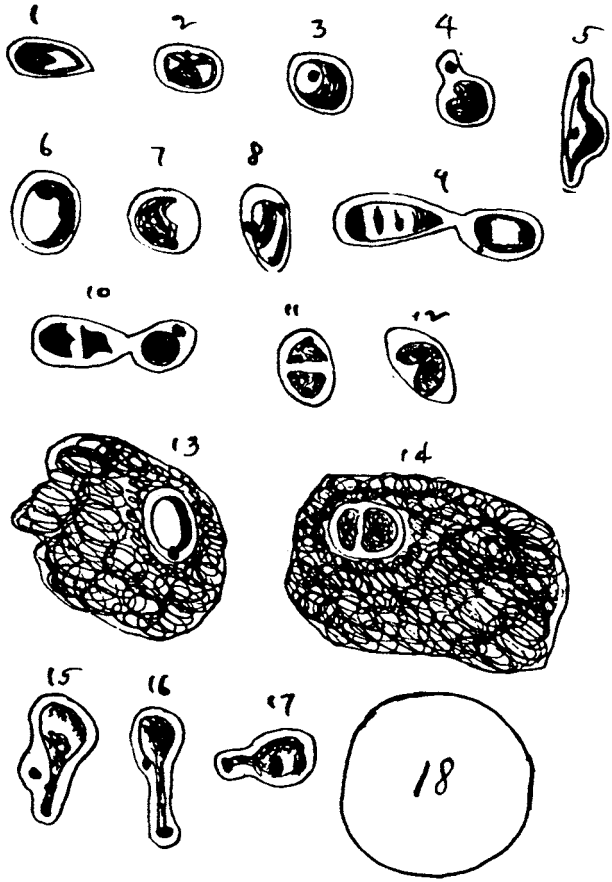

Fig. 1.—(× 2000), 1 to 8, forms of parasite; 9, 10, 11, 12 manner of subdivision; 13, 14, parasites within nuclei of spleen cells; 15, 16, 17, flagellate forms; 18, alveolar epithelial cell containing parasites.

Fig. 5. First illustration of *Histoplasma capsulatum*. (Darling, 1906).

developments in North America during the nineteen-thirties transformed the mycopathological scene. It was in the United States that a series of highly trained young mycologists were appointed to posts in the Department of Health, universities, and hospitals where they could work in close collaboration with clinicians and it soon became apparent that the major differential character of 'medical fungi' was pathogenicity to man and higher animals. They exhibited sexual and asexual phases and could be satisfactorily characterized without reference to their pathogenicity. Much confused taxonomy was elucidated and the corresponding nomenclature

given greater precision. In addition, a number of up to then rare pathogenic fungi (and also others including some ringworm fungi) were isolated with increasing frequency from soil, animal dung, and other substrata and the conclusion reached that many of the fungi causing mycoses are what has come to be termed 'opportunistic'; that is, they establish themselves as pathogens only when a subject is by chance exposed to an exceptionally high concentration of their spores or when the subjects are 'compromised', that is their immunity is decreased by another disease, for example diabetes, or by treatment with antibiotics, immunosuppressants, etc., such as that which precedes organ transplantation. In marked contrast to plant pathogens, few if any fungi pathogenic to man and higher animals are dependent on a host for survival. They are able to grow saprobicly and regarding their nutritional requirements it is interesting to note that, in marked contrast to bacteria, these have been shown to be less exacting for the highly pathogenic than for the weakly pathogenic.[13] Another major distinction between mycotic disease in plants and animals is due to the possession of an immune system by the latter so that serological techniques may be employed to detect current and past infections, in therapy and preventative treatment, and also for the identification of the pathogens.

Treatment of mycotic disease like that of disease in general has shown extreme diversity over the centuries and much, especially early, therapy was irrational if tempered by the empirical approach of practising physicians, which tends to promote the survival of regimes which appear to be the more successful or meet the patients' expectations. Only recently have therapeutic agents, including antibiotics, been derived from laboratory investigations.

After an overenthusiastic acceptance of fungi as the cause of infectious disease in man and animals followed by a period of neglect and then one of what might be called confusion, the last fifty years have seen the relationship of mycopathology to medicine and veterinary science firmly established. It is now clear that while fungi are the principal cause of disease in plants they play a relatively minor, if still significant, role in diseases of man and higher animals. Forty years ago Chester Emmons wrote:

> In *Vital Statistics of the United States for 1942*, 1,385,187 deaths were reported. Of these 359 were attributed to fungi. This is less than 0.03% of the total, but in this registration area it is nearly twice as many as the total of known deaths due to paratyphoid fever, undulant fever, smallpox, rabies, leprosy, plague, cholera, yellow fever, and relapsing fever together; it is greater than the number due to all the typhus-like diseases together; and it is more than half the number due to

either typhoid, tetanus, or poliomyelitis. In fairness in comparison it should be pointed out that many of these better known diseases rarely cause death, because of effective prophylactic and control measures.[14]

and the position is much the same today.

Some mycotic diseases of the skin and superficial tissues of worldwide incidence are at least a costly inconvenience – the annual expenditure on medicaments for ringworm infections in the United States during the nineteen-sixties and seventies has been estimated as 25 million dollars[15] – and a number of widespread, if more localized, systematic mycoses have an incidence measured in millions where they are endemic. Both superficial and systematic mycoses may prove chronic or fatal because of therapeutic deficiencies, but fungi are unlikely to compete in importance with bacteria and viruses as disease-inducing agents in man and his domesticated animals. Many fungi are typically only potentially pathogenic, they are saprobes of man's environment able under favourable circumstances to cause disease and this possibility is one that should always be borne in mind when investigating a condition of unknown aetiology.