Homei A, Worboys M. Fungal Disease in Britain and the United States 1850–2000: Mycoses and Modernity. Basingstoke (UK): Palgrave Macmillan; 2013.

Chapter 3 Candida

A Disease of Antibiotics

Initial reporting of penicillin as a wonder drug emphasised the fact that it was derived from a fungus, and a common one at that. Fungi of the genus *Penicillia* are ubiquitous in the soil and rotting matter across the world. They are most commonly seen in the bluish mould growing on old fruits and bread, and there are specific species associated with types of cheese: *P. camemberti* and *P. roqueforti*. Indeed, the species that Alexander Fleming derived his pioneering antibacterial from agent was the common *P. chrysogenum* (formerly *P. notatum*), that was common enough in London to blow in through the window of his laboratory.[1] The main antibiotics that followed penicillin were also derived from fungi: streptomycin from *Streptomyces griseus*, tetracycline from *Streptomyces rimosus*, cephalosporin from *Cephalosporium acremonium* and, as discussed in the previous chapter, griseofulvin from *Penicillium griseofulvum*. These discoveries changed the profile of fungi in popular culture, from agents of contamination and decay to those of medical progress and human improvement, and there was renewed recognition of their role in food and drink production.[2] Antibiotics affected fungal infections in medicine in two main ways: first, they prompted a search for antifungal as well as antibacterial agents and second, antibiotics seemed to open the body to new types of invasive fungal infection, the most serious of which was with *Candida albicans (C. albicans)*, which was well known as the cause of thrush or yeast infections.[3] Thrush was commonly seen as an oral infection, especially in babies, and a genital infection in adults, particularly women.

In medicine, the success of antibiotics in treating bacterial infections defined what many historians have termed the ‘Therapeutic Revolution’ of the mid-twentieth century.[4] The better control of bacterial infections allowed more ambitious surgical procedures and the pharmaceutical industry produced drugs for the cure or better management of a seemingly ever growing range of diseases. However, assessments of the impact of antibiotics nowadays balance the optimism of effective cures for bacterial infections, with the increase in the number and seriousness of antibiotic resistant bacteria.[5] In fact, antibiotic resistance was recognised in the early 1940s and by the early 1950s, streptomycin, which had radically altered the prospects of tuberculosis sufferers, had to be taken with two other drugs, isoniazid and para-aminosalicylic acid (PAS), in part, to overcome antibiotic resistance.[6] Less well recognised, and an important theme of this chapter, is of how antibiotics opened the body to new types opportunistic infections, with systemic mycoses amongst the most difficult to manage. Writing in 1955, Ernest Jawetz, a microbiologist at the University of California Medical Center, San Francisco, wrote that that the ‘ “rise of the yeasts” during antibiotic administration has been noted quite generally’ and that the ‘pathogenic potential of these fungi has caused concern’.[7] At this time the causal organism was known as *Monilia albicans* (*M. albicans*) and the infection moniliasis, but this changed to candidiasis or candidosis with the renaming of the pathogen.[8] In this chapter we keep to the terms used by doctors and others in context; but be warned there were no sudden changes, thus, old and new terms coexisted for many years.

We begin the chapter with a discussion of thrush in the nineteenth and early twentieth centuries and its transition from an oral infection of weak children to a genital infection of women. In both cases, doctors framed the disease in terms of the metaphor of ‘seed and soil’; namely, that to spread and develop pathogenic fungi required vulnerable human tissue, weakened by poor nutrition or other diseases. We then discuss the ‘Antibiotic Era’ and the inter-connected development of fungi as sources of antibiotics, including antifungals, and the claims that the use of antibiotics precipitated a general increase in fungal infections and new types of systemic fungal disease. The iatrogenic consequences of antibiotics have been discussed by doctors and historians in relation to the development of bacterial resistance, but hardly at all with regard to fungal infections.[9] The most prevalent of the new infections was systemic or invasive candidiasis, which was present in new patient groups; firstly, patients with leukaemia and those being treated for other cancers with steroids; later, transplant patients, and finally in the 1980s, people with HIV/AIDS. The common factor was that all were immunocompromised or -suppressed, showing once again the importance of the relationship between bodily ‘soil’ and fungal ‘seeds’. We end the chapter with a discussion of one of the great popular health crazes of the last quarter of the twentieth century – ‘The Yeast Connection’ – whose advocates argued that many of the new chronic and debilitating ailments of modernity were due to *C. albicans* overgrowth in the body.

Thrush: Weak children

In the mid-nineteenth century, oral thrush was regarded by doctors as a form of stomatitis, the symptomatic name for inflammation of the mouth, which also included ulcers, bleeding gums and, most seriously, cranum oris or noma, a gangrenous infection of gums or cheek with tissue destruction. Typically, a thin white membrane covered the palate, with white spots on the tongue, but in serious cases the tongue, cheeks and lips were covered, with possible spread to the throat and oesophagus. The condition was most prevalent amongst premature babies and then at weaning, when food matter stuck to gums and the mouth lining, acting as both an irritant and medium for infection.[10] Local epidemics were reported in lying-in hospitals, mostly alleged to be spread by poor hygiene amongst breast feeding mothers. While the disease was typically short-lived, disappearing as the baby gained weight, in a minority of cases it spread to the gut or lungs, and death usually followed. Mothers would say that thrush had 'gone through' their children.[11]

With children, it was an important skill for doctors to be able to diagnose differentially thrush from diphtheria; indeed, before the notion of specific infections was accepted, doctors believed that the white growth of thrush often transformed into the membrane of diphtheria as the child's health deteriorated.[12] The only treatment was to clean the mouth after meals, irrigate the mouth with glycerine borax and improve the general diet. Public health doctors saw thrush as a marker of poverty; it was most common in children with poor dietary and digestive troubles, which had progressed to general debility and fatigue. Although said to be common, thrush was rarely discussed in the medical press because it was either readily treated or self-limiting. However, it was occasionally reported in adult patients in the terminal stages of consumption and cancer, which resonated with the common observation that fungi flourished on dying or dead matter.

Thrush: Women and the 'Whites'

With hindsight, medical mycologists have identified the first publication on vaginal thrush as being that of Stuart Wilkinson in the *Lancet* in 1849.[13] This article appeared in the context of the contemporary interest in fungal theories of disease and was published in the same issue as a discussion of the alleged cholera fungus.[14] Wilkinson wrote that he had observed filamentous fungi in discharges from a woman that he traced to her uterus, but noted the 'healthiness of the vaginal wall'. Interestingly, today the vaginal wall understood to be the main site of infection, so it is debatable if this was really the first ever case.[15] The report stands alone in nineteenth-century medical literature and there was little or no direct discussion of fungal infection of the vagina again until the twentieth century. So, what happened to Wilkinson's thrush? This is, of course, the wrong question. What Wilkinson described was not vaginal thrush in the modern sense of specific infection, but an instance of 'leucorrhoea' or 'the whites', discharges that doctors defined against 'red' menstrual conditions.

Leucorrhoea was difficult terrain for many doctors because it involved intimate examination of women and was associated with venereal diseases, which might mean difficult questions for patients.[16] Speaking in 1862, Grailly Hewitt, one of London's leading gynaecologists, observed,

> [L]et it be remembered that it is impossible for the practitioner to exercise too great caution in pronouncing an opinion for or against the specific nature of a discharge from the female generative organs. In the words of the late Dr Ashwell, 'it is always his duty to cure the disease, but rarely to venture upon an exposition of its nature. If he can positively affirm that it is of simple origin, let him do so, if suspicion has been aroused; if not, it is better to avoid any distinct allusion to the matter.'[17]

Nineteenth-century medical books on the 'diseases of women' discussed leucorrhoea as a symptom rather than a disease condition in its own right. White discharges pointed either to constitutional disease, anything from tuberculosis to hysteria, or to local problems with the ovaries, fallopian tubes, uterus, cervix or vagina, any of which might be related to gonorrhoea, syphilis or venereal disease. The doctor's prime task was differential diagnosis, prognosis and treatment. If local treatment was recommended, it tended to be the use of anti-inflammatories or 'milder' antiseptics, such as mercury, boric acid, permanganate of potash or silver nitrate.

The direct association of leucorrhoea and specific fungal infection was first made in 1931 by Everett Plass, Henry Hesseltine and Irving Borts, obstetricians and gynaecologists from Iowa, who identified a condition they termed 'Monilial vulvovaginitis'.[18] Their finding emerged from a study of vaginal discharge in two pregnant women, where gonorrhoea was first suspected as the cause, but all tests had proved negative.[19] The broader context for this work was

the venereal disease services that were developed after the First World War, through which venereologists became more interested in conditions other than syphilis and gonorrhoea, especially non-gonococcal urethritis (NGU).[20] NGU was an interesting condition, its diagnosis combined clinical and laboratory methods and it was essentially defined by what it was not: persistent genital discharge from which gonococci were absent.[21] NGU was almost exclusively reported in men, with very few women acknowledged suffering similar symptoms due to inflammation of the urethra, vagina or cervix.[22] However, in women the principal infective agent found in cases of leucorrhoea and vaginitis was *Trichmonas vaginalis*, a protozoan that seemed to be more prevalent in the United States than Europe, and *C. albicans*.[23]

The other important context was Rhoda Benham's work on *Monilia* fungi and disease.[24] Benham worked at the Columbia-Presbyterian Medical Center, where she and her colleagues became leaders in the field of medical mycology in the United States.[25] In a paper in the *Journal of Infectious Diseases* in September 1931, she argued that *M. albicans* was a 'well defined species which can be recognized and differentiated from related forms by its morphologic and cultural characteristics' and that many other organisms, previously regarded as distinct, were in fact the same species.[26] She stated the case directly:

> The evidence brought out by the different methods of study of this group of organisms gave remarkably concordant results. The strains isolated from thrush, whether called *Monilia* or *Endomyces*, the strains called *M. psilosis*, isolated from sprue, and the strains from erosion inter-digitalis, mycotic paronychia, mycotic intertrigo, perleche and superficial glossitis all showed essentially the same morphology, the same fermentations, essentially the same antigenic properties, both on direct agglutination and on absorption of agglutinins, and the same pathogenicity for rabbits. If one were ignorant of the source of these cultures, one would be unable to distinguish, for example, *M. albicans* isolated from thrush from *M. psilosis* isolated from sprue, and it would seem necessary for the present to regard such forms as merely strains of one species.[27]

In the following year, she published a short paper in the *American Journal of Public Health*, again emphasising that *M. albicans* was the main pathogenic 'yeast' found in humans.[28] She showed that the *Monilia* infecting plants and animals were distinct, and suggested keeping the term *Monilia* that for the plant pathogens and adopting Berkhout's term, *Candida* spp., for human pathogens.[29] Many mycologists thought the term *Candida albicans* unsatisfactory because it literally meant 'whitening, white'. Writing in 1940 from Duke University School of Medicine, Donald Martin and Claudius Jones quoted a French study that had identified 102 synonyms for *C. albicans*, while an Italian review had listed 121, with only 51 overlapping![30] In 1935, Benham wrote what turned out to be a forward-looking chapter on 'Monilia and moniliasis' in Frederick Gay's encyclopaedic *Agents of Disease and Host Resistance*.[31] She stressed the role of the *Monilia* spp. in the following: occasional epidemics of oral thrush and in association with gingivitis; some skin lesions and allergic reactions; infections of the vaginal mucous membrane and of the penis; infection of the eyes of the newborn; some bronchial and pulmonary infections; and generalised disease, often affecting the brain.

Thrush: Mothers and babies

Gynaecologists and obstetricians also took more interest in fungal infections in the 1930s, especially in pregnant women, in whom hormonal changes were reported to increase susceptibility.[32] In 1937 Brooke Bland and Abraham Rakoff of Jefferson Medical College, Philadelphia described a study in which 12 pregnant women and 12 non-pregnant women were infected with *C. albicans*. As we might expect for the time, there is no evidence that informed consent was sought or given; though as a minor, mostly self-limiting infection, doctors would have judged any danger to patients as negligible and justifiable for the progress of medicine. They found that ten out of 12 pregnant women acquired the infection, against four who were not pregnant.[33] This experiment was followed up by infecting a further 38 pregnant women, 25 of whom developed disease. Thrush was also reported to be common in diabetics, who had the new status of being maintained with insulin injections.[34] One idea was that high glucose levels in the blood could precipitate infection, another was that poor peripheral circulation and changes in pH predisposed diabetics.[35] Thrush was one of the many infections that made the new diabetes 'a disease of complications'.[36]

In the late 1930s, doctors noted that thrush in newborn babies (neonates) was likely caught from mothers during parturition, and there was cross-infection across sites in the body.[37] In 1940 Glen Liston and Lewis Cruickshank published two studies of leucorrhoea in 200 pregnant women in Edinburgh that showed 49 (25%) had *C. albicans*

infection, as against 75 with *Trichomonas* and four with gonorrhoea.[38] Their work was discussed in the *Lancet*, in an editorial on 'Vaginal Discharge' in September 1940 that pointed to personal and social issues for the patient.[39]

> One of the most distressing complaints that the gynaecologist and general practitioner are called on to treat is vaginal discharge. To the patient it is demoralising, because of its intractability, and in a sensitive woman it may cause considerable mental trauma. To the layman, moreover, a vaginal discharge carries a sinister innuendo – many an innocent woman has suffered unmerited blame from husband or family for a non-venereal infection, and a discharge has even been the starting point of an action for divorce.[40]

The importance of differential diagnosis, of what was also termed 'vaginal mycosis', was emphasised, along with the new possibilities for treatment.

The *Lancet* editorial was followed up by three letters. Dr Mary Michael-Shaw of the Royal Free Hospital and Salvation Army Mothers' Hospital in London recommended using specialist laboratories for diagnosis. Along with the other correspondents, she discussed treatment and recommended Stovarsol (branded as Spirocid and Arsetosone), an arsenical originally produced in the Ehrlich's series that gave the world Salvarsan. Stovarsol was No. 594 and sometimes recommended for syphilis.[41] In his letter, Lewis Cruickshank recommended 'bi-weekly painting of the whole vagina, external genitalia, thighs and pubic region with 2% aqueous gentian violet', while other doctors described their successful treatments with antibacterial douches, using products such as Eli Lilly's Negatan (also called Negatol) and Monsol.[42] Drug companies, increasingly aware of the new market created by thrush infections, developed new formulations and carriers for topical antiseptics, such as gentian violet, marketed as 'gentia-jel'.

The accepted 'reference' study of neonatal oral thrush in Britain as an emerging problem was published in 1942 by two bacteriologists from Edinburgh, G. B. Ludlam and J. L. Henderson.[43] It was based on a survey of babies born at the Royal Infirmary in the city in 1940. The incidence of the condition diagnosed clinically was 6.4% (163 cases) in that year, down from 7.2% (168 cases) in the previous year, but the figure was believed to be higher, as many babies only showed symptoms after discharge. A group of '60 unselected infants' was tested by swabbing and laboratory testing, which revealed the fungus in 18.3% (11 cases), almost three times that diagnosed symptomatically. The authors suggested that the difference pointed to a significant level of latent disease, or benign presence of the fungus. Amongst babies with symptoms, the incidence was highest in premature babies, then in those partly or wholly bottlefed, and lowest in those breast-fed. There was seemingly no discussion over whether thrush was increasing because of the rise in the number of hospital births, or the switch from breast to bottle feeding that was being reported in the 1940s.[44]

Paediatricians showed more interest in *Candida* infection as a potentially serious condition and warned that it could rapidly change from trivial to life threatening. If it spread to the oesophagus, stomach and intestines, symptoms were diffuse and often missed, with *Candida* infection often only recognised at post mortem.[45] Such concerns added to the uncertainties about the nature and management of thrush. On the one hand, it appeared to be very common and in the great majority of cases cleared up quickly, but on the other hand it might be a sign of poor general health or a warning of very serious underlying disease.[46] In succeeding years the clinical picture worsened further with claims that *Candida* infection could also spread to the lungs and even develop as systemic disease, similar to septicaemia.[47]

In 1952, Ian Donald, later a pioneer of ultrasound in obstetrics, then a Reader in obstetrics at the University of London, published on the infections seen at the Institute of Obstetrics and Gynaecology's 'D' Clinic in London over the previous five years.[48] The breakdown of the cause of infections in women, after gonorrhoea had been excluded, was *Trichomonas* vaginitis (TV) – 37.4%; *Monilia* – 16.2%, TV and *Monilia* – 7.7%; – miscellaneous 33.5%, and – 'insufficient information' 5.1%. The following year, in a series of 'Refresher Courses for General Practitioners', Scott Russell, Professor of Obstetrics and Gynaecology at the University of Sheffield, recommended rigorous cleansing and disinfection of the vagina before childbirth to flush out *Candida* and other pathogens.[49] There were critics who maintained that such measures made infection more likely, causing irritation and inflammation. They also argued that it was better to encourage the normal micro-flora of the body, which helped make the bodily soil less vulnerable to infection. Doctors also speculated that new clothing fashions and materials, such as tight-fitting nylon underwear that kept the skin warm and moist, had contributed to the increase in the incidence of thrush in women.[50] It was not without irony then that the most talked about underwear of the 1950s, though only seen in newspaper photographs and not by movie theatregoers, were the panties worn by Marilyn Monroe when she stepped into the updraft from the subway grate in the movie 'The Seven Year Itch'.[51]

Yeasts and 'the antibiotic era'

In June 1951, the Council on Pharmacy and Chemistry of the American Medical Association (AMA) agreed that a statement should be printed on bottles of three leading antibiotics (aureomycin, chloramphenicol and terramycin) to warn 'that patients receiving these drugs may be more susceptible to 'Monilial or other yeast-like organisms'.[52] This initiative was made in the context of patients showing all manner of adverse reactions to the new antibiotics. From the first use of penicillin, there had been many, many celebratory assessments of lives saved and improved by the new 'wonder drugs', but by the early 1950s these celebrations had been tempered. Concerns were expressed by doctors and the public about antibiotic use on several fronts: resistance in certain bacteria; allergic reactions in patients, including anaphylactic shock; and a growing incidence of superficial and invasive fungal infections.[53] In 1951, a collection of essays was published entitled *Penicillin Decade 1941–1951: Sensitizations and toxicities*.[54] Some of the most prominent side effects were noticed on the skin, in the form of rashes, and in the mouth, with inflammation and infection of various types, including *C. albicans* growth.[55] What attracted most attention was the development of so-called 'superinfections', as when *Staphylococcus aureus* colonised tissues from which other bacteria had been cleared by broad-spectrum antibiotics. Previously, doctors had used the term to refer to a secondary infection of the same pathogen, especially in cases of syphilis and tuberculosis, but in the 1950s the 'super' came largely to refer to secondary infections of a different pathogen and, in the case of secondary mycotic infections, the term 'fungal overgrowth' was coined.[56]

It is often forgotten that until the mid-1950s penicillin and other antibiotics were largely administered by injection or used topically, because the formulations available were poorly absorbed by the gut.[57] For external infections, penicillin was administered in creams and other carriers, including mouthwashes and pessaries, while aerosols were developed for throat and bronchial infections.[58] For most serious infections, penicillin was given by injection into muscles or via saline drip, which meant that it was most readily given to hospital patients. General practitioners were required to make three or four home visits each day to give injections to keep up the levels of the antibiotic in the system.

The awareness of the adverse effects of antibiotics grew with the arrival in the late 1940s of tetracycline, which was both broad spectrum and taken orally, and could cause the yellowing of teeth in infants and photosensitivity. Initially, fungal overgrowth was well down the list of concerns, top of which were allergic and toxic reactions, vitamin deficiency, the development of resistance and bacterial overgrowth.[59] Indeed, many reviewers implied that the extent and seriousness of fungal overgrowth had been overstated by medical mycologists talking up the importance of their specialism. The first clinical discussion of fungal overgrowth was in June 1949, when Harold Harris spoke at the New York Academy of Medicine on treating patients suffering from brucellosis with aureomycin and chloramphenicol.[60] He suggested that overgrowth was due to a combination of *C. albicans* gaining virulence in the absence of bacterial competition, the destruction of intestinal bacterial flora, and the lowering of the vitality of gut tissues. He worried too about the permanence of the changes and the development of more virulent strains of the fungus. In June 1951, James Woods and colleagues, from the Watts and McPherson Hospitals in Durham, North Carolina, published a study of 25 patients who had developed *C. albicans* infection after treatment with various antibiotics.[61] The study found no evidence that antibiotics had a stimulating effect of the fungus, but confirmed the view that the removal of competing bacteria cleared the gut for fungal colonisation. The report also suggested that treatment with vitamin B complex offered some amelioration, but could give no reason why, other than perhaps it improved the general nutritional status of the body. However, the immediate reason for the intervention of the Council on Pharmacy and Chemistry in June 1951 was because of reports that aureomycin, chloramphenicol and terramycin could precipitate fungal infection of the lungs, whereas the bowel infections noted previously had been 'of little consequence'.

Cases of broncho-pulmonary moniliasis had been reported in medical journals for decades.[62] The increased attention given to tuberculosis after the Second World War, because of mass X-ray screening and effective antibiotic treatment, revealed a greater prevalence of broncho and pulmonary mycotic disease.[63] A study by Robert Oblath and colleagues in California, published in July 1951, argued that *C. albicans* should be added to the list of mycotic pulmonary organisms alongside *Coccidioides immitis* and *Histoplasma capsulatum*, which we discuss in the next Chapter.[64] There were also reports of *C. albicans* infection of the heart (endocarditis) and kidneys. This gave wider recognition to the possibility that moniliasis was changing from an irritating, though relatively mild disease of mucous membranes in the mouth and genitalia, to a serious, often fatal disease of major internal organs. An editorial in the *British Medical Journal* in June 1951 noted the decision of the Council of Pharmacy and Chemistry, but was sceptical of the need for a similar warning about tetracycline in Britain. [65] The writer suggested that 'there was much more

extensive use of these drugs generally in America' and that it had brought to light complications which were unfamiliar to doctors in Britain.

A year after the call for warnings on tetracycline packaging, an editorial in *JAMA* reaffirmed the action and concluded that 'The occurrence of moniliasis as a complication of antibiotic therapy has been definitely established.'[66] This claim was contested by Albert Kligman, whose work was discussed in Chapter 2.[67] Kligman argued that, with respect to the impact of wide-spectrum antibiotics, the 'incrimination of moniliasis as the cause of numerous side-reactions requires critical reappraisal'. He advanced four points. Firstly, much of the evidence for the enhancement of fungal growth came only from *in vitro* experiments.[68] Secondly, he suggested that 'reported instances of localized moniliasis are not actually cases of this disease', but rather instances of inflammation due to many causes, where *C. albicans*, a common non-pathogenic presence in many part of the body, might be expected to be found.[69] Thirdly, he argued that diagnoses had been made on insufficient evidence and, fourthly, that mycotic diseases had complex aetiologies, where a single factor, such as the presence of an antibiotic, was unlikely to be sufficient to produce disease. Kligman ended by warning that the development of antibiotic resistance in staphylococcal and streptococcal bacteria 'is likely to be of far greater significance than the problem of superinfections with fungi'.[70] Ernest Jawetz complained that Kligman was minimising the dangers of moniliasis, saying that 'the overgrowth of yeasts was mainly a saprophytic surface phenomenon'.[71]

However, Kligman's views were supported by clinical assessments in the mid-1950s. Louis Weinstein and Lois Finland, writing in the *New England Journal of Medicine* in February 1953 on 'Complications induced by antimicrobial agents', mentioned fungal infection very briefly and focused on hypersensitivity and superinfections from antibiotic-resistant bacteria.[72] In a paper the following year, Weinstein announced his findings on 3015 patients treated with antibiotics, where 52 or 1.74% developed superinfections, of which only seven were due to *C. albicans*.[73] In a study published in the *Lancet* in 1954, Jessie Sharp reported that the incidence of *C. albicans* in the throat, sputum and rectum of patients had doubled during oxytetracycline therapy. However, presence of the fungi was not necessarily associated with disease and the only concern expressed was that these patients would spread *C. albicans* at home when discharged.[74]

Despite the relatively low case incidence, antibiotic induced moniliasis (or as it was increasing referred to candidosis or candidiasis) attracted interest, not least because doctors linked it to the new phenomenon of systemic *Candida* infection in patients who were severely debilitated or immunocompromised from other diseases, or receiving toxic treatments for leukaemia, such as nitrogen mustard therapy.[75] The general point made by medical mycologists was that recent innovations were changing the internal milieu of the body to achieve radical therapeutic advances, but that this led to *C. albicans* emerging as a serious pathogen because it was already present in the healthy body, usually harmless or perhaps even in a symbiotic relationship.[76]

Nystatin – The first antifungal antibiotic

The narrative of the antifungal drugs in the antibiotic era is dominated by the discovery of nystatin by Elizabeth L. Hazen and Rachel F. Brown at the Albany Laboratory of the New York State Department of Health. Their story has been told in Richard Baldwin's book *The Fungus Fighters: Two Women Scientists and Their Discovery*.[77] Hazen had worked as a bacteriologist since 1931 and took the special course in medical mycology at the College of Physicians and Surgeons of New York, befriending Rhoda Benham. Brown was an organic chemist who had joined the Albany Laboratory in 1926 and worked on serum diagnoses, including the Wassermann Reaction for syphilis. They began to work together to try to find antifungal agents against *Coccidioides* and *Candida*, and in the fashion of the time turned to the soil and the chemicals produced by fungi.[78] Within two years, in a soil sample from a friend's garden, they found that the fungus *Streptomyces noursei* had yielded an antifungal compound, which they called fungicidin. It was both fungistatic – preventing the multiplication of organisms – and fungicidal – actually killing organisms.[79] The discovery was announced at a regional meeting of the National Academy of Science in October 1950.[80]

Two years later, Selman Waksman, who was then Professor of Microbiology at Rutgers University, New York and soon to accept the 1952 Nobel Prize in Physiology and Medicine for the development of streptomycin, bemoaned the fact that screening of new chemotherapeutic agents had been mostly for antibacterial, rather than antifungal activity.[81] He argued that there was no *a priori* reason why fungi had not developed antagonistic reactions to other fungi as well as bacteria. Indeed, both penicillin and tetracycline had proved effective in the treatment of actinomycosis, then classified as a fungal disease.[82] Waksman suggested that, as there were many effective topical antifungals, the

research ‘prize’ would go to anyone finding an antifungal that could be injected, or taken orally to attack topical infections from within and combat the emerging problem of systemic infections. He pointed out that such chemicals would also be very useful in veterinary medicine, where fungal diseases were found to be endemic and often epidemic. Waksman identified the actinomycetes as the most promising group for antifungals and particularly *Streptomyces* spp., the potential of which had been demonstrated by Hazen and Brown. However, he was only able to report promisingly fungistatic and fungicidal results in laboratory studies.

Nystatin was introduced as ‘Mycostatin’ in 1954. Finance for its development came from a private foundation, the Research Corporation for Scientific Advancement (RCSA). This organisation, which had been created in 1912, received and distributed funds for what would now be termed near-market research and with nystatin the RCSA dealt with patents, licences and development. The drug was produced under an agreement, between E. R. Squibb and Sons, the RCSA, and Hazen and Brown, which saw part of the income from sales and royalties reinvested in research by the RCSA and in the newly created Brown-Hazen Fund. An indication of the success of nystatin was that by 1960, income to the fund had risen to $200,000, which was used mainly to support training programmes in medical mycology.[83]

Squibb issued Mycostatin in powder form, which doctors and pharmacists made up into ointments, lotions, pessaries and sprays with appropriate carriers.[84] However, it was soon available in tablets for oral administration to treat intestinal moniliasis where non-absorption was a boon as the compound remained at high levels in the gut.[85] It was marketed for the treatment of three conditions: oral thrush, vaginal thrush and ‘monilial overgrowth’ in the intestines. Doctors reported good results, and in topical applications patients welcomed not having to suffer the indignity of having their mouths and other parts painted with gentian violet.[86] There were no reported side effects from the topical application of nystatin, but when doctors tried injecting the drug there were problems: pain at the site of injection; then shaking, chills, fever and general malaise, and some long-term effects, such as sclerosing of the veins. Nystatin prompted the first international symposium on fungal therapy in Los Angeles in June 1955, where one question, perhaps surprisingly given the profile of nystatin, was: Why is topical therapy for the superficial mycoses so ineffective?[87] In all, there were 56 papers on every possible aspect of the topic, as the contents page revealed: ‘therapy, epidemiology, biology, ecology, reservoir pathogenicity, and immunization in fungus diseases, a number of factors bearing indirectly on therapy, such as laboratory controls and hormonal influences’.[88] Nystatin was more effective than previously available compounds, but it was not a cure-all in the clinic.

The first British clinical report of the use of nystatin for vaginal thrush was in March 1955. Two women who had suffered for many months and endured the irritation, inconvenience and often the embarrassment of using gentian violet, enjoyed rapid symptomatic relief with nystatin pessaries.[89] The following March, two general articles on nystatin were published in the *British Medical Journal*, which prompted letters on local experience in Oxford and London.[90] In September 1956, details of larger clinical trials began to appear. Harry Pace and Samuel Schantz, from Brooklyn, presented details of 59 patients with laboratory confirmed *C. albicans* vaginitis that were treated simply by the insertion of nystatin tablets into the vagina. The average success rate was 98.3%: 100% amongst the 31 women who were pregnant and 96.3% in the non-pregnant.[91] A similar study by Warren Lang and colleagues at the Jefferson Hospital, Philadelphia, with 70 patients, again showed prompt symptomatic relief and near total success.[92] However, other reports were more mixed; for example, one study from Los Angeles published in 1957 showed ‘excellent’ results in 43% of patients, ‘good’ results in 53% and fair results in 4%.[93]

Trials in Britain were similar. In January 1957, Roy Jennison and J. D. Llywelyn-Jones at St Mary’s Maternity Hospital, Manchester, reported 88% success with nystatin in cases of thrush, compared to 47% with gentian violet. Later that year, William Barr, at the Western Infirmary in Glasgow, published his trials with 64 women: 55 (86%) were ‘completely cured’ (mycologically clear); 62 (97%) were cured symptomatically; and only 10 (16%) relapsed.[94] He also gave the outcomes of 12 diabetic women with infection, where results were less positive: nine (75%) were cured symptomatically, but two of these had relapsed. Barr linked this to raised levels of sugar in the urine that provided a substrate for the fungi to develop.

In the 1950s, the most controversial use of nystatin was for intestinal *Candida* overgrowth in patients taking tetracyclines. In fact, the initial promotion of ‘Mycostatin’ had suggested its use in the ‘prevention and treatment of intestinal moniliasis, or candidiasis, especially for patients taking oral antibacterial antibiotics for prolonged periods’.[95] Many studies had shown that after taking oral antibiotics, particularly for long periods, the number of patients with *C. albicans* in their faeces rose dramatically.[96] There were contrary views about what this meant. Some

doctors argued that it caused diarrhoea and intestinal conditions; others suggested that most patients with positive rectal swabs had ‘no complaints of diarrhoea, burning sensation on defecation, or soreness of the anus and surrounding skin’.[97]

One solution to the alleged problem of *Candida* overgrowth in the gut was to give patients on antibiotic regimes nystatin as a prophylactic. Andrew Childs at Ruchill Hospital, Glasgow, trialled this protocol in 1954 and in 1955 Squibb introduced ‘Mysteclin’, a combination of tetracycline and nystatin.[98] Squibb’s advertising claimed that ‘Mysteclin’ was valuable for ‘many common infections’, including bronchitis, meningitis, pneumonia and tonsillitis, and by halting the overgrowth of *C. albicans*, it would also protect against ‘gastrointestinal distress, anal pruritis, vaginitis, and thrush’, any of which on occasion ‘may have serious and even fatal consequences’. Such drug combinations worried those doctors concerned about the development of bacterial resistance and other complications of antibiotic therapy, and they were unhappy that the drug tacitly accepted the theory of antibiotic-induced fungal overgrowth.[99]

In the 1960s ‘Mysteclin’ became controversial in the new context of drug regulation. It was one of the antibiotic combinations that prompted an investigation, sponsored by the National Academy of Sciences and National Research Council, into fixed drug combinations in 1969.[100] Such drugs were seen by many physicians as ‘irrational’ and typical of the ‘avaricious marketing’ of pharmaceutical companies, but others worried at the impact of regulations.[101] In the event, ‘Mysteclin’ was banned by the FDA.[102] Squibb started a counter offensive. This gained notoriety when it emerged that the company had facilitated the writing of letters from physicians asking for the ban to be lifted and enrolled the heads of Harvard and Yale Medical Schools, who were also paid consultants to the company, to give evidence.[103] Squibb came up with a new combination, ‘Mysteclin-F’, in which nystatin was replaced by amphotericin B; the original formulation became ‘Mysteclin-V’.[104]

By this time amphotericin B was a well known and widely used for systemic fungal infections. It had been isolated, like nystatin from a *Streptomyces* species (*S. nodosus)*, in an antibiotic screening programme at the Squibb Institute for Medical Research in 1953.[105] Purification produced two compounds: amphotericin A and amphotericin B, and the latter was shown to counter systemic mycoses in experimentally infected mice and rats, and to do so through oral administration. Amphotericin B was licensed in 1955.[106] For a while, amphotericin B promised to be the penicillin of internal fungal infections, but its clinical use proved problematic. The compound was not readily absorbed by the gut, though Squibb overcame this setback by producing a suspension that could be given intravenously. It was tried with some success against localised and systemic cryptococcosis, blastomycosis, histoplasmosis and coccidioidomycosis, but the side effects were many, severe and potentially fatal.[107] Reactions included fever, and nausea and vomiting, and serious kidney damage. However, the drug was used in patients with life-threatening systemic fungal infections in what was sometimes called salvage therapy, with doctors and families calculating that the chance of a cure was worth the risks.

By the 1960s the two most common types of *Candida* infection, oral and vaginal thrush, were well understood by doctors, not least because the availability and success of nystatin had prompted greater medical interest. Oral thrush was readily diagnosed by the characteristic white patches and, if necessary, samples for microscopy and culturing were easily obtained. In neonates doctors found that infection was mostly caught from nurses and mothers; in Britain the incidence of *Candida* infection in pregnant women was around 15%.[108] However, diagnoses were a problem because of the problematic position of medical mycology. Rosalinde Hurley, who then held a joint clinical and microbiology post at Queen Charlotte’s Maternity Hospital, London, pointed to a tension between laboratory-based, ‘botany types’ and clinic-based, ‘medical types’ in the specialism.

> A ridiculous situation had in the past been reached in clinical microbiology in which the microbiologist believed Candidal vaginitis to be a clinical diagnosis and the clinician believed it to be a mycological diagnosis. The two groups rarely seemed to have discussed the problem. The situation had now improved, if only to the point of admitting that a problem existed.[109]

It seems that the arrival of nystatin, with its broad-spectrum activity, meant that medical interest in the actual fungi producing infection, which had never been high, remained cursory.

The success of nystatin also led pharmaceutical and disinfectant companies to introduce products with, allegedly, similar properties, such as ‘Sporotacin’, candidicin, pimaracine and hamycin.[110] There is no doubt that self-treatment

with the new topicals was widely practised. New prescription antifungals continued to be launched by pharmaceutical companies, including topical amphotericin B, with claims of 85–95% cure rates, though often several courses of treatment were necessary.[111]

The market leader from the 1970s was Bayer's 'Canesten', the active principle in which was clotrimazole, developed in its laboratories by Prof Karl Heinz Büchel and marketed in cream, spray and tablet forms. It was mainly used for vaginal infection, where it offered excellent symptomatic relief, but it was no cure-all, as the recurrence of infection was common.[112] Initially, 'Canesten' was a prescription product, but in the 1990s it became available over the counter. In pessary form, it remained the market leader for vaginal infection in 2000 and sold well in cream form for topical infections, including tinea pedis.[113]

Systemic candidiasis: 'A disease of the diseased'

The first book devoted solely to *Candida albicans* was published in 1964.[114] Its authors were Howard Winner and Rosalinde Hurley, both of whom worked in clinical pathology at the Charing Cross Hospital, London.[115] Hurley, who qualified in both medicine and law, went on to a distinguished career in medical microbiology, always championing mycology, and eventually working in medical regulation. The authors saw their book as a response to the increased incidence of the disease and the burgeoning literature on the topic, yet they were puzzled by the lack of agreement on many issues.[116] One key point of contention was, had there been a 'real' increase in the incidence of *C. albicans* infection, or was the increase only apparent and due to greater awareness and improved diagnostic methods? Winner and Hurley suggested it was the latter. A key piece of evidence was that reported mortality from systemic candidiasis (moniliasis had gone out of fashion) showed no increase at all in recent decades.[117] If there had been more infections in the general population, they argued, there should have been more deaths in special groups, as there would have been a greater likelihood of the development of systemic disease. They thought it unlikely that the availability of nystatin and amphotericin B had changed therapeutic outcomes in terminal cases. The only change in mortality from fungal disease since 1940 was the decline in deaths from actinomycosis, which was susceptible to penicillin.[118]

A second question was, to what extent was systemic candidiasis a primary rather than secondary disease? Winner and Hurley went with the latter, endorsing the old adage that *Candida* infection was primarily the 'local expression of a very bad state of the whole system', or was 'a disease of the diseased'. External infections were associated with predisposing conditions, so it seemed logical that the same applied to internal disease. Winner and Hurley were quite sceptical of the near orthodoxy that antibacterial antibiotics were an important predisposing factor to candidiasis and concluded, 'One is left unable to advance a precise explanation of the nature of the imbalance between host and parasite which changes a harmless symbiotic relationship into a disease which may have lethal consequences.'[119] The mortality rate with systemic candidiasis was nearly 90%, which was perhaps unsurprising as most sufferers had prior serious illnesses.[120]

The first international symposium on *Candida* infection was held in London in 1966, supported by the pharmaceutical company E. R. Squibb & Sons. The proceedings were edited by Winner and Hurley, and covered all aspects of the infection, but most attention was given to systemic disease, for which Squibb's amphotericin B remained the treatment of choice.[121] In the same year, Mildred Seelig, of New York Medical College, published on 'The role of antibiotics in *Candida* infection.' She noted that a review of mycotic disease in 1945 by Downing and Conant had observed that systemic or disseminated infections with *C. albicans* were rare.[122] Two decades later it was clear things had changed, for over half of Seelig's paper was devoted to systemic disease. The increased incidence was said to be hard to quantify, but Seelig was in no doubt that there had been a major change. She argued that this was due firstly to normally saprophytic organisms becoming pathogenic; and secondly, to the creation of new groups of vulnerable patients with altered internal bacterial flora and depressed immune systems. The former related to the increased use of antibiotics, especially combined and broad-spectrum formulations, while the latter was due to more invasive surgery and new therapeutics, such as with cortisone.[123] One example of the change was candidal endocarditis, which was rare in the 1940s, yet by 1961 it was 'an emerging peril in cardiovascular surgery'.[124] The predisposing factors were: the use of multiple antibiotics and adrenal corticosteroids; catheterisation and intravenous fluids; and general poor health of patients.[125] The number of cases associated with cortisone and adrenocorticotropic hormone (ACTH) was small, but they pointed to a new situation where deepseated fungal infections developed as the result of the body's immunological and physiological functions deliberately altered by therapeutic regimes.[126] The novelty of such complications in the 1950s meant that many were written up for publication as rare or atypical cases, giving systemic fungal infections a profile that was greater than their clinical incidence.

The most controversial site for medical debates about the pathogenicity of *C. albicans* was the lungs, and this went back to tea taster's cough in Sri Lanka in the 1920s. Doctors had debated whether *C. albicans* was a harmless saprophyte as it was found widely in the sputum of children and adults, which acted as a reservoir for lung and tracheal infection.[127] Bronchopulmonary candidiasis was investigated in the laboratory and the clinic, with some studies suggesting that fungal infection worsened asthma and tubercular infection by altering lung tissue and function.[128] The number of cases was small, but they were challenging to diagnose and treat, with suspicions that broncho-mycotic disease was greatly underreported. Despite there being very few cases, chest physicians invested some effort in devising criteria to determine whether primary infection was due to *C. albicans*. These standards were very tight, requiring the fulfilment of Koch's postulates to confirm *C. albicans* and exclusion of other infections, such as tuberculosis.[129]

Winner and Hurley's view of bronchopulmonary candidiasis in 1964 was that nothing had been resolved 'due to the chronic nature of the disease, to the fact that histopathological studies are made later in the course of the illness … and that there is no clear-cut association of a particular clinical and a particular pathological feature at all stages of the disease'.[130] One question was, did it matter whether *C. albicans* was the primary or secondary infection? A second was, does this matter as the treatment would be the same? For many doctors it did matter and not only to help resolve aetiological uncertainties. They complained again that there had in fact been an 'overgrowth' of laboratory-based medical mycologists, which had led to fungal infections being over diagnosed and their clinical significance overstated.

Systemic candidiasis gained a higher medical profile in the 1960s and 1970s from its association with immunocompromised patients, either amongst those with diseases affecting the immune system, principally leukaemia in the 1960s, and in the growing number of patients on immunosuppressant therapies, principally anti-inflammatory drugs or anti-rejection drugs in transplant patients in the 1970s. In fact, the most important anti-rejection drug cyclosporine had been isolated from a fungus (*Tolypocladium inflatum*) by researchers at the Sandoz Company in Basel, Switzerland and initially viewed as an antifungal antibiotic.[131] However, in the 1980s the numbers of immunocompromised patients expanded greatly in profile and number with the arrival of HIV/AIDS. Very early in the epidemic, oral and oesophageal candidiasis were reported as opportunistic infections in AIDS sufferers; indeed, it was considered, along with Kaposi's sarcoma and pneumocystis pneumonia, as a marker of the disease.[132] By the mid-1980s, some estimates were that 75% of AIDS patients had oral candidiasis and doctors were recommending that any patient presenting with oral *Candida* infection in a high risk group should be screened for the infection.[133] From the early 1990s, when doctors differentiated between those who had AIDS related complex (ARC), – an early phase of the infection, and those with AIDS, the respective figures for *Candida* infection were 33% and 90%, respectively.[134]

From the early 1980s, doctors used nystatin and amphotericin B for oral thrush in AIDS patients, but the new azoles seemed to hold more promise.[135] They proved effective for the oral and oesophageal forms of candidiasis common in AIDS patients, though results for systemic disease were mixed.[136] However, another azole, fluconazole, came along in the mid-1980s. This drug, developed by Pfizer as 'UK-49,858' in their laboratories at Sandwich in Kent, was trialled as a superior alternative to ketoconazole, especially for all forms of candidiasis.[137] In 1989, de Wit and colleagues at the St Pierre University Hospital, Brussels, published the first trial comparing the new drug with ketoconazole in the treatment of oropharyngeal candidiasis in patients with AIDS and ARC.[138] They reported that fluconazole was not only more effective, but was less toxic and better tolerated.[139] However, it was unavailable in the United States and when the 'People with AIDS Health Group' heard of the potential of the drug, it acted as a buyer's club for patients. The Group announced that it would import the drug pending US approval, which was on an accelerated track, though not finally sanctioned by the FDA until January 1990.[140] Doctors added fluconazole to the range of drugs used, but treatment regimes varied greatly depending on the type of infection, likely patient compliance and cost. In addition, drugs were chosen in relation to the other fungal infections affecting AIDS patients, such as cryptococcosis, histoplasmosis and coccidioidomycosis.[141]

Candidiasis in AIDS patients, though common, was reasonably well controlled with azoles, along with better-tolerated forms of amphotericin B. Reported mortality from candidiasis peaked in HIV/AIDS sufferers in the mid-1990s, having done so in all patients in 1989.[142] What these trends meant was disputed. Frank Odds argued that the reported mortality for candidiasis was likely to be quite unreliable because it was not notifiable and diagnosis was variable. From close analysis of the available data for the United States, England and Wales, he concluded that while

it was likely that there had been a 'real' increase in candidiasis mortality over the 1970s and 1980s, this had probably been 'exaggerated by a rise in enthusiasm for the study of candidosis [Odds preferred this term] and improved methods of diagnosis'.[143] However, he was in no doubt that the clinical incidence of the disease was higher because of the continuing rise in the numbers of immunocompromised patients and greater awareness of *Candida* infection.[144]

The fact that patients treated for systemic candidiasis were relatively small in number and typically had multiple disease problems meant that clinical trials with antifungals had not been of the same rigour as in other fields. In 1977, the NIH and National Institute of Allergy and Infectious Diseases (NIAID) had sought to develop better clinical trials with systemic fungal infections and convened a group to explore the matter. They met at Atlanta Airport and submitted a bid, led by William Dismukes, at University of Alabama School of Medicine in Birmingham for NIH funding.[145] The other members of the group were John Bennett (NIH), Gerald Medoff (St. Louis), Richard Duma (Virginia), Merle Sande (Virginia) and Harry Gallis (Charlotte) and they became known as the Mycoses Study Group (MSG). The MSG was awarded their first contract by NIAID in the following year and others followed for 27 years. This support allowed the establishment of 'a Central Administrative Core Unit based at the University of Alabama School of Medicine at Birmingham, a Central Biostatistics Unit, distinctly focused disease or population at-risk study groups with designated principal investigators, an annual meeting, and partial funding for various types of clinical trials or epidemiologic studies'.[146] The first trial, comparing amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis, was funded by NIAID and the John A. Hartford Foundation, and published in the *New England Journal of Medicine* in July 1979.[147] A year later they published guidelines for clinical trials with antifungal drugs and many other studies followed.[148]

A new problem in the final decades of the twentieth century was candidaemia – *C. albicans* infection of the blood that was mostly found as nosocomial infections, that is, those acquired in hospital. The 1979 edition of Frank Odds's *Candida and Candidosis* had no chapter on the condition, but the second edition in 1988 did, driven by the growing medical and public concern about hospital-acquired *Staphylococcus aureus* and in particular Methicillin-Resistant *Staphylococcus aureus* (MRSA).[149] Most nosocomial infection was bacterial, but up to 10% and rising was due to fungi, with *C. albicans* the most prevalent; indeed, mycoses were ranked third or fourth overall. Intensive care units were important places of infection because of the proliferation of sites where *C. albicans* could either enter the body (e.g. catheters) or grow (monitoring sensors). In some cases, suspected septicaemia, the great dread of those managing high-dependency patients, was found to be candidaemia, which was soon placed amongst a number of systemic blood infections, termed 'fungaemia'. A review in 1995 claimed that over the 1980s the incidence of blood-stream infection due to *Candida* spp. increased by almost 500%, though again the question had to be asked, how much of this was due to greater awareness and better laboratory testing?[150]

The requirement for laboratory tests to confirm candidaemia and the new methods of identifying pathogens revealed that the dominance of *C. albicans* as the major cause of candidiasis was under threat from other species.[151] Whereas previously, *C. albicans* infection had been the default, the new molecular technologies of identification enabled faster and more accurate differentiation of species. These methods were used because clinicians needed to monitor the type and number of fungi due to the emergence of resistance to antifungal drugs. The development of resistance had been feared in the 1950s from the overuse of nystatin and amphotericin B, but this proved less of a problem in fungi than bacteria because resistance is not readily transmitted between strains. However, resistance did emerge in the late 1980s, following from the extensive and intensive use of fluconazole with AIDS patients. Initially, resistance was partial and overcome by increasing the dose, though in time other drugs became available, notably posaconazole and voriconazole. The pattern of drug use also affected the epidemiology of infective species; for example, use of fluconazole reduced the incidence of *C. albicans*, but facilitated the increase in *C. krusei*, which was resistant to the drug.[152] These epidemiological discoveries were made from case reviews and surveys of the usual suspects: patients with leukaemia; cancer sufferers and other patients on immunosuppressant therapies; those in intensive care or high-maintenance therapy, and those with HIV/AIDS. Moreover, it was of course around this group that the notion that candidiasis was 'the disease of the diseased' gained use and acceptance.

'The Yeast Connection'[153]

Writing in 1988 in the second edition of his book on *Candida*, Frank Odds was clear that there had been a 'public revolution in *Candida* consciousness' in the 1980s.[154] However, this was not due to greater awareness of systemic candidiasis, candidaemia, or infection in those with HIV/AIDS, but to two popular books: William Crook's *The Yeast Connection: A Medical Breakthrough* (1982) and Orian Truss's *The Missing Diagnosis* (1983).[155] Crook was a

paediatrician, who had founded a Children's Clinic in the 1950s and served on the staff of the Jackson-Madison County General Hospital in West Tennessee. He developed an interest in chronic conditions in children, such as bedwetting, colic, migraine, fatigue and hyperactivity, coming to favour the idea that many of these were due to food allergies. He was a populariser, publishing in 1963 a general parenting advice book, *Answering parent's questions*, in the vein of Benjamin Spock, before three books on food allergies in the 1970s: *Your allergic child: a pediatrician's guide to normal living for allergic adults and children* (1973); *Can your child read? Is he hyperactive? A pediatrician's suggestions for helping the child with hyperactivity, behavior and learning problems* (1975); and *Are you allergic? A guide to normal living for allergic adults and children* (1978).[156] In 1979, Crook claimed that his life changed – he came across an article by Orian Truss on *Candida* infection and chronic diseases in adults in the *Journal of Orthomolecular Psychiatry*.[157]

Orian Truss had a private practice in Birmingham, Alabama and an interest in allergy and infection.[158] He was influenced by Linus Pauling's ideas on orthomolecular medicine.[159] Pauling had coined the term in 1968 to refer to 'the maintenance of health and cure of disease by regulating the concentration in the body of substances naturally found there'; this meant, literally, striving to have the 'right' chemicals at the 'right' levels in the body.[160] Pauling pursued this, most famously, in his support for megavitamin treatments, particularly vitamin C to manage the common cold, but initially his focus was on psychiatry. The subject was debated extensively in the early 1970s as dietary management was an attractive alternative to many of the new neuroleptic drugs and their side effects, but a report for the American Psychiatric Association in 1973 was highly critical.[161] However, orthomolecular medicine enjoyed popularity as an 'alternative' therapy, and, very unusually, one endorsed by a Nobel Prize winner for Physiology and Medicine.[162] Orthomolecular medicine was one of a number of alternative or fringe medical movements in the 1970s and 1980s that challenged orthodox medicine at every level and over the nature and treatment of most diseases.[163]

Orian Truss first aired his views on the health effects of yeast allergies and infections at the eighth Scientific Symposium of Academy of Orthomolecular Psychiatry in Toronto in May 1977. His talk was published in 1979. Truss argued that the persistence of a chronic infection in the body required 'the absence of an effective immunologic response to the pathogen' and that in chronic candidiasis, as in leprosy and tuberculosis, disseminated disease can be due to an 'antigenic load' overwhelming the immune defences.[164] In turn, a weakened immune system would predispose patients to local and general pathological conditions. He painted a picture of the patient with chronic candidiasis that would become very familiar in succeeding years; hence, it is worth quoting at length.

> A careful history that traces the illness from its onset suggests the diagnosis. It invariably includes a story of futile efforts by many competent specialists to establish an organic basis for the chronic illness, and of the almost irresistible recommendation of psychiatric therapy. Attention in the history should be directed to the influence of repeated pregnancies, birth-control pills, antibiotics, and cortisone and other immunosuppressants. The onset of local symptoms of yeast infection in relation to the use of these drugs is especially significant and usually precedes the systemic response. Repeated courses of antibiotics and birth-control pills, often punctuated with multiple pregnancies, lead to ever-increasing symptoms of mucosal infections in the vagina and gastrointestinal tract. Accompanying these are manifestations of tissue injury based on immunologic and possibly toxic responses to yeast products released into the systemic circulation. Many infections are secondary to allergic responses of the mucous membranes of the respiratory tract, urethra, and bladder, necessitating increasingly frequent antibiotic therapy that simultaneously aggravates and perpetuates the underlying cause of the allergic membrane that allowed the infection. Depression is common, often associated with difficulty in memory, reasoning and concentration. These symptoms are especially severe in women, who in addition have great difficulty with the explosive irritability, crying, and loss of self-confidence that are so characteristic of abnormal function of the ovarian hormones. Poor end-organ response to these sex hormones is confirmed by the common association of acne, impairment or total loss of libido, and the whole range of abnormalities of menstrual bleeding and cramps, as well as a very high incidence of endometriosis in those who have undergone hysterectomy. Many of these patients also start developing multiple intolerances to foods and chemicals, making it increasingly difficult for them to live in a normal environment. Many or all of these intolerances disappear as the yeast problem is brought under control.[165]

Truss's treatments aimed to restore immunological 'competence' and, as seen below in Table 3.1, while his preventive and treatment regimens recommended avoiding antibiotics and immunosuppressants, they included the use of

antifungal drugs. Therefore, while presenting himself to readers as a holistic, alternative practitioner, Truss was a quite pragmatic in his clinical work and used the full range of orthodox drugs, including nystatin and the new azoles.

Truss also drew inspiration from the work of Theron G. Randolph, the 'father of clinical ecology' and his idea that a key determinant for health in modern societies was to avoid exposure to chemical contaminants of air and water, including antibiotics.[167] Clinical ecologists were on the fringe of American medicine, as signalled in 1981, when the California Medical Association (CMA) adopted the position that clinical ecology does not constitute a valid medical discipline. The critique, widely endorsed by medical organisations, stated that scientific and clinical evidence does not support the diagnosis of 'environmental illness' and 'cerebral allergy', and that evidence is lacking for the concept of massive environmental allergy.[168]

In the preface of *The Yeast Connection*, William Crook wrote that he had read Truss's paper on *C. albicans* and chronic illness in the summer of 1979 and immediately tried the suggested treatment regime on one of his difficult patients, 'a 41-year old woman (I'll call her Nancy Jones) with severe chronic hives [urticaria], accompanied by mental confusion, fatigue and depression'.[169] He started her on nystatin and a yeast-free, low carbohydrate diet. Within six days her hives had improved, in weeks they disappeared and after almost a year all her symptoms had improved. Crook reported trying the regimen with another 20 patients.

> Nearly all were adults with complex health problems, including headache, fatigue, depression, recurrent vaginal infection, joint pain and sensitivity to chemical odours and additives. Almost without exception, they improved. And some improved dramatically.[170]

He continued ad hoc variations in his treatments, extending the range of conditions and ages, eventually to include his paediatric patients. In the meantime, Truss had been featured in the 'Dan Freeman Report' on CNN in September 1981, an appearance that allegedly brought more responses than any previous programme.

In was not long before Truss and Crook joined forces and they did so first at an 'informal' conference they called on '*C. albicans* and the relationship to human disease' in Dallas, Texas, in July 1982.[171] This was attended by 20 physicians and an equal number of patients. Crook made his television debut on the subject in Cincinnati in January 1983, in a broadcast that led to 7,300 requests for more information and his decision to write *The Yeast Connection*. In the meantime, Truss self-published *The Missing Diagnosis*; but it was Crook and his book that gained the public's attention, not least because he was accessible to the media and an effective communicator. The first print run of *The Yeast Connection* in 1983 quickly sold out. He claimed that 270,000 copies were purchased in the first two years. Crook wrote in the preface that, already, 'my recognition of "the yeast connection" has changed my life and my practice and had enabled me to help many, many patients conquer previously disabling illnesses'. The book was in its fourth edition in 1986.

Crook soon had wider ambitions, hoping to forge what he saw as 'The Coming Revolution in Medicine'.[172] He had written *The Yeast Connection* as a self-help manual, with checklists, diagrams, illustrations and clear preventive and therapeutic advice on necessary changes in lifestyle and diet, including recipes, and special measures for different patient groups. One of the most controversial features of the book was its 10-point self-diagnosis schedule, where three or four 'yes' answers suggested that 'yeasts played a role in your symptoms'.[173] The explanation of the causes of yeast overgrowth was presented in words and graphics. Crook's advice was threefold: first, 'avoid foods which promote yeast growth'; second, seek a prescription from your doctor for 'medication which helps rid your body of yeast germs' (nystatin or ketoconazole); and, third, make changes to your lifestyle and behaviour. In the early 1980s, taking prescription antifungal drugs was an integral part of the treatment and the merits of nystatin and ketoconazole were discussed in some detail.[174] However, later and in the hands of other advocates, the self-help and 'alternative' features took over, as the regime moved to a natural therapy, not least because many doctors refused patients antifungal drugs as they did not accept that 'fungal overgrowth' was a disease or syndrome at all.

The popular success of Truss and Crook brought imitators who linked *Candida* overgrowth directly to other, so-called, 'twentieth century diseases'.[175] In the hands of Truss and Crook, 'fungal overgrowth' had always been linked to allergies and infection, and to chemical sensitivities, hyperactivity and mental disorders.[176] Soon the illnesses they had identified were medicalised by other doctors, with such names as the *Candida* syndrome, *Candida* allergy syndrome, the yeast syndrome, polysystemic chronic candidiasis, chronic candidiasis syndrome and, most commonly, candidiasis hypersensitivity syndrome (CHS). In June 1984, Crook branched out from popular writing and

appearances to advance ‘The Yeast Connection’ to the American medical profession. His chosen subject was depression and he wrote a letter to the *Journal of the American Medical Association* suggesting that the condition was ‘commonly related to prolonged or repeated courses of broad-spectrum antibiotics or to birth control pills, which promote the overgrowth of *C. albicans* on mucous membranes’.[177] He acknowledged that the ‘mechanisms involved still have not been clearly elucidated’, but wrote that he had good evidence ‘from clinical history, followed by a therapeutic response to oral nystatin and a yeast-free, low-carbohydrate diet’. His views were rounded upon by several correspondents, who dismissed his claims as lacking evidence and being based on multiple misconceptions.[178]

The following year, several medical organisations attacked Crook, Truss and their followers. The American Academy of Allergy and Immunology was worried by the attention being given to CHS and in August 1986 published a position statement in its journal.[179] The Practice Standards Committee found ‘multiple problems with the candidiasis hypersensitivity syndrome’; principally that ‘the concept is speculative and unproven’ and that ‘elements of the proposed treatment program are potentially dangerous’. The Committee stated that ‘basic elements of the syndrome would apply to almost all sick patients at some time’ and that ‘the broad treatment program would produce remission in most illnesses regardless of cause.’ Moreover, there was ‘no published proof that *C. albicans* is responsible for the syndrome’ or that ‘treatment … with specific antifungal agents … benefits the syndrome.’ The dangers in the treatment regimes were that the promiscuous use of drugs would produce resistant strains of *C. albicans* and of that there could be long-term effects with patients on systemic antifungals for many years. In November 1987, at a meeting on Controversies in Infectious Disease, John E. Edwards of (UCLA) attacked Crook and those on his bandwagon.[180] His description nicely captured the frustrations of regular medicine.

> Certain generalizations can be made regarding ‘the yeast connection.’ The symptoms described by the authors are generalized and affect nearly every organ system. As listed, some symptoms are widely diverse; for instance, both fatigue and hyperactivity are included. Nearly every normal individual has had certain of these symptoms during the course of a normal lifespan. Case reports are anecdotal. Possibly none of the authors have had formal training in the disciplines of allergy and immunology, infectious diseases, or mycology. After nearly a decade since the original description, no articles on this disease appear in peer reviewed journals included in the Index Medicus. There are no prospective controlled therapeutic studies, and there are no animal model data.[181]

A year later, the Canadian Paediatric Society warned that, ‘Physicians must not be swayed by the attention that the syndrome has attracted in the lay press.’[182]

The Yeast Connection was published in Britain in the summer of 1988. Chronic candidiasis had been discussed in the popular press for a couple of years and linked to myalgic encephalomyelitis (ME) or post-viral fatigue syndrome (PVFS).[183] In *The Observer*, Sue Finlay wrote that ME was ‘An illness doctors don’t recognise’, but which she had overcome by following the diet recommended in Leon Chaitow’s *Candida albicans: Could Yeast Be Your Problem?*[184] Clinical ecologists also gained a hearing in Britain. One described *Candida* overgrowth as ‘the quiet epidemic that is ruining modern lifestyles’, due to the specific condition of ‘dysbiosis [abnormal intestinal flora]’ and to ‘[t]he burgeoning of complex viral infections such as AIDS and ME – and, to a lesser extent, Herpes’.[185] In these conditions, it was claimed, ‘candidiasis was almost always present as an immune-sapping illness’.

Although there was a pathological theory behind *The Yeast Connection*, Crook relied on the claim that the real test of his ideas and recommendations was in the clinic. He once said, ‘There’s not a single test to prove it, but it works’ and used emotive case histories to great effect; such as that of Darlene Lindbom of Paris, Tennessee, who ‘went to two universities in a wheelchair. “You’ve got something like MS”, they told her – she had spinal taps, biopsies, the lot. I put her on my special diet and nystatin. Now she’s fit and runs a successful business.’[186] Crook visited London to promote his ideas in June 1988, which the *Guardian* styled the ‘thrush theory’. He stressed the link to food allergies and found a forum with the British Society for Allergy and Environmental Medicine, which had links with the British Society for Nutritional Medicine.[187] Both meetings were regarded as ‘alternative’ by the mainstream British medical profession and studiously ignored.

In 1989 the first clinical trials with patients reporting the ‘Yeast Connection’ were published. Lisa Renfro and colleagues at the Department of Pediatrics and Family Medicine at Farmington, Connecticut, reported on 100 consecutive patients suffering from chronic fatigue, eight of whom believed their symptoms were due to chronic candidiasis.[188] The article concluded that the authors were ‘unable to find physical or laboratory findings that were

different from the 92 other patients with chronic fatigue'. However, they did find that 'patients with the yeast connection were more likely to be taking high doses of vitamins and were more likely to be getting help from non-medical caretakers. In fact, these caretakers might be the source of the diagnosis.'[189] They went on to conclude that all but one sufferer had depression or an anxiety disorder, and that, from the point of view of achieving a positive outcome, not dismissing chronic candidiasis might be beneficial in allowing a therapeutic relationship between doctor and patient to be maintained. The following year a similar study was published by doctors at the University of Alabama Medical School in Birmingham, Crook's local stomping ground.[190] This was a state-of-the-art randomised, doubleblind trial of nystatin therapy in CHS, which concluded that, while patients on the trial improved, as was to be expected, the study had provided 'additional objective evidence that the syndrome is not a verifiable condition'.[191] An accompanying editorial in the *New England Journal of Medicine* anticipated that supporters of the yeast connection would not be impressed and, as expected, Crook and others wrote in pointing to successful treatment in with many patients.[192]

In Britain, the yeast connection only attracted sustained medical criticism in the early 1990s and then in the context of a complex debate that linked allergies, food intolerance and alternative medicine. These issues crystallised in a report by the Royal College of Physicians on *Allergy: Conventional and Alternative Concepts*, in 1992, which stated the '*Candida* theory is unsubstantiated'.[193] Responses quickly appeared in 'alternative' medical publications, particularly in the *Journal of Nutritional Medicine*; however, the specifics of the '*Candida* theory' were lost in a larger dispute on the status of 'alternative' medicine.[194] In July 1992, Keith Mumby, Britain's most high-profile clinical ecologist, appeared before the General Medical Council (GMC) and was found guilty of 'touting for charges' and failing to give a patient adequate medical attention.[195] This led the main author of the College's Report on *Allergy*, Barry Kay, to argue that the 'GMC should consider censoring all forms of diagnosis and treatment which, by reasonable standards, have consistently failed to show clinical efficacy'. Mumby was allowed to reply in an article entitled 'Science or flat earthers? The clinical ecologist replies'.[196] This was almost the last word, as the stridency and frequency of the medical establishment's assault of alternative practitioners waned, though patient demand in Britain and the United States continued to grow.[197] In medicine, CHS was gradually absorbed into a number of, what became known as, 'symptom-based conditions', which included chronic fatigue syndrome, fibromyalgia, multiple chemical sensitivities, sick building syndrome, Gulf War syndrome and irritable bowel syndrome.[198] Crook continued to publish, seeking niche markets with cook books and patient-specific audiences: women, children with, attention deficit disorder and autism, and people with chronic fatigue syndrome.[199] Many other authors expanded the genre, with titles such as *The Candida Control Cookbook* (1996), *Feast Without Yeast: 4 stages to better health* (1999), and *Complete Candida Yeast Guidebook: everything you need to know about prevention, treatment, & diet* (2000). However, the medical profession increasingly ignored CHS, except to dismiss it, especially because of the new emphasis on evidence-based medicine and the Gold Standard of double blind controlled clinical trials.[200]

Antibiotics were the icon of mid-twentieth-century medical progress and their development influenced *Candida* infection in complex ways. As thrush, the disease came to the fore in the post-war years when nystatin, the first antifungal antibiotic, was introduced and brought women with the vaginal infection to the clinic. Doctors believed that previously the condition had been self-treated or accepted, perhaps self-limiting, but had certainly been underreported. At the same time, the use of antibacterial antibiotics, especially broad-spectrum formulations, by clearing the body of its natural microbial fauna, seemed to open the body to topical infection. New clothing may have been a factor too, with stretch synthetic fabrics making underwear more close fitting and impermeable. Antibiotics were also implicated in systemic or invasive candidiasis, as the numbers of vulnerable patients multiplied. Amongst cancer patients, steroid and other treatments depressed the immune system, as did blood cancers like leukaemia. Some of the new systemic candidiasis patients suffered from iatrogenic conditions. The principal groups were transplant patients, those in intensive care, those maintained with serious chronic conditions and then people with HIV/AIDS. However, the rising tide of candidiasis was met with new antifungal antibiotics, especially azole drugs and, by the 1990s the management of systemic candidiasis was more successful. In the 1980s another new type of candidiasis emerged, CHS, which although dismissed by mainstream medicine as a fiction and a fad, became the archetypal 'disease of modernity'. Its alleged cause, overgrowth of *C. albicans* in the body, was linked to many features of modern life, including the overuse of antibiotics. It was not without irony, therefore, that, alongside lifestyle and dietary changes, taking the antifungal antibiotics produced by the modern pharmaceutical industry was also recommended.

Footnotes

1 Macfarlane, G., *Alexander Fleming: The Man and the Myth*, Oxford, Oxford University Press, 1984.

2 Christensen, C. M., *The Molds and Man: An Introduction to the Fungi*, Minneapolis, University of Minnesota Press, 1951.

3 The Oxford English Dictionary dates the first use of the term for a disease to none other than Samuel Pepys and a diary entry for 17 June 1665, when he wrote of someone: 'He hath a fever – a thrush and a Hickup', OED online. Accessed 8 August 2012.

4 Vogel, M. J. and Rosenberg, C. E., eds, *The Therapeutic Revolution: Essays in the Social History of American Medicine*, Philadelphia, University of Pennsylvania Press, 1979.

5 Li, J. W.-H and Vederas, J. C., 'Drug discovery and natural Products: End of an era or an endless frontier?' *Science*, 2009, 325: 161–165.

6 Medical Research Council, 'Treatment of pulmonary tuberculosis with streptomycin and para-aminosalicylic acid', *BMJ*, 1950, ii: 1073–1085; Medical Research Council, 'Various combinations of isoniazid with streptomycin or with PAS in the treatment of pulmonary tuberculosis', *BMJ*, 1955, ii: 435–445.

7 Jawetz, E., 'Infectious diseases: Problems of antimicrobial therapy', *Ann Rev Med*, 1954, 5: 6.

8 Earlier in the century, *M. albicans* had been known as *Oidium albicans*.

9 Kane, R. L., 'Iatrogenesis: Just what the doctor ordered', *Journal of Community Health*, 1980, 5(3): 149–158; Whorton, J., 'Antibiotic abandon: The resurgence of therapeutic rationalism', in Parascandola, J., ed, *The History of Antibiotics: A Symposium*, Madison, Wis, American Institute of the History of Pharmacy, 1980, 125–136.

10 Sáez-Gómez, J. M. and Romero-Maroto, M., 'Scientific ideas on muguet (Thrush) in the XVIII century', *Journal of Dental Research*, 2010, 89: 571–574.

11 Goodhart, J. F., *The Diseases of Children*, 6th Edn, London, J. & A. Churchill, 1899, 114.

12 West Walker, J., 'On diphtheria', *BMJ*, 1863; i: 504, 551 and 660.

13 Stuart Wilkinson, J., 'Some remarks upon the development of epiphytes: With the description of a new vegetable formation found in connexion with the human uterus', *Lancet*, 1849, ii: 448–451.

14 Pelling, M., *Cholera, Fever and English Medicine*, Oxford, Clarendon Press, 1976.

15 Wilkinson, 'Some remarks', 450.

16 Bashford, A., *Purity and Pollution: Gender, Embodiment and Victorian Medicine*, Palgrave, 1998.

17 Hewitt, G., 'Lectures on the diagnosis and treatment of diseases of women', *BMJ*, 1862, i: 54.

18 Hurley, R., 'Candidal vaginitis', *Proc R. Soc Med*, 1977, 70(Suppl 4): 1–2; Also see: Hurley R., and de Louvois, J., '*Candida* vaginitis', *Postgrad Med J*, 1979, 55: 645–647.

19 Plass, E. P. et al, 'Monilial vulvovaginitis', *Am J Obstet Gynecol*, 1931, 21: 320.

20 Semon, H. C., 'The non-venereal affections of the genitalia', *Br J Vener Dis*, 1929, 5: 114–127.

21 Harkness, A. H., 'Non-gonococcal urethritis', *Br J Vener Dis*, 1933(3), 173–186 and 187–191.

22 Sharp, B. B., 'Vulvo-vaginitis', *Br J Vener Dis*, 1930(6): 301.

23 Sharman, A., 'The significance of leucorrhoea', *BMJ*, 1935, ii: 1199–1201: Bland, P. D. et al, 'Vaginal trichomoniasis in the pregnant woman', *JAMA*, 1931, 96: 157–163; Solomon, E. and Dockeray, G. C., 'Vaginal discharges', *Irish Journal of Medical Science* 1936–1937, 11, 548–551.

24 See Chapter 2.

25 Georg, L. K., 'Rhoda Benham, 1894–1957', *Arch Dermatol*, 1957, 76(3):363–364.

26 Benham, R., 'Certain *Monilias* parasitic on man: Their identification by morphology and by agglutination', *J Infect Dis*, 1931, 49: 183–215.

27 Ibid., 212. Sprue was a tropical disease of the small intestine.

28 Berkhout, M. C., *De schimmelgeslachten Monilia, Oidium, Oospora en Torula, Scheveningen*, Edauwe & Johanssen, 1923;

Shrewsbury, J. D., 'The genus *Monilia*', *J Path Bact*, 1934, 38: 213–254,

29 Skinner, C. F., 'The yeast-like fungi: *Candida* and Brettomyces', *Bacteriol Rev*, 1947, 11(4): 227–274.

30 Martin, D. S. et al, 'A practical classification of the Monilias', *J Bacteriol* 34, 1937: 99–129; Martin, D. S. and Jones, C. P., 'Further studies on the practical classification of the Monilias', *J Bacteriol*, 1940, 39: 609–630.

31 Gay, F. P., *Agents of Disease and Host Resistance*, Baltimore, Charles C. Thomas: 1935, 1118–1123.

32 Cruickshank, R. and Sharman, A., 'Hormones and vaginitis', *J Obst Gynecol*, 1934, 41: 190.

33 Bland, P. D. et al, 'Experimental vaginal and cutaneous moniliasis: Clinical and laboratory studies of certain monilias associated with vaginal, oral and cutaneous thrush', *Arch Derm Syphilol*, 1937, 36: 760.

34 Tattersall, R., *Diabetes: A Biography*, Oxford, Oxford University Press, 2009, 82–85.

35 Hesseltine, H. C., 'Diabetic and mycotic vulvovaginitis: Preliminary report', *JAMA*, 1933; 100(3): 177–178.

36 Feudtner, C., *Bittersweet: Diabetes, Insulin, and the Transformation of Illness*, Chapel Hill, NC, University of North Carolina Press, 2003,

37 Woodruff, P. and Hesseltine, H. C., 'Relationship of oral thrush to vaginal mycosis and the incidence of each', *Am J Obstet Gynecol*, 1938, 36: 467.

38 Liston, G. and Cruickshank, L. G., 'On thrush, with special reference to vaginal thrush', *Edin Med J*, 1940, 47: 369–390; Liston, G. and Cruickshank, L. G., 'Leucorrhoea in pregnancy: A study of 200 cases', *Br J Obstet Gynaecol*, 1940, 47: 109–129.

39 Comment, 'Vaginal thrush', *Lancet*, 1940, i: 1174; Editorial, 'Vaginal discharge', *Lancet*, 1940, ii: 300. Also see: Bland, P. B. and Rakoff, A. E., 'Leukorrea: Clinical and therapeutic aspects', *JAMA*, 1940, 115(12): 1013–1018.

40 Editorial, 'Vaginal discharge', 300.

41 Cregor, F. W. and Gastineau, F. M., 'Stovarsol in the treatment of syphilis: A preliminary report', *Arch Derm Syphilol*, 1927, 15(1): 43–53.

42 *The Medical Annual 1941: A Year Book of Treatment and Practitioner's Index*, Bristol, John Wright, 1941.

43 Ludlam, G. B. and Henderson, J. L., 'Neonatal thrush in a maternity hospital', *Lancet*, 1942, i: 64–70.

44 Menzies, M. F., 'Hospital or domiciliary confinement?', *Lancet*, 1942, ii: 35–38 and 201.

45 McNeil, C., 'Death in the first month and the first year', *Lancet*, 1940, i: 819–821.

46 'Thrush in infants', *BMJ*, ii: 1950: 1430–1431.

47 Wagner, J. M. and Kessel, I., 'Complications of *C. albicans* infection in infancy', *BMJ*, 1958, ii: 362–366.

48 Donald, I., 'Aetiology and investigation of vaginal discharge', *BMJ*, 1952, ii: 1223–1226.

49 Russell, C. S., 'Leucorrhoea', *BMJ*, 1953, ii: 91–93. Also see: Anon, 'Any questions? Vaginitis', *BMJ*, 1952, ii: 813–815 and 1954, i: 59.

50 Collins, J. H., 'Vulvovaginitis', *Obstet Gynecol Surv*, 1952, 7(2): 224–227; Thomas, H. H., 'Candidal vulvovaginitis: Treatment with mycostatin', *Obstet Gynecol*, 1957, 9(2): 163–166.

51 Smith, G., 'The Subway grate scene in the seven year itch: "The staging of an appearance-as-disappearance" ', *Cinémas: Journal of Film Studies*, 2004, 14(2–3): 213–244.

52 Report, 'Council on pharmacy and medicine', *JAMA*, 1951, 145: 1267.

53 Bud, R., *Penicillin: Triumph and Tragedy*, Oxford, Oxford University Press, 2007, 105–107.

54 Smith, L. W. and Walker, A. D., *Penicillin Decade 1941–1951: Sensitizations and Toxicities*, Washington, Arundel Press, 1951.

55 Scales, I. K. et al, 'Oral fungus infection: Candidiasis albicans', *Oral Surg Oral Med Oral Pathol*, 1956, 9: 970–977.

56 Colgan, M. T., 'The bacterial flora of the intestinal tract: Changes in diarrheal disease and following antimicrobial therapy', *Journal of Pediatrics*, 1956, 49: 214–228; Editorial, 'Antibiotics and monilial infection', *Lancet*, ii, 532.

57 Hirst, H. L. et al, 'Methods of administration of penicillin', *J Lab Clin Med*, 1947, 32: 32.

58 Lane, S. L., ‘A review of current opinion on the hazards of indiscriminate antibiotic therapy in dental practice’, *Oral Surg Oral Med Oral Pathol*, 1956, 9: 952–961.

59 Hussar, A. E. and Holley, H. L., *Antibiotics and Antibiotic Therapy*, New York, Macmillan, 1954, 12–34. Also see: Binns, T. B., ‘Gastro-intestinal complications of oral antibiotics’, *Lancet*, 1956, i: 336–338.

60 Harris, H. J., ‘Aureomycin and chloramphenicol in Brucellosis: With special reference to side effects’, *JAMA*, 1950, 142: 161–165.

61 Woods, J. W. et al, ‘Monilial infections complicating the therapeutic use of antibiotics’, *JAMA*, 1951, 145: 207–211.

62 Joekes, T. H. and Simpson, R. H., ‘Bronchomoniliais’, *Lancet*, 1923, ii: 108–111; Anon, ‘An investigation into bronchomoniliais’, *Lancet*, 1924, i: 714.

63 Greer, A. E., ‘The synergism between mycotic and tuberculous infections of the lungs’, *Dis Chest*, 1948, 14: 33–40; Brown, T. G., Pulmonary mycosis, *Edin Med J*, 1947, 54: 414–422.

64 Oblath, R. W. et al, ‘Pulmonary moniliasis’, *Ann Intern Med*, 1951, 35: 97–116.

65 Editorial, ‘A danger of the newer antibiotics’, *BMJ*, 1951, i: 1196.

66 Editorial, ‘Fungus infection complicating antibiotic therapy’, *JAMA*, 1952, 149: 762–763.

67 Kligman, A. M., ‘Are fungus infections increasing as a result of antibiotic therapy’, *JAMA*, 1952, 149: 979–983.

68 Huppert, M. D. et al, ‘Pathogenesis of *C. albicans* infection following antibiotic therapy. I. The effect of antibiotics on the growth of *C. albicans*’, *J Bacteriol*, 1953, 65: 171–176.

69 Kligman, ‘Are fungus infections’, 979.

70 Ibid., 983; Editorial, ‘Antibiotic therapy and fungous infections’, *N Engl J Med*, 1952, 247, 491–492.

71 Jawetz, ‘Infectious diseases’, 6.

72 Finland, M. and Weinstein, L., ‘Complications induced by antimicrobial agents’, *N Engl J Med*, 1953, 248, 220–226.

73 Weinstein, L. et al, ‘Infections occurring during chemotherapy’, *N Engl J Med*, 1954, 251: 251–259.

74 Sharp, J. L., ‘The growth of *Candida* albicans during antibiotic therapy’, *Lancet*, 1954, i: 390–392.

75 Cannon, P. R., ‘The changing pathologic picture of infection since the introduction of chemotherapy and antibiotics’, *Bull N Y Acad Med*, 1955, 31: 89–91.

76 Kozinn, P. J. et al, ‘Candida albicans: Saprophyte or pathogen? A diagnostic guideline’, *JAMA*, 1966, 198(2): 170–172.

77 Baldwin, R. S., *The Fungus Fighters: Two Women Scientists and Their Discovery*, Ithaca, Cornell University Press, 1981.

78 Ibid., 75.

79 Hazen, E. L. and Brown, R., ‘Two antifungal agents produced by a soil actinomycete’, *Science*, 1950, 112: 423; idem, ‘Fungicidin, an antibiotic produced by a soil actinomycete’, *Exp Biol Med*, 1951, 76: 93–97.

80 Hazen, E. L. and Brown, R., ‘Nystatin’, *Ann N Y Acad Sci*, 1960, 27, 89: 258–266.

81 Waksman, S. et al, ‘Antifungal antibiotics’, *Bull World Hlth Org*, 1952, 6: 163–172.

82 Garrod, L. P., ‘The sensitivity of actinomyces to antibiotics’, *BMJ*, 1952, i: 263; Hussar and Holley, *Antibiotics*, 366–369.

83 Espinel-Ingroff, A. V., *Medical Mycology in the United States: A Historical Analysis (1894–1996)*, Dordrecht, Kluwer Academic Publishers, 2003, 86 and 94–96.

84 The powder was also used in laboratories as an antifungal agent, to suppress the contamination of sera, tissue cultures, culture plates, and other in vitro media. See: Report, ‘Mycostatin available for laboratories’, *Journal of the Franklin Institute*, 1956, 261: 285.

85 Brabander, J. O. W. et al, ‘Intestinal moniliasis in adults’, *Canad Med Assoc J*, 1957, 77: 478–483.

86 Shrand, H., ‘Thrush in the newborn’, *BMJ*, 1961, ii: 1530–1533, i: 186 and 567.

87 Sternberg, T. H. and Newcomer, V. D., *Therapy of Fungal Diseases: An International Symposium*, Boston, Little Brown & Company, 1956.

88 Ibid., ‘Contents’.

89 Sloane, M. B. ‘New antifungal antibiotic: Mycostatin (Nystatin) of the treatment of moniliasis: A preliminary report’, *J Invest Dermat*, 1955, 24: 569–571.

90 Chesney, J., ‘ “Nystatin” (“Mycostatin”)’, *BMJ*, 1956, i: 1043–1044.

91 Pace, H. and Schantz, S., ‘Nystatin (Mycostatin) in the treatment of monilial and nonmonilial vaginitis’, *JAMA*, 162, 1956: 268–271.

92 Lang, W. R. et al, ‘Nystatin vaginal tablets in the treatment of *Candida*l vulvovaginitis’, *Obstet Gynecol*, 1956, 8: 364–367.

93 Wright, E. T. et al, ‘Treatment of moniliasis with nystatin’, *JAMA*, 1957, 163: 92–94.

94 Barr, W., ‘Nystatin’, *Practitioner*, 1957, 178: 616–617.

95 Baldwin, *Fungus Fighters*, 99–101.

96 Loh, W. P. and Baker, E. E., ‘Fecal flora of man after oral administration of chlortetracycline or oxytetracycline’, *Arch Intern Med*, 1955, 95(1): 74–82; McGovern, J. J. et al, ‘The effect of aureomycin and chloramphenicol on the fungal and bacterial flora of children’, *N Engl J Med*, 1953, 248(10): 397–403.

97 Sharp, ‘The growth of *Candida*’, 392; Sakewitz, A. B., ‘Treatment of genitourinary moniliasis with orally administered nystatin’, *Ann Intern Med*, 1955, 42(6): 1187–1199.

98 Childs, A. J., ‘Effect of nystatin on growth of *C. albicans* during antibiotic therapy’, *BMJ*, 1956, i: 660–662; Gimble A. I. et al, ‘Nystatin and tetracycline in the treatment of bacterial infections’, *Antibiot Annu*, 1955–1956; 3: 676–680. Lederle introduced a version number the brand ‘Lederstatin’. Anon, ‘Gastrointestinal complications of treatment by broad spectrum antibiotics’, *Drugs and Therapeutic Bulletin*, 1964, 2: 69–71; Anon, ‘Old and new tetracyclines’, *Drugs and Therapeutic Bulletin*, 1967, 5: 77–80.

99 Another practice that reinforced the idea was antibiotic ‘sterilisation’ of the colon before surgery with the antibiotic neomycin and nystatin. See: Cohen, I. and Longacre, A. B., ‘Neomycin-Nystatin preoperative preparation of the colon’, *Am Surg*, 1956, 22: 301–307.

100 Report, ‘Fixed combinations of antimicrobial agents. national academy of sciences – national research council division of medical sciences drug efficacy study’, *N Engl J Med*, 1969, 280: 1149–1154.

101 McMahon, F. G., ‘Drug combinations: A critique of proposed new federal regulations’, *JAMA*, 1971, 216: 1008–1010.

102 Report, ‘Council on drugs’, *JAMA*, 1962, 182(1): 63–66.

103 Silverman, M., and Lee, P. R., *Pills, Profits and Politics*, Berkeley, University of California Press, 1974; Anon, ‘Ebert and Squibb’, *Harvard Crimson*, 6 December 1972. http://www.thecrimson.com/article/1972/12/6/ebert-and-squibb-pbwbhat-are-the/. Accessed 1 March 2013.

104 Butler, W. T., ‘Pharmacology, toxicity, and therapeutic usefulness of amphotericin B’, *JAMA*, 1966, 195: 371–375.

105 Oura, M. et al, ‘A new antifungal antibiotic, amphotericin B’, *Antibioc Annu*, 1955–1956, 3: 566–573; Dutcher, J. D., ‘The discovery and development of amphotericin B’, *Chest*, 1968, 54: 296–298. The soil came from the Orinoco Basin in Venezuela, which illustrates the breadth of the search for new antibiotic compounds.

106 Newcomer, V. D. et al, ‘Current status of amphotericin B. in the treatment of the systemic fungus infections’, *J Chron Dis*, 1959, 9: 354–374; Newcomer, V. D. et al, ‘The treatment of systemic fungus infections with amphotericin B’, *Ann N Y Acad Sci*, 1960, 89: 221–239.

107 Crounse, R. G. et al, ‘Cryptococcosis; case with unusual skin lesions and favorable response to amphotericin B. therapy’, *Arch Derm*, 1958, 77(2): 210–215; Derbes, B. and Krafchuk, J. D., ‘Response of North American blastomycosis to amphotericin’, *Bull Tulane Univ Med Fac*, 1958, 17(3): 157–163; Littman, B. et al, ‘Coccidioidomycosis and its treatment with amphotericin B’, *Am J Med*, 1958, 24(4): 568–592; Baum, B. and Schwarz, J., ‘Clinical experiences with amphotericin B’, *Antibiot Annu*, 1959–1960, 7: 638–643.

108 Hurley, R. and Morris, E. D., ‘The pathogenicity of Candida species in the human vagina’, *Br J Obstet Gynaecol*, 1964, 71(5): 692–695.

109 Hurley, R., ‘General discussion’, *Proc R Soc Med*, 1977, 70, Suppl 4: 30. On Hurley, see: Duerden, B., ‘Obituary, Dame Rosalinde Hurley’, *BMJ*, 2004, ii: 516.

110 Winner and Hurley, *Candida*, 139.

111 Hurley, ‘Candidal vaginitis’, 2.

112 Sobel, J. D. et al, ‘Clotrimazole treatment of recurrent and chronic Candida vulvovaginitis’, *Int J Gynecol Obstet*, 1989, 29(4): 386.

113 Elewski, B. et al, ‘Long-term outcome of patients with interdigital tinea pedis treated with terbinafine or clotrimazole’, *J Am Acad Dermatol*, 1995, 32(2–1): 290–292.

114 Winner, H. I. and Hurley, R., *Candida albicans*, London, Churchill 1964.

115 Duerden, B., ‘Obituary: Rosalinde Hurley’, *BMJ*, 2004, 329: 516. Also see: *J Obstet Gynaecol*, 2004, 24(7): 847. Howard Winner was Professor of Bacteriology at Charing Cross from 1965 to 1982. Wright, D. J. M., ‘Obituary: H. I. Winner’, *BMJ*, 1993, 306: 1335.

116 Winner and Hurley, *Candida*, 56–61.

117 Winner and Hurley, *Candida*, 59.

118 Hussar and Holley, *Antibiotics*, 367.

119 Winner and Hurley, *Candida*, 59–60.

120 Newcomer, V. D. et al, ‘Current status of Amphotericin B in the treatment of the systemic fungus infections’, *J Chron Dis*, 1959, 9: 353–374.

121 Winner, H. I. and Hurley, R., *A Symposium on Candida Infections*, Edinburgh, E. & S. Livingstone, 1966, 221–244.

122 Seelig, M. S., ‘The role of antibiotics in *Candida* infection’, *Amer J Med*, 1966, 40: 887–917; Downing, J. G. and Conant, N., ‘Mycotic infections’, *N Engl J Med*, 233, 153 and 181.

123 Cantor, D., ‘Cortisone and the politics of drama, 1949–1955’, in Pickstone, J. V., ed, *Medical Innovation in Historical Perspective*, Basingstoke, Macmillan, 1992, 225–245.

124 Wikler, A. et al, ‘Mycotic endocarditis: Report of a case’, *JAMA*, 119, 1942: 33; Caplan, H., ‘Monilia (*Candida*) endocarditis following treatment with antibiotics’, *Lancet*, 1955, ii: 95; Utz, J. P. and Roberts, W. C. ‘*Candida* endocarditis’, *Ann Intern Med*, 1961, 54: 1058.

125 Sanger, P. et al, ‘*Candida* infection as a complication of heart surgery: Review of the literature and report of two cases’, *JAMA*, 1962, 181: 108.

126 Birt, A. R., ‘The increasing problem of drug reactions’, *Can Med Assoc J*, 1957; 77: 709–715; Smith, T. J., ‘Antibiotic-induced disease’, in R. H. Moser, ed, *Diseases of Medical Progress*, Springfield, Ill, Charles C. Thomas, 1963.

127 Plummer, N. S., ‘*Candida* infection in the lung’, in Winner and Hurley, *Symposium*, 214.

128 Cohen, A. C., ‘Pulmonary moniliasis’, *Amer J Med Sci*, 1953, 226: 16–23; Seelig, ‘Role of antibiotics’, 903–906.

129 Cohen, A. C., ‘Pulmonary’, 23.

130 Winner and Hurley, 110–113.

131 Borel, J. F. et al, ‘The history of the discovery and development of cyclosporine (Sandimmun®)’ in Vincent, J. et al, eds, *The Search for Antiinflammatory Drugs*, Boston, O. Birkhauser 1995; Amor, K. T. et al, ‘The use of cyclosporine in dermatology: Part I’, *J Am Acad Dermatol*, 2010, 63: 925–946.

132 Gottlieb, H. S. et al, ‘Pneumocystitis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency’, *N Engl J Med*, 1981; 305: 1425–1431; Waterson, A., ‘Acquired immune deficiency syndrome’, *BMJ*, (Clin Res Ed) 1983; 286: 743–746; Seligmann, M. et al, ‘AIDS – An immunologic re-evaluation’, *N Engl J Med*, 1984; 311: 1286–129.

133 Klein, R. S. et al, ‘Oral candidiasis in high-risk patients as the initial manifestation of the acquired immunodeficiency syndrome’, *N Engl J Med*, 1984; 311: 354–358; Pranatharhti, H. and Molinari, J. A., ‘Oral candidiasis: Forerunner of acquired immunodeficiency syndrome (AIDS)?’ *Oral Surg Oral Med Oral Path*, 1985, 60: 532–534.

134 McCarthy, G. M., ‘Host factors associated with HIV-related oral candidiasis: A review’, *Oral Surg Oral Med Oral Path*, 1992, 73: 181–186.

135 ‘Fluconazole: A major advance for cryptococcal meningitis and other systemic fungal infections?’ *AIDS Treatment News*, 1987, 41.

136 Maertens, J. A., 'History of the development of azole derivatives', *Clin Microbiol Infect*, 2004, 10 Suppl 1: 3–4.

137 Troke, P. F., 'Efficacy of UK-49,858 (Fluconazole) against *Candida* albicans experimental infections in mice', *Antimicrob Agents Chemother*, 1985, 28(6): 815–818; Odds, F. C. et al, 'Antifungal effects of fluconazole (UK-49858), a new triazole antifungal, in vitro', *Antimicrob Agents Chemother*, 1986, 18: 473–478; Hay, R. J., 'Fluconazole', *J Infect*, 1990, 21: 1–6; Richardson, K. et al, 'Discovery of fluconazole, a novel antifungal agent', *Clin Infect Dis*, 1990, 12: S267–271.

138 de Wit, S. et al, 'Comparison of fluconazole and ketoconazole for oropharyngeal candidiasis in AIDS', *Lancet*, 1989, i: 746–748.

139 *Lancet*, 1989, i: 1130–1131.

140 Anon, 'Products in development: Progress continues in search for AIDS-related drugs', *Aids Patient Care*, August 1988, 2(4): 28–33; Williams, R. D., 'Living with AIDS: New treatments give hope', *FDA Consumer*, January-February 1992, 26; Lindemann, E., 'Importing AIDS drugs: Food and drug administration policy and its limitations', *George Washington Journal of International Law and Economics*, 1994, 28: 133–170.

141 British Society for Antimicrobial Chemotherapy Working Party, 'Antifungal chemotherapy in patients with acquired immunodeficiency syndrome', *Lancet* 1992: 648–651. Coleman, D. C. et al, 'Oral *Candida* in HIV infection and AIDS: New perspectives/new approaches', *Crit Rev Microbial*, 1993; 19: 61–82.

142 McNeill, M. et al, 'Mortality in the United States, 1980–1997, due to candidiasis, aspergillosis, and other mycoses in persons infected and persons not infected with HIV trends in mortality due to invasive mycotic diseases in the United States, 1980–1997', *Clin Infect Dis*, 2001, 33(5): 641–647.

143 Odds, *Candida*, 1988, 5.

144 Fisher-Hoch, S. P. and Hutwanger, L., 'Opportunistic candidiasis: an epidemic of the 1980s', *Infect Dis*, 1995, 21(4): 897–904.

145 Dismukes, W. E., 'Antifungal therapy: Lessons learned over the past 27 years', *Clin Infect Dis*, 2006, 42: 1289–1330.

146 Ibid., 1290.

147 Bennett, J. E. et al, 'A comparison of amphotericin B. alone and combined with flucytosine in the treatment of cryptococcal meningitis', *N Engl J Med*, 1979, 301(3): 126–131.

148 Dismukes, W. E. et al, 'Criteria for evaluation of therapeutic response to antifungal drugs', *Rev Infect Dis*, 1980, 2(4): 535–545; idem, 'Antifungal Therapy', passim. Flucocystine, had been developed as an anti-cancer compound in the 1950s, however, it proved ineffective and it was only in the 1960s that its antifungal properties were recognised. It was effective against cryptococcosis and candidiasis, but its value was limited by the development of resistance, hence combined usage, and toxicity, though it was less so than amphotericin B. J. E. Bennett, 'Flucocystine', *Ann Intern Med*, 1977, 86(3): 319–321.

149 Ayliffe, G. and English, M., *Hospital Infection: from Miasmas to MRSA*, Cambridge, Cambridge University Press, 2003.

150 Pfaller, M. A., 'Nosocomial fungal infections: Epidemiology of candidiasis', *Journal of Hospital Infection*, 1995, 30 (Suppl): 329–338.

151 Ibid., 330–333.

152 Odds, F. C., 'Epidemiological shifts in opportunistic and nosocomial *Candida* infections: mycological aspects', *Int J Antimicrob Agents*, 1996, 6: 141–144.

153 For a popular account of the 'yeast connection', see Barrett, S., 'Unproven "Allergies": An Epidemic of Nonsense "Environmental illness" and the "yeast connection" ', in Barrett S. and Jarvis, J. T., eds, *The Health Robbers; A Close Look at Quackery in America*, New York, Prometheus Press, 1993.

154 Odds, *Candida* (1988), 233.

155 Crook, W. G., *The Yeast Connection: A Medical Breakthrough*, Jackson, T., Professional Books, 1983; O. Truss, *The Missing Diagnosis*, Birmingham, The Missing Diagnosis, Inc., 1983.

156 Crook, W. G., *Answering Parent's Questions*, Jackson, Professional Books, 1963; idem, *Your Allergic Child: A Pediatrician's Guide to Normal Living for Allergic Adults and Children*, New York, Medcom Pres, 1973; idem, *Can Your Child Read? Is He Hyperactive?: A Pediatrician's Suggestions for Helping the Child with Hyperactivity, Behavior and Learning Problems*, Jackson, Tenn, Professional

Books 1975; idem, *Are You Allergic?: A Guide to Normal Living for Allergic Adults and Children*, Jackson, Tenn, Professional Press, 1977.

157 Truss, C. O., 'The role of Candida Albicans in human illness', *Orthomolecular Psychiatry*, 1981, 8: 228–238; Truss, C. O., 'Tissue injury induced by *C. albicans*: Mental and neurologic manifestations', *J Orthomol Psychiatr*, 1978, 1, 17–37.

158 Brief details of Truss's career are given at http://www.trussmd.com/about.html. Accessed 26 April 2012.

159 Goertzl, T. and Goertzl, B., *Linus Pauling: A Life in Science and Politics*, New York, HarperCollins, 1995; Hager, T., *Linus Pauling and the Chemistry of Life*, New York: Oxford University Press, 1998.

160 Pauling, L., 'Orthomolecular psychiatry: Varying the concentrations of substances normally present in the human body may control mental disease', *Science*, 1968, 160: 265–271; Pauling, L. et al, 'On the orthomolecular environment of the mind: orthomolecular theory', *Am J Psychiatry*, 1974, 131: 1251–1267. Orian Truss was born on 1 December 1922 and died in Birmingham, Alabama on 10 September 2009.

161 Task Force Report 7, *Megavitamin and Orthomolecular Therapy in Psychiatry*, Washington, DC, APA, 1973; Editorial, 'Molecules and mental health', *BMJ*, 1975, i: 296.

162 Williams, R. J. and Wright, D. K., *A Physician's Handbook on Orthomolecular Medicine*, New York Pergamon Press, 1977.

163 Hess, D. J., *Evaluating Alternative Cancer Therapies: A Guide to the Science and Politics of An Emerging Medical Field*, New Brunswick, NJ, Rutgers University Press, 1999; idem, *Can Bacteria Cause Cancer?: Alternative Medicine Confronts Big Science*, New York, New York University Press, 1997.

164 Truss, C. O., 'Tissue injury induced by *Candida albicans*: Mental and neurologic manifestations', *J Orthomol Psychiatr*, 1978, 7(1): 17: 37; idem, 'Restoration of immunologic competence to *C. albicans*', *J Orthomol Psychiatr*, 1980, 9: 287.

165 Ibid., 289.

166 Truss, C. O., 'Restoration of immunologic competence to Candida Albicans', *J Orthomol Psychiatr*, 1980, 9: 290.

167 Randolph, T. G., *Human Ecology and Susceptibility to the Chemical Environment*, Springfield, Ill: Thomas, 1962; Buscher, D., 'Obituary: Theron G. Randolph, MD, 1906–1995', *Journal of Nutritional & Environmental Medicine*, 1996, 6: 245–246.

168 Task Force on Clinical Ecology, 'Clinical ecology – a critical appraisal', *West J Med*, 1986, 144: 239–245.

169 Crook, W. G., 'Letters depression associated with *C. albicans* Infections', *JAMA*, 1984: 51: 2928–2929.

170 Crook, *Yeast Connection*, vi.

171 Crook summarises the meeting in Chapter 37 of *The Yeast Connection*.

172 Ibid., vi and Crook, W. G., 'The coming revolution in medicine', *Journal of the Tennessee Medical Association*, 1983, 76: 145–149.

173 Crook, *Yeast Connection*, viii.

174 Quinn, J. P. et al, Ketoconazole and the yeast connection, *JAMA*, 1986, 255, 3250.

175 Morgan, P. P., 'Should scientists study "20th-century disease"?', *Can Med Assoc J*, 1985, 133: 961–962; Zimmerman, B. and Weber, E., '*Candida* and "20th-century disease" ', Ibid., 1985 133: 965–966; Maclennan, J. G., '*Candida* and "20th-century disease" ', Ibid., 1986 134: 1112–1113; Lornzani, S., *Candida: A Twentieth Century Disease*, New Canaan, Conn, Keats Publishing, 1986; Murphy, M., *Sick Building Syndrome and the Problem of Uncertainty: Environmental Politics, Technoscience, and Women Workers*, Durham, NC, Duke University Press, 2006.

176 For a popular presentation see: Rovner, S., 'HEALTHTALK: The yeast theory',*Washington Post*, Mar 9, 1984: D5.

177 Haas, A. et al, 'The "Yeast Connection" meets chronic mucocutaneous candidiasis', *N Engl J Med*, 314: 854–855, 1986.

178 Coleman, III, W. P. and Edwards, D. E., 'Letters depression and *Candida* – Reply', *JAMA*, 1985, 253: 3400.

179 Anderson, J. A. et al, 'Position statement on candidiasis hypersensitivity', *J Allergy Clin Immunol*, 1986, 78: 271–273.

180 Edwards, J. E., 'Systemic symptoms from *Candida* in the gut: Real or imaginary?', *Bull N. Y. Acad Med*, 1988, 64(6): 544–549.

181 Ibid., 548.

182 Infectious Diseases and Immunization Committee of the Canadian Paediatric Society, 'Candidiasis: current misconceptions', *Can*

Med Assoc J, 1988, 139: 729; Blonz, E. R., 'Is there an epidemic of chronic candidiasis in our midst?', *JAMA*, 1986, 256: 3138–3139.

183 Aronowitz, R., 'From myalgic encephalitis to yuppie flu: a history of chronic fatigue syndromes', in Rosenberg, C. and Golden, J., eds, *Framing Disease: Studies in Cultural History*, New Brunswick, NJ: Rutgers University Press, 1992, 155–181; Jenkins, R. and Mowbray, J. F., eds, *Post-viral Fatigue Syndrome: (myalgic encephalomyelitis)*, Chichester: John Wiley & Sons, 1992.

184 Finlay, S., 'An illness doctors don't recognise', *Observer*, 1 June 1986, 43. Also see follow up article: Finlay, S., 'Voice for sufferers', *Observer*, 2 August 1987, 39; Chaitlow, L., *Candida Albicans: Could Yeast be Your Problem?*, Wellingborough, Thorsons, 1985.

185 Collings, J., 'The quiet epidemic that is ruining modern lifestyle', *Guardian*, 4 February 1988, 13.

186 Crook, *The Yeast Connection*, v–vi.

187 Mildenhall, R., '*Candida* views', *Observer*, 26 June 1988, 37.

188 Renfro, L. et al, 'Yeast Connection among 100 patients with chronic fatigue', *Amer J Med*, 1989, 86, 165–168.

189 Ibid., 168.

190 Dismukes, W. E. et al, 'A randomized double-blind trial of nystatin therapy for the candidiasis hypersensitivity syndrome', *N Engl J Med*, 1990, 323: 1717–1723.

191 Ibid., 1723.

192 Correspondence from Crooks, W., Truss, C. O. et al, W. J. Ledger et al, and M. Crandall, *N Engl J Med*, 1991, 324: 1592–1594.

193 Kay, A. B. and Lessor, M. H., *Allergy: Conventional and Alternative Concepts*, London, Royal College of Physicians of London, 1992.

194 Downing D. and Davies, S., ' "Allergy: Conventional and Alternative Concepts": A critique of the Royal College of Physicians of London's Report', *Journal of Nutritional Medicine*, 1992, 3: 331–349.

195 Kay, A. B., 'Alternative allergy and the general medical council', *BMJ*, 1993, i: 122–124, 328–331 and 582.

196 Mumby, K., 'Science or flat earthers? The clinical ecologist replies', *BMJ*, 1993, ii: 1055–1056.

197 Eisenberg, D. M. et al, 'Trends in alternative medicine use in the United States, 1990–1997:Results of a follow-up national survey', *JAMA*, 1998, 280: 1569–1575.

198 Hyams, K., 'Developing case definitions for symptom-based conditions: The problem of specificity', *Epidemiologic Reviews*, 1998, 20(2): 148–156.

199 Crook, W. G., *Nature's Own Candida Cure*, Alive Books, 2003; Crook, W. G. et al, *The Yeast Connection and Women's Health*, Square One, 2007; Crook, W. G., *Tired So Tired: and the Yeast Connection*, Square One, 2007.

200 Weig, M. et al, 'Clinical aspects and pathogenesis of *Candida* infection', *Trends in Microbiology*, 2012, 20(8): 468.

Tables

Table 3.1 Treatment of chronic candidiasis[166]

I.	**Non-immunologic measures that retard yeast proliferation**
A.	Passive: measures of avoidance
1.	Diet: low in carbohydrates and in foods with high yeast or meld content
2.	Antibiotics
3.	Contraceptive hormones
4.	Environments characterised by high meld-spore exposure
B.	Active: therapy with antifungal drugs: nystatin, amphotericin-B, flucytosine, ketoconazole
II.	**Measures to strengthen the immune response of the host**
A.	Passive (avoidance): immunosuppressant drugs
B.	Active
1.	Diet: adequate nutrients for proper immune response
2.	Correction of unrelated conditions that impair the immune response, for example, hypothyroidism
3.	Use of extracts of *C. albicans*
a.	Extracts
b.	Testing
c.	Treatment

Bookshelf ID: NBK169215