

A short history of invasive aspergillosis, 1920 to 1965
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The aspergillus website contains a database of historical papers and books, which grew out of one of the team's undergraduate project work. The majority of the 399 listed items are only given as references, but increasingly copies of the items are being located and made available through the website as pdf files.

The accessible papers are predominantly from the period 1928 to 1965. Approximately half relate to cases of aspergillosis (aspergillus infection) in people or experimental animals, or related mycotic (fungal) infections, chiefly candida (also known as monilia). The papers show a marked increase in number and severity of cases of 'deep' mycotic infections around 1950, and concern in the medical community that this might be in part the result of the widespread use of antibiotics, and steroids such as ACTH, and the early trials of bone marrow depressants in the search for effective treatments against acute leukaemia. The papers also caution doctors against relying solely on the use of roentgen films in diagnosing tuberculosis, since pulmonary aspergillosis had been misrecognised as TB in several cases.

This increase in frequency and morbidity of mycotic infections in patients called for responses from treating physicians and laboratory researchers, in the development of reliable diagnostic techniques and effective treatments for infection. Many patients being treated with antibiotics for a bacterial infection went on to develop another which was resistant to the drugs being used, or to experience fungal infections which seemed to increase in virulence if further antibiotics were administered. In the 1950s much research was conducted into the effects of antibiotics and steroids on the immune system and on bacteria and fungi (Seligman, 1953). The early antifungal agents, nystatin and amphotericin B, were developed in the 1950s, and offered some hope of controlling those infections which did not resolve with a regime of iodides.

The aspergillus infections described fall into three main categories:
pulmonary aspergillosis, including acute and chronic cases of lung disease;
mycotic endocarditis caused by aspergillus, where the heart is infected;
and mycotic meningitis caused by aspergillus, where infection reaches the brain.

Cases were also reported of serious infection in the spleen following operations to that organ, and in bone. Cases of non-invasive aspergillosis have also been reported where the infection is localised in the ear, patches of skin, nails, and genital tissue. The most frequent species of aspergillus responsible for infections, where identified, were *Aspergillus fumigatus* and *Aspergillus flavus*.

The usual treatment for aspergillosis was iodide therapy, until physicians started experimenting with the use of the sulphonamide anti-bacterial agents in the 1930s and then the first antibiotics in the late 1940s, to see if the new wonder drugs were also efficacious in the management of fungal infections. Occasionally, surgery or radiotherapy were used with some success. The first trials of antifungal agents began at the end of the 1950s.

Pulmonary aspergillosis

The condition was first described by Hughes Bennett in 1842. The early records of such infection were typically of infections taking hold in patients who already had suffered substantial lung damage from tuberculosis, but in the 1890s, several cases had been documented where it seemed that aspergillus was the primary infection: aspergillus as the cause of the lung disease, not an infection taking hold in an already diseased lung (Wahl & Erickson, 1928). By 1928, there were fifty-four cases covered in medical literature.

Journals of the 1930s and early 1940s show much research being conducted into the role of moulds in allergic reactions in the respiratory system. There was also a marked increase in interest in pulmonary aspergillosis in the 1930s, when physicians began to address the difficulty of diagnosing the condition and the implications of misdiagnosis. Some doctors suspected that patients were being wrongly sent to TB sanatoria when suffering from primary aspergillosis, and that secondary infections were also being missed in TB sufferers, because roentgen films could not distinguish between the two kinds of lung damage and blood cultures frequently failed to reveal the cause of the suspected infection (Fawcitt, 1936). Journals carried debate over the best ways to identify aspergillus as the culprit. Experts recommended sending extracted or expectorated samples to specialist laboratories, and treating with iodide in the meantime, on grounds that if an infection responded it was almost certain to be fungal in nature (Peterson, 1944).

Farm workers or others who had contact with birds, soil or grains by virtue of occupation, seemed particularly susceptible to aspergillosis (Henrici, 1940). By 1945, pulmonary aspergillosis was recognised by the courts in America as an occupational disease (Cawley, 1947), though this has since been cast into doubt in subsequent debate over whether aspergillosis can ever be considered a primary infection.

By the close of the 1940s, it was widely recognised that mycotic infections, if not treated in a timely manner, could become exponentially more serious over time. Those inside the body could increase in severity very gradually at first, leading patient and doctor to assume that the patient's immune system would resolve the matter unaided. But in patients with damaged lungs or immune systems, the infection could become systemic, or invasive, once particles spread through the patient's blood supply (Gerstl, Weidman & Newmann, 1948). Doctors were increasingly trying alternative drugs where iodide therapy was unable to control infection or was causing too many side-effects in their patients, treating mycotic infections more aggressively.

The 1940s also saw pulmonary aspergillosis subdivided into distinct clinical subtypes, with different prognoses and different suitable courses of treatment, similar to those in use today (Yesner & Hurwitz, 1950).

By the close of the 1940s, there was debate about the effects of sulphonamides and antibiotics on the progression of aspergillus infections from benign localised conditions to life-threatening systemic disease (Gerstl et al, 1948). This will be covered more in the section on treatment.

Mycotic endocarditis

A published account of three cases of mycotic endocarditis, one caused by *Candida* and two by *Aspergillus*, stimulated much debate in the 1950s about the origins of fungal disease in the heart, but it was noted that no cases of *Aspergillus* endocarditis had been previously reported (L.E. Zimmerman, 1950). Fungal infections in the heart have been rare in medical literature. An earlier paper listed ten case reports in medical journals, but the specific organism had not been identified in many cases. It is therefore hard to assess how prevalent was aspergillosis of the heart (Cassels & Steiner, 1944).

L.E. Zimmerman's substantial article gave detailed guidance on diagnostic techniques for identifying which specific organism was responsible for an infection. The author discussed the role of antibiotics in the dissemination of infection through the blood stream, allowing a fungus to reach many major organs. The author also noted that steroid treatments being administered to patients with rheumatic conditions seemed to lower the power of the immune system dangerously so that fungal infections could take hold. Finally, the author commented on the discoveries by Sydney Farber and colleagues, working in Boston at that time on the first chemotherapy protocols which were bringing about temporary remissions in children with acute leukaemia. Bone marrow depressants interfered with cellular defence mechanisms, and the chemotherapy frequently damaged the mucous membranes making it easier for aspergillus or candida to enter the blood vessels and lymphatic system. Other predisposing conditions listed included diabetes (for *Candida* infections only), and intravenous heroin use.

More cases of aspergillus endocarditis were reported over the next few years. Papers were published giving accounts of patients succumbing to widespread aspergillosis after splenectomy and heavy use of anti-inflammatory steroids and antibiotics, giving support to Zimmerman's hypothesis that mycotic endocarditis was made more likely with the use of these medical interventions and drugs (Welsh & Buchness, 1955; Kirschstein & Sidransky, 1956). Attention focused not just on what might possibly control such infections, but primarily on what caused them to gain such strength in patients and to occur more frequently than had hitherto been observed. Was it just better diagnostic techniques leading to mycotic infections being recognised as such? Or was the increase in incidence and virulence the result of inappropriate treatments, or earlier bouts of ill-health, damaging patients' ability to fight off infectious agents not normally so pathogenic?

Mycotic Meningitis

Cases of mycotic infection in the central nervous system were also very rare before the 1950s. Four cases of meningitis due to *Candida albicans* were documented in 1933, 1943, 1945, and 1947 (S.L. Zimmerman, 1947). Cases of *Aspergillus* in the brain had been reported since 1897, some with sinus involvement and some without. Brain lesions had been observed in patients with systemic disease, and had been found in localised disease, though the course of aspergillus meningitis was universally poor at this time, with surgery the most effective treatment (Ziskind, Pizzolato & Buff, 1958).

Understanding of this disease increased markedly over the next ten years, with more than 60 new cases discussed in medical journals (Pore & Larsh, 1968). It became clear that cortisone made experimental animals approximately ten times more likely to develop aspergillosis when inoculated with fungal material than their cage-mates not given the steroids pre-exposure.

Treatment

Potassium iodide was the standard recommended treatment for fungal infections from the dawn of the twentieth century until the end of the Second World War (Delikat, 1945). Radiation therapy seemed to control infection for some suffering from localised aspergillosis in bone, although no follow-up account is provided so it is unclear whether this approach gave lasting relief (Shaw & Warthen, 1936).

The sulphonamide drugs were tried in the 1940s, possibly as a result of the successful use of related compounds in ointments for aspergillus infections confined to the skin (Lynch, 1923). There was a measure of success in a few cases (Cassels & Steiner, 1944), but no positive effect in most. Extensive sulphonamide therapy could also lead to bone marrow depression, thus making patients more susceptible to aspergillosis rather than less.

The first antibiotics to be available to physicians and patients, penicillin and streptomycin, were also tried on infections of unknown type (bacterial and fungal), and on those identified as fungal, when iodides and sulphonamides were not controlling infection (S.L. Zimmerman, 1947). Doctors were at pains to point out, when it appeared that a new drug had been effective, that it was impossible to tell whether the effect had been against the fungi or some complicating other infection.

By 1950, some physicians were beginning to ask if antibacterial agents were making mycotic infection worse rather than better. Both the British Medical Journal and the Journal of the American Medical Association carried frequent editorials on this issue. Dissemination of disease seemed to be occurring more often, and an alarmingly high proportion of people taking antibiotics for bacterial infections developed minor candida colonies in their mouths or genitals (Kligman, 1952). Drug manufacturers were legally obliged to state the substantial risk of *Candida* infection on the packaging of the antibiotic chloramphenicol. Some cases of moniliasis or aspergillosis became invasive and fatal if use of antibiotics for a bacterial infection was continued. The suppression of regular healthy bacteria in the patient's body and of the patient's immune function appeared to allow an invading fungus to grow unchecked (Smith, 1952). Warning statements became increasingly stark: "The use of antibiotics in the presence of the fungous infections is dangerous... It is probable that in the present case dissemination of the fungi was promoted by chloramphenicol" (Rankin, 1953).

It was also well documented in medical journals that steroids administered to control inflammation left patients with apparently badly compromised immune systems, and this connection was thoroughly analysed in human populations and in studies on laboratory animals (Crepea, Magnin & Seastone, 1951; Lurie et al, 1953, Mankowski & Littleton, 1954). The conclusion was that steroids too should be avoided for

patients known to be suffering from a fungal infection, even if called for by another condition needing treatment. Diagnosing *Aspergillus* infections was very difficult, since sputum and blood samples even from patients who later died from systemic aspergillosis were frequently consistently negative for fungi, so this recommendation did not make much difference to the treatment paths of many patients.

Children enrolled on the first trials of chemotherapy protocols for acute leukaemia were especially prone to invasive moniliasis or aspergillosis, since they were receiving antibiotics, steroids, bone marrow depressants, and drugs which increased the chance of ulcerated mucous membranes (Craig & Farber, 1953; L.E. Zimmerman, 1950). Current care for such patients emphasises mouth care and regular prophylactic use of nystatin, a well-tolerated antifungal, to prevent fungi finding a home in patients' bodies when they are so compromised.

In the 1950s, the first antifungal drugs were developed and released for clinical trials. The first of these was nystatin. Now, nystatin is not considered as a treatment for most patients with aspergillosis, as it is nowhere near as powerful as the other drugs available, but at the time of its production it was seen as notably effective in efforts to bring cases of localised aspergillosis under control.

In the wake of Fleming's discovery of the power of penicillin against pathogenic bacteria, research laboratories channelled more resources into the search for other agents that might combat infections in patients. The Albany laboratory of the New York State Health Department undertook to survey organisms growing in soil that might be useful for controlling mycotic infections. Elizabeth Hazen first identified the extract later known as nystatin (named after New York state), a fraction derived from *Streptomyces noursei*, in 1950. She worked with colleague Rachel Brown to develop techniques which would permit its production on a scale large enough for clinical trials. This agent was effective against *Candida* and had some effect against other fungi, but crucially was not toxic to humans. Their work was taken over by the pharmaceutical company Squibb once the technicalities of mass production grew beyond the scope of the lab. By 1954, nystatin was available as an oral or topical treatment and preventative for moniliasis arising in skin, genital tissue, or intestinal tract, as a complication of antibiotic therapy. As it is insoluble and toxic in laboratory animals, it is not possible to administer it for invasive mycotic infections.

Amphotericin B, in contrast, is sufficiently soluble, if complexed with desoxycholate or lipid, for intravenous use, allowing it to reach infection sites deep in the body. It can have severe infusion or kidney side-effects, and research since its initial development has concentrated on ways to make it available in forms less toxic to patients. Initial batches were probably contaminated with bacterial components, increasing its toxicity.

Amphotericin B was first developed at the same time as nystatin, but mass production seemed impossible, until Squibb reported the approach they had used to successfully scale up nystatin manufacture and to package it in forms useable for patients. The two antifungal agents have very similar chemical structures, and techniques transferred easily, resulting in the clinical availability of this powerful weapon against systemic aspergillosis.

The first trial of amphotericin B against pulmonary aspergillosis was undertaken on a 61-year-old woman in 1959. She showed a strong response to the drug, although supplies ran out before she was cured (Kelmenson, 1959). Further trials were reported in the following years, and thus began the development of the current approach to controlling severe cases of aspergillosis. The patient website includes a history of antifungal agents currently considered effective for treatment of aspergillus infections, and some details of others under investigation for possible future use.

Primary or secondary?

There has long been debate about whether aspergillus infections can ever be considered primary or if instead they are always secondary to some predisposing condition.

A momentous paper from 1959 defined primary aspergillosis as that originating usually in the lung, often from prolonged exposure to grain, grain dust, or birds, and noted that disseminated primary aspergillosis was very rare (Finegold, Will & Murray, 1959). Secondary aspergillosis, in contrast, was defined as infection taking hold in already damaged tissue, such as the lungs following pneumonia, or an ulcer in the bowel. Crucially, this paper included amongst the category of primary and localised aspergillosis the allergic reactions experienced by some patients manifesting asthma type symptoms when exposed to the spores.

Primary aspergillosis was seen as being usually the result of occupational exposure or other unusually extensive exposure to the fungus, resulting in increased sensitivity to it. Secondary aspergillosis was argued to be more commonly seen in patients with underlying serious illness or wound, or with a history of heavy use of steroids, antibiotics, or bone marrow suppressors. Epidemiological studies in the mid 1950s indicated that while the number of primary fungal infections had not substantially increased, the number of secondary infections had, which supported this view (Esponel-Ingroff, 2003).

Debate in the 1960s started to turn away from the view that occupational exposure could lead to primary pulmonary infection with aspergillus, in the light of re-examination of all recorded cases and the apparent insufficiency of evidence that the mycotic infections seen were aspergillus and that no pre-existing lung disease was present (Macartney, 1962). By 1970 it seemed possible to dismiss the possibility of primary infection for the vast majority of presenting cases, if not all (Young et al, 1970). There is still disagreement between experts about whether or not aspergillosis develops, except in the allergic form, in otherwise healthy individuals.

Classification of aspergillus: debates since 1959

Up until the middle decades of the twentieth century, the forms of aspergillosis predominant in medical literature and research were chronic conditions, or local infections, or allergic reactions to aspergillus spores. However, with the vast increases in numbers of patients suffering from systemic disease, in some sense aspergillosis *became* the invasive form of the disease. Reclassifications of aspergillosis in

frequently cited review articles in popular medical journals have taken place periodically which have resulted in a shift in the meaning of 'aspergillosis' to that of systemic invasive disease, which is far removed from the definition of the term at the start of our period. A separate paper will treat this subject in greater detail.

This may simply be a product of the stunning increase in the number of cases of invasive aspergillosis seen since 1950, linked with increasing use of steroids, antibiotics, and anti-cancer chemotherapy, and with the development of organ transplantation surgery. Immunocompromised patients have been demonstrated to be much more likely to suffer from disseminated disease than people otherwise in good health, as they have fewer of the specialist white cells required to combat fungal invaders. Similarly, this large increase in the number of cases, coming from people treated for solid tumours or leukaemia, kidney or heart failure, and other serious illnesses, may well have resulted in the move towards viewing aspergillosis as always secondary, as noted above.

As fungal infections became an important area for researchers and clinicians treating people with cancer or organ transplants in the 1960s, so the balance of work done on aspergillus as a pathogen tipped towards systemic disease as opposed to localised or chronic infection. Cancer patients and the first recipients of kidney transplants brought with them additional funding from government and industry, and media attention (Esponel-Ingroff, 2003).

In one 1970 paper, the authors argued that there was still insufficient attention paid to invasive aspergillus infections, in comparison with a substantial body of work on allergic and chronic disease caused by the mould (Young et al, 1970). This is no longer the case. Perhaps the pendulum has now swung too far, in that work on non-invasive aspergillosis rarely carries the same degree of prestige as research on its more glamorous cousin.

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