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Chapter 2 Athlete's Foot

A Disease of Fitness and Hygiene

In May 1939, a review of the American yearbook of dermatology and syphilology observed:

> As usual they make a prominent feature of an introductory article on some branch of therapeutics, and this year they deal with the treatment of the deeper fungous infections of the skin, including ringworm of the scalp and bearded regions, and the comparatively rare fungous affections of the subcutaneous tissues. As a matter of fact this subject is not of great practical importance in the British Isles, especially in England, where the incidence of ringworm of the scalp has been reduced to quite a trivial number of cases per annum, and ringworm of the beard has become an actual rarity. No doubt the state of affairs is otherwise in the United States, where the standard of living, both among the large negro population and also to a lesser extent among the more recent immigrants from Central Europe, is such that these infections are much commoner; moreover, a considerable area of the U.S.A. boasts a subtropical climate in which parasitic fungi are far more active than in the temperate zones.[1]

While this statement rightly reflects on improvements in Britain, its perception of ringworm in the United States was wrong. Across the Atlantic, it was not a problem amongst immigrants and African Americans; rather it had been framed as a public health menace in the affluent classes, especially amongst those who frequented swimming pools, and college students and, of course, athletes. While its prevalence had seemingly shifted up the social scale and from children to adults, its principal site of infection had moved too, from head to toe, with 'athlete's foot' being one of the most common and most talked about diseases in America in the 1930s.[2]

Manufacturers of popular remedies gave ringworm of the foot the name 'athlete's foot' and this was adopted by the public, but in medicine the infection was known as tinea pedis. It was seen as new disease, or in modern parlance an emerging infection, having been first described by Arthur Whitfield, a dermatologist at King's College Hospital, London in 1908.[3] Nonetheless, it was in the United States that tinea pedis became an epidemic, seemingly spread by modern lifestyles and hygiene practices, and encouraged by modern socks and shoes, which made infection liable to chronicity by keeping the feet moist and warm. It is perhaps surprising, given the unhygienic conditions of previous centuries and the ubiquity of ringworm of the scalp, that the feet of Europeans and Americans had been seemingly free of ringworm infection until the mid-twentieth century. Nonetheless, there was a clear understanding in the inter-war years that tinea pedis was new disease and one linked to modernity. One consequence of the growth of medical attention to tinea pedis was the stimulus it gave to the specialism of medical mycology, with investment in diagnostic services, research on the conditions in which mycoses spread and their treatment. In turn, this led to the creation of a cadre of medical mycologists, who identified more fungal infections in specific social groups and the general population.

We begin this chapter with a discussion of the development of medical mycology, especially in the United States, which led the world in the creation of centres of expertise, training and research. We then discuss the movement of medical and public concern about ringworm from children's heads to athlete's toes. In the 1940s, the condition was also recognised as a problem amongst soldiers and miners, and was seen in terms of greater exposure to new pathogenic species of fungi and the increased vulnerability of the human soil in tropical and specific work conditions. While orthodox medicine approached tinea pedis as something that was difficult to treat and needed to be prevented, proprietary medicine companies peddled remedies that filled the therapeutic vacuum with numerous 'certain cures'. We follow the controversies around popular and medical treatments, and the emergence in the late 1950s of medically approved, clinically trialled antifungal drugs, modelled on the antibiotics developed for bacterial infections. The most important of these was griseofulvin, which promised to be effective and safe with topical and oral administration. This was followed in the 1970s with a range of azole drugs. These antifungals accelerated the disappearance of athlete's foot as a medical, if not public term, thereby divorcing ringworm from its locus of infection or site of contagion, making it a type of dermatophytosis, literally, skin fungal infection.

Medical mycology: 'An Orphan Science'[4]

Glenn S. Bulmer has recently characterised the manner in which work on human fungal diseases developed in the inter-war period as the result of the movement and coalescence of specialists: 'botany types came forth and usually joined Departments of Microbiology &/or Immunology – two subjects that most had never taken in school'.[5] He may have had in mind the founders of the first specialist medical mycology laboratory in the United States, which opened in 1926 at the Columbia-Presbyterian Medical Center (C-PMC). One leading light was the botanist was Bernard O. Dodge, who then worked at the New York Botanical Gardens.[6] He was known for his work on genetics and for introducing T. H. Morgan to *Neurospora*, an organism that became a widely used experimental model in genetics.[7] Dodge was interested in fungal diseases in humans and animals, and between 1928 and 1939 he was a consultant in mycology at the C-PMC, while at the same time lecturing on dermatology at the College of Physicians and Surgeons. The other founder as a clinician, the dermatologist J. Gardner Hopkins, who worked at the C-PMC's Vanderbilt Clinic; previously he had worked on a cure for the plague with Hans Zinsser in Serbia during the First World War.[8] Indeed, his research spanned infectious diseases, especially syphilis and moniliasis. In the 1920s and 1930s it was mainly 'botany types', with the ability to identify types of fungi, who dominated the new field, which was principally concerned with diagnosis, requiring microscopy and culturing skills, combined with taxonomy. In 1926, Hopkins hired Rhoda W. Benham – a botanist by training – to undertake mycological diagnoses, and went on to develop a research laboratory from this base.[9] His initiative was aided by a grant of $50,000 from the Rockefeller Foundation in 1929, which eventually enabled Columbia to develop the first specialist training in human fungal diseases in 1935.

Hopkins's laboratory became an influential research centre, producing key figures such as Chester W. Emmons (1900–1985), the first medical mycologist employed by the National Institutes of Health (NIH) in Bethesda.[10] Emmons took his PhD with Robert A. Harper in the Botany Department at Columbia on the subject of mildew, before working with Dodge and publishing two articles on dermatophytes in *Archives of Dermatology and Syphilis*. Neither author was medically qualified. Emmons stated later that when he sought a reference to move to Hopkins's laboratory, Harper had asked, 'Why do you want to study those abortive and uninteresting medical fungi?'[11] Indeed, Emmons referred to medical mycology as 'an orphan science' as it was never taught by mycologists, whose main interest, outside of taxonomy, reproduction and other purely biological matters, was in plant pathology. In his first medical publications, Emmons proposed redefining the genera of the main fungal causes of skin infection: *Microsporum*, *Trichophyton* and *Epidermophyton*. His approach was to use their morphologies, rather than their pathological effects, pioneering what became the preferred method of standardising diagnoses and avoiding the variability and inconsistency of clinical criteria.[12] Emmons then worked with Arturo Carrión in Puerto Rica on chromoblastomycosis, publishing in the *Puerto Rico Journal of Public Health and Tropical Medicine*. In the event, the move to fungal diseases turned out well, as his appointment at NIH was as principal mycologist. He stayed for 30 years, becoming recognised as one of 'founding fathers' of medical mycology in the United States.

The first monograph in the field was Harry Jacobson's *Fungous Diseases: A Clinico-Mycology Text* published in 1932. The author was a dermatologist in Los Angeles and he presented ten chapters on 'dermomycoses, moniliasis, maduromycoses, sporotrichoses, blastomycoses, actinomycoses, coccidioides, toruloses and aspergilloses'.[13] A review in *Archives of Dermatology* concluded that the book was 'useful' and, perhaps surprisingly, observed that 'the mycologic aspects of the subject are better handled than the clinical aspects'. The second monograph was published from Harvard, where there had been instruction since 1924, and it was this course that was written up in 1935 by Carroll W. Dodge, a botanist who was no relation of Bernard O. Dodge.[14] The book was compiled at the suggestion of Roland Thaxter, who was medically trained, but had switched to botany, eventually becoming professor of cryptogamic botany at Harvard. Carroll Dodge's *Medical Mycology: Fungous Diseases of Man and Other Animals* was the first use of 'medical mycology' in a book title. Here, and in later works, the primary focus was on fungi and their identification, with little on the pathology of the infections they caused. Before publication, Dodge had moved to become professor of botany at Washington University and continued to research fungal diseases in Central America, before moving to Lichenology after 1950.

Writing the *New England Journal of Medicine* in August 1936, Jacob H. Swartz, of the Department of Cryptogamic Botany at Harvard University, maintained that,

> Mycology is no longer a mysterious subject known only to a few. It has been proved to be a part of medicine just as bacteriology, physiology and so forth. Some knowledge of mycology is necessary for a better understanding of disease.[15]

He was contributing to a discussion on fungi and internal medicine, where the focus was not on skin diseases, but on systemic infections and allergy, with an emphasis on the importance of predisposition – the human soil – as a factor with infection. Many contributors stressed the role of the laboratory in confirming clinical diagnoses; though Swartz worried that since the 'mystery' of fungi had been largely solved, clinicians were no longer turning to the laboratory and were relying solely on clinical signs. The 'orphan science' had been adopted by doctors, but it was not being nurtured. Swartz closed the discussion demanding the creation of a mycological department in every medical school and hospital, stating that 'Mycology at present is in chaos' and calling for the field to be 'simplified and made useful to all branches of medicine'.[16] Arthur Greenwood, a dermatologist at Massachusetts General Hospital, suggested the way forward was to create more people trained to work between clinicians and mycologists.[17] One factor fuelling the demand for more medical mycologists, reflected in the discussion prompted by Swartz, was recognition of geographically localised foci of fungal disease, which we examine in Chapter 4. Meanwhile, athlete's foot or tinea pedis was emerging as a dominate concern for dermatologists and nascent medical mycologists.

Athlete's foot

Infection in areas other than the scalp came to the fore in the First World War, when ringworm of the groin ('dhobi itch') was found to be prevalent amongst American and British troops in France.[18] Some doctors thought that damp and crowded conditions of the Western Front increased susceptibility and were ideal for contagion; others believed a new fungus had been brought to Europe and the Americas by troops returning from the tropics.[19] The bacteriological facilities available to the military medical services meant that specific pathogens were identified, using the methods developed by Sabouraud in the 1900s. Most cases were of *Trichophyton interdigitalis*, but there were increasing reports of *Trichophyton rubrum*, though at this time there was little interest in the epidemiology of types of infection.[20] Rather, discussion focused on the observation that, paradoxically, tinea pedis was a disease of hygiene. In the British military, the highest rates of infection were found amongst officers, who through bathing regularly opened themselves to infection through contact and softening of the skin. Also, tightly laced, anklehigh army boots, worn in hot, damp environments, for long periods without changes of socks, were understood to provide ideal conditions for tinea pedis to flourish.[21]

In the United States too, ringworm of the feet was 'discovered' as a malady of soldiers in the First World War. Two West Coast American doctors, Oliver Ormsby and James Mitchell, put ringworm of the feet on the medical map in the United States in 1916, in an article on infection of the hands and feet.[22] The alleged first use of the term 'athlete's foot' was in December 1928, in an article in the *Literary Digest*, prompted by reports from Dr Charles F. Pabst, of Greenpoint Hospital Brooklyn.[23] Pabst claimed that the condition was already well-known in the United States, with an estimated ten million sufferers, three quarters of whom were unaware of the infection. The article stated that the problem was of recent origin, but that 'at least half the adult population suffer from this malady at some time'. However, the term athlete's foot took hold, not as a disease of the masses, but one of the America's affluent classes, who could now afford to enjoy leisure activities and modern hygiene facilities. Pabst, perhaps revealing his limited social circle and awareness, claimed that 'almost everyone who uses a swimming-pool, golf club, athletic club, or any place where there is a common dressing room, has the infection on his feet'.[24] Further medical recognition came in May 1929, when three doctors, working at the University of California student health service, published data that showed tinea pedis was endemic amongst students.[25] They wrote that many students arrived at college with the infection: 53% of males and 15% of females, and the incidence rose to 85% in those final year students who took gymnasium classes. In a follow up study, the doctors showed at the end of their first year, the incidence amongst freshmen had risen from 53% to 78%, but was only 2% higher in female students.[26] The sex differences suggested to contemporaries four factors in the emergence of tinea pedis: the new male enthusiasm for using gymnasia, swimming baths and other sports facilities; the poor facilities for changing and showering at these locations; male indifference to personal hygiene; and the types of socks and shoes worn for sport and after, where the lighter, open shoes of women militated against infection taking hold. Athlete's foot was also possibly a consequence of public sanitary facilities, where the sexes, social classes, races and different ages mingled, and where anyone might be a 'carrier'.

Awareness of the problem grew quickly. The link between tinea pedis and athletes was evident in 1931 when the *Los Angeles Times* termed it the 'gymnasium malady'.[27] In the same year, W. L. Gould, a physician from Albany, New York State, reported to the United States Public Health Service that possibly 50% of all adults suffered from tinea pedis and that its incidence was particularly high in the states bordering the Gulf of Mexico and in California, due to heat and humidity.[28] At the 1932 Olympic Games in Los Angeles, special antiseptic footbaths were provided to

prevent infection.[29] By the mid-1930s there was recognition that it was not just students and athletes who were vulnerable. J. H. Swartz wrote of 'the addiction of our generation to the frequenting of gymnasiums (*sic*), baths and locker rooms … and the tendency to exercise violently and perspiring in unsterilizable socks and body clothing'. He went on to wonder if the Romans were similarly affected?[30] Dermatologists also saw tinea pedis as threat to the family, through cross-infection in the home, where baths and showers were becoming more common.[31] However, Ayu Majima has shown that ringworm amongst the poor – even tinea pedis – was never described with the neologism of athlete's foot and sufferers remained stigmatised.[32]

Doctors prescribed a variety of remedies for tinea pedis, but because of mixed results, their advice was mainly that prevention was better than cure. Thus, anyone visiting a swimming baths and showering in public facilities was told to disinfect their feet where possible, to avoid walking on floors in bare feet, to dry their feet and toes after bathing, never to share towels or clothing, and to wash socks at high temperatures. The main remedies were topical antifungal creams. The standbys were Whitfield's ointment (the active ingredients were 5% salicylic acid and 3% benzoic acid in petroleum jelly) and Castellani's carbol-fuchsin paint. However, the variable presentation of the condition and its tendency to chronicity encouraged innovations, both in combinations of remedies and new chemicals.[33] There were many complaints of overtreatment.[34] Proprietary medical companies, which already had a significance market with topical antiseptic remedies, seized on the new epidemic, producing new products and rebranding older ones as having antifungal as well as antibacterial properties.[35] The most prominently advertised remedy in newspapers and magazines was a derivative of a veterinary liniment – 'Absorbine Jr.', marketed by W. F. Young, Inc.[36] The company claimed to have coined the term athlete's foot and in the late 1930s, the advertisements for Absorbine Jr. echoed public posters against venereal disease and referred to earlier fears, from the time of Typhoid Mary, to unrecognised carriers (see Figure 2.1).

Older products for 'skin disorders of the feet', such as Dr Scholl's 'Solvex', were rebranded to target the new consumers, thus, its advertisement claimed it was effective against 'gym or athlete's foot', 'foot itch' and 'golfer's itch'.[37] While doctors promoted the possibilities of prevention and commercial drug companies sold 'sure-cure remedies', there was also a sense that the high prevalence of tinea pedis meant that it was an inevitable consequence of wearing socks and shoes; or, as it was later put, 'a penalty of civilization'.[38]

In Britain there was less medical and public awareness of tinea pedis and the term athlete's foot was not widely adopted until the late 1930s. Medical writings concentrated on diagnosis and treatment in individual patients rather than any social group. However, doctors noted that it was a disease with 'something of the nature of a social qualification, being commonly met among the upper and middle classes' and, being mostly spread through bathing; it was, then 'paradoxically … a penalty of cleanliness'.[39] This changed in the 1940s, when Britain found its equivalent of American athletes – coal miners. Tinea pedis was identified as the commonest cause of miner's dermatitis, a new condition resulting, again paradoxically, from the provision of pithead baths for communal bathing at the end of underground shifts. The Sankey Commission, which had reported on the future of the coal industry in 1919 had recommended measures to improve the health and welfare facilities for miners and the largest proportion of its expenditure (35%) went on pithead baths.[40] Baths were introduced only slowly and the prevalence of tinea pedis only gained a national profile during the Second World War, when absenteeism due to illness and injuries was a threat to production in a pivotal industry.

Soldiers and miners

Concern about the incidence of tinea pedis amongst military personnel had been expressed between the wars. A study for the United States Navy published as early as 1924, showed 13% of all ranks were affected, but levels were as high as 91% amongst officers recruited from college. The same scenario was reported in the late 1930s in the Royal Navy, with the condition being prevalent amongst all ranks in tropical stations. Surgeon-Commander J. C. Souter expressed the opinion that tinea pedis was a submerged problem, where itching and discomfort was tolerated by men, 'yet every sufferer is a potential casualty' should the condition worsen, as it might on active duty when changes of clothing were difficult, or in the tropics.[41]

During the Second World War, skin diseases were a major cause of invalidism due to poor skin hygiene in combat locations, communal washing facilities and exposure to new pathogens.[42] In tropical theatres there were reports that skin conditions were responsible for three quarters of sick bay attendances in the Pacific.[43] One response at home was that in 1943, the Walter Reed Army Medical Centre in Washington established a mycology laboratory headed by

Norman Conant who had started his career in Botany at Harvard, training with Raymond Sabouraud in Paris before taking a post in the Department of Microbiology at Duke University, specialising in mycology. He had worked on allergies and tinea, but gained international recognition in 1944 with the publication of a *Manual of Clinical Mycology*, co-authored with D. S. Martin, D. T. Smith, R. D. Baker and J. L. Callaway, all from Duke's Medical faculty. There were also problems at home amongst soldiers being exposed to geographically specific fungi at training bases in Western and Midwestern states, which we discuss in the Chapter 4.

However, the highest profile incident with tinea pedis during the war concerned a treatment on the home front. A mixture of phenol and camphor was very popular, but there were reports of overtreatment and high levels of exposure, leading to deaths.[44] The remedy was championed by Paul de Kruif in an article, entitled 'A Working Cure for Athlete's Foot' in *The Reader's Digest* in May 1942.[45] De Kruif is best known today for his book *Microbes Hunters* and for assisting Sinclair Lewis in the writing of *Arrowsmith*, but in the 1920s and 1930s he was a significant figure in American medicine.[46] He had worked for the Rockefeller Institute and become as publicist for medical science, serving as secretary to the President's Commission for Infantile Paralysis in 1934. However, by the 1940s he had become a controversial personality, mainly through publicising various medical innovations, of which his athlete's foot cure was seen as another questionable example.[47] Indeed, such was de Kruif's reputation that the FDA issued a public warning against the use of phenol camphor mixture later in 1942.[48]

Amongst British forces in South East Asia, the prevalence of all forms of ringworm was so serious that the Royal Army Medical Corps set up a research unit there on soldier's dermatitis. Surveys by unit staff revealed that amongst soldiers in Malaya and Hong Kong, 79.5% had tinea pedis and 33.5% had tinea corporis, tinea cruris or all three.[49] However, ringworm received most attention in Britain, not because of its military toll, but due to its incidence in workers at home, along with the investment in fungus research prompted by the discovery of the antibiotic properties of penicillin and emerging problem of systemic mycoses. In Britain, the Medical Research Council (MRC) appointed a Medical Mycology Committee in 1943.[50] One goal was to rationalise taxonomies and tinea pedis was a particular problem. At the time the following terms were used by doctors across the Empire: 'athlete's foot'; 'Hong Kong', 'Shanghai' and 'Singapore foot'; 'gym', 'golfers' and 'swimmers' itch; 'toe-rot'; 'ringworm of the feet'; 'Cantlie's foot tetter', 'eczematoid ringworm of the extremities'; 'dermatomycosis'; 'epidermomycosis'; and 'epidermophytosis'.[51] Perhaps this variety was further evidence of the novelty of the infection, or even the diversity of specific pathogens producing different types of lesion, but most likely it reflected the multiplicity of practitioners, locations and presentations.

The Committee's work during the war focused on coal miners. The first detailed study was made in 1943 by R. B. Knowles in the coalfields of the north Midlands and South Yorkshire. He confirmed the widely held view that the introduction of pithead baths in the 1920s and 1930s had created the problem.[52] After the nationalisation of the industry in 1946 and the creation of the National Coal Board (NCB), surveys and reporting on the welfare of miners increased.[53] One study of miners in Warwickshire in 1946 found that 52% of the men had 'intradigital disease', 15% had 'foot lesions other than fungus infection', and only 33% had 'healthy feet'.[54] It was against this background that in November 1951, a Committee on Industrial Epidermophytosis (CIE) was established within the MRC's Industrial Health Research Board (IHRB). The Committee's membership indicates how tinea pedis had become a multi-specialist problem. The CIE was chaired by John T. Ingram, a dermatologist from Leeds, who had considerable experience in the army and was joined by two other dermatologists, George H. Percival (Edinburgh) and H. Renwick Vickers (Sheffield).[55] Geoffrey C. Ainsworth provided mycological expertise, D. D. Reid from the London School of Hygiene and Tropical Medicine dealt with medical statistics, while R. E. Lane from the University of Manchester provided wider occupational health expertise.[56] Another member was Archibald L. Cochrane, who was then at the MRC's Pneumoconiosis Research Unit in Penarth, and later became a champion of randomised clinical trials, where his legacy has been institutionalised in the network of Cochrane collaborations.[57] Also on the Committee were T. E. Howell, the Principal Medical Inspector of Mines at the Ministry of Fuel and Power, and J. M. Rogan, Principal Medical Officer at NCB.[58]

The initial brief was quite wide, but Ingram argued that the CIE should 'deal in the first place especially with epidermophytosis of the feet in coal miners and to leave all side issues … until later'.[59] Rogan stressed the NCB's economic objectives of reducing absenteeism and other costs, wanting the CIE to focus on practical measures, such as prevention and methods for mass treatment.[60] However, Ingram had other ideas and fostered work across specialisms

in epidemiology, the natural history of the disease, clinical and mycological diagnosis, research on fungal growth, the chemistry of the skin and the histopathology of the condition.[61]

Finding out the nature and scale of the problem in miners was the priority. Epidemiological studies were commissioned from J. G. Holmes, a dermatologist in Cardiff, and Jimmy Gentles, a mycologist who, during his term of appointment, moved to the University of Glasgow. Early results came from a pilot that Rogan arranged for Holmes to conduct at a colliery in Allerton Bywater, near Leeds.[62] There were issues with compliance and Holmes complained that miners showed a 'lack of footconsciousness, thoughtlessness and in a few cases, selfishness'.[63] A larger study of 2,101 men working in mines across the country was published in 1956.[64] Clinical examinations found that 1,900 men (90%) had some abnormality of the skin of the foot, yet in only 438 cases (21%) was there laboratory-confirmed fungal infection. However, rates varied, from 50% in one East Midlands pit to 3.5% in the Yorkshire coalfield overall. The problems of reconciling clinical and laboratory diagnoses were shown by the fact that 75 patients 'showed so-called "diagnostic" lesions without any evidence of fungus being found', while 4% of those with 'clinically normal feet' tested positive in the laboratory.[65]

The Medical Mycology Committee's post-war survey on the incidence of mycoses in Britain, published in 1948, confirmed a view widely held within the medical profession, that the incidence of tinea capitis, the new term for ringworm of the scalp, in children had risen during the war. The rise was attributed to the suspension of X-ray treatment, the relaxation in school hygiene, and to the evacuation of children, with a consequent decline in hygiene and greater exposure to cats, dogs and cattle.[66] An increase in tinea pedis in adults was explained by continuing improvements in hygiene, the exposure of men to infection in military settings, and the circulation of ringworm species around the world with troop movements.[67] A particular concern was the importation of *T. rubrum* to Europe from the Far East, as it was one of the most difficult ringworm species to treat. However, the reported incidence of tinea pedis in Britain was nowhere near that in the United States. In 1950, Jacqueline Walker reported on a survey of 1,010 army recruits, 857 of whom were free of infection and of the 123 suspected cases, only 39 (4%) were confirmed in the laboratory.[68] One reason for the low incidence was the relative paucity of sports and college facilities, and there were certainly fewer homes with bathrooms where infection could spread within families. The place where the spread of tinea pedis was most common was in elite public schools, which had the best sports facilities.[69]

One problem in surveys was the discrepancy between clinical and laboratory diagnoses. Doctors accepted that microscopy and culturing were more reliable than clinical methods; however, there were few laboratories available to provide the tests and a reluctance amongst dermatologists to use them.[70] For some, the reliability of laboratory results was a moot point. They depended on many factors: from the quality of the skin sample taken, through to the competence of staff in particular laboratories. Accuracy mattered more in epidemiological studies than it did in clinical practice. False positives in a low incidence population would skew the result significantly, whereas dermatologists and general practitioners were prescribing broad spectrum, topical fungicides for all presentations of 'inter-digital dermatitis' without laboratory confirmation. Better-targeted treatment would have prevented what one doctor later termed 'a chemical assault' on the feet of the nation in the post-war era.[71]

The uncertainties over diagnosis, especially when fungi were found without clinical disease in 'symptomless carriers', reopened the question: were the fungi causing tinea pedis external contagious agents caught from other people, or were they saprophytic parasites of the skin that only caused disease in certain conditions?[72] While patterns of infection in particular groups and the identification of infective fungi on floors in baths and showers pointed to the overriding importance of contagion, some doctors argued that infection was more complicated. The seed and soil analogy was used to suggest both that prior physico-chemical changes had to make the skin open to infection, as in pre-pubescent children, or that a 'factor X' was involved.[73] Such views were important because doctors were only too aware of the limitations of topical remedies and, hence, were keen to promote specific and general preventative measures.

Chemical abuse of the nation's feet

In the late 1940s, the American market was flooded with topical treatments for athlete's foot. Writing in *JAMA* in 1946, G. B. Underwood and colleagues wrote on the 'unbelievable chemical abuse' of the feet of Americans.[74] In their practice they reported:

> Feet are seen daily, painted all the colors of the rainbow or daubed so thick with salves that removal with a tongue blade is necessary to view the underlying dermatitis. The shoes smell of solution of formaldehyde and are caked on the inside with fungicidal powders. The patients, when questioned about the number of remedies used, shrug their shoulders and exclaim 'I couldn't begin to recall. I've used everything. You are the sixth or seventh doctor I have seen. I've had this stuff between my toes for years. Just when I think it is well, it's back again. Each time it comes back I try something else. I've spent a small fortune for remedies, and look at my poor feet.' These patients are sure of the cause of their dermatitis. It is the 'athlete's foot' or the 'fungus.'[75]

They reproduced examples of the ways that companies selling topical remedies portrayed athlete's foot as dire threats to individual and public health. Potions were said to 'Kill Athlete's Foot Germs on Contact', to cure 'Factory Feet' and warned 'YOU PROBABLY HAVE ATHLETE'S FOOT or will get it'. Brands had names like 'Soretone', 'Korium', 'Octofen' and 'Desitin'. Some remedies were cure-alls, such as '$3X^{B}$ ', which also helped with 'minor wounds, blisters resulting from ivy poisoning, or similar conditions, corns, calluses, tired feet, chafing, prickly heat or similar skin conditions'. Underwood and his colleagues reported analyses of 106 popular remedies, finding the most common ingredients were phenol, ethyl aminobenzoate and, most worryingly, mercurial compounds. The Mennem Company's leading brand 'Quinsana', whose advertising regularly featured the threat of catching athlete's foot on the beach, contained Hydroxy-Quinolene, Magnesium stearate and boric acid. Underwood and his colleagues ended with a plea to dermatologists to 'take steps to prevent the commercial commandeering of scientific reports and formulas', and called for the regulation of popular skin treatments.

Whether the rash of new products was due to a real increase in the incidence of fungal skin infections is unclear, but the post-war increase in tinea capitis in American schools suggests that there was more ringworm in communities.[76] Infected children were treated with X-rays, as well as topical remedies and there were calls for public health agencies to take up the matter.[77] Laboratory reports showed that the main cause was no longer *Microsporon canis* caught from pet and farm animals, but *Microsporon audouini*, the main European ringworm species.[78] State and county authorities started campaigns, which were claimed to be effective. The reported incidence of tinea capitis fell in the 1950s, even though X-rays, the former treatment of choice, was dropped because of concern about the long term health effects of exposure to radiation.[79]

The most notorious example of the enthusiasm for developing and trialling treatments for athlete's foot were the investigations on prisoners undertaken by Arthur Kligman in Pennsylvania and discussed in Arthur M. Hornblum's book *Acres of Skin*.[80] Kligman worked in the Department of Dermatology at the University of Pennsylvania Medical School, then headed by David Pillsbury. Prior to his work with prisoners, Kligman had made experimental studies of children in mental defective homes to test the effects of X-rays used to treat tinea capitis.[81] He wrote in 1952 that,

> The work was carried out at a state institution for congenital mental defectives … The experimental circumstances were ideal in that a large number of individuals living under confined circumstances could be inoculated at will and the course of the disease minutely studied from its very onset. Biopsy material was freely available. By contrast, Sabouraud's researches were largely limited to the clinical opportunities presented by ringworm patients appearing at the Paris clinic.[82]

This work was part of wider studies of treatments for ringworm, especially the new topical creams versus depilation, either mechanically or by X-rays.[83]

In 1957, Kligman published an article with John Strauss that opened with the following statement.

> So much has been written about the subject of athlete's foot that one can hardly add still another paper to an already mountainous pile without some justification. We thought we could gain some fresh appreciation of this disease by studying it experimentally in a prison population. With this group it was possible to do a number of things which would otherwise have been rather difficult. Rigid control over the subjects, adult males in the age range of 20–50 years, offered many experimental advantages.[84]

Kligman's research at the prison, which ran from 1951 to 1974, grew from initial studies of athlete's foot treatments, to medications for a wide range of other skin conditions and cosmetics. He worked closely with pharmaceutical companies and prisoners were paid to be human guinea pigs. Kligman became infamous because of the ethical status

of his trials, however, in American dermatology he remained a hero, with his death marked by an article with the by-line 'Albert the Magnificent' and no mention of the criticisms of his work.[85] Controversy was fed by the fact that Kligman was unapologetic; he considered retrospective judgements of the ethics of his work unfair and that he defended it, arguing that medicine had benefited and 'no prisoner suffered long-term harm, as far as he knew'.[86] Nonetheless, the furore caused by criticisms of his work in the 1970s, including the development of the anti-wrinkle cream Retin- A, prompted stricter Federal regulations on medical experiments with prisoners and human subjects more widely.[87]

In both the United States and Britain, the reported prevalence of tinea capitis waxed and waned in the 1960s. One clear trend in the United States was the growing importance of infection with *T. tonsurans*, seemingly imported from Central America and the Caribbean, with *M. audouinii* seemingly in decline across the northern hemisphere.[88] Some dermatologists speculated that the fall in incidence in the late 1960s was due to the fashion for long hair in both men and women, and for 'Afros' amongst African-Americans, both being protective against hair root infection.[89]

Griseofulvin: 'Epoch making' antifungal treatment

From the early 1940s, state and pharmaceutical company laboratories sought novel approaches to fungal infections following the model of antibiotics with bacteria; that is, chemicals that could be injected or taken orally, that would act as 'magic bullets', affecting the pathogenic microorganism and not the host's cells. There had been hopes in the early 1940s that penicillin, or similar fungally derived products, would be antagonist to pathogenic fungi, but these were unfulfilled. Nonetheless, the treatment of fungal infections did benefit from the increase in the scale and intensity of biomedical and pharmaceutical research.[90] Nystatin, which we discuss in Chapter 3, introduced in the early 1950s, was the only success in the search for antifungal antibiotics for a decade; but it was ineffective against ringworm and could not be taken orally. Researchers turned to other approaches. One was to build upon the observation that vulnerability to tinea capitis seemed to end at puberty, which pointed to changes to the chemistry of hair follicles and the identification of heavy fatty acids that seemed to have antifungal properties. The most important was undecylenic acid and its salts.[91] The effectiveness of this fatty acid was similar to compounds already in use, but it had the advantage, allegedly, of being less irritant because it was 'natural'. In Britain, the following proprietary preparations that were widely used from the late 1940s, all contained zinc undecylenate: 'Tineax' from Burroughs Wellcome and Co.; 'Mycota' from Boots and 'Desenex' from Wallace and Tierman. The salts of two other fatty acids, proprionic and caprylic, were also used in the same way. The market leader in Britain was 'Mycil', produced by British Drug Houses (BDH). Its active substance was *p*-chlorophenyl-*a*-glycerol ether, marketed as 'chlorphenesin' and discovered in 1947 by Frank Hartley, then Research Director at BDH, in 1947.[92] In the United States, 'Desenex' ointment and foot powder, produced by Wallace and Tiernan, led the way, and were used in the Korean War and later enjoyed endorsement from celebrities from the National Football League, such as Johnny Unitas.

An editorial in the *Lancet* in July 1946 had wryly observed that most doctors 'take a personal interest in tinea pedis, for – like piles, toothache, and sore throats – if we manage to escape it ourselves, it will not be long before some member of our family is clamouring for attention'.[93] The editorial bemoaned the fact that, despite the flood of new remedies, most treatments had limited effectiveness, particularly in the longer term. Over a decade later, reviewing treatments for general practitioners in May 1958, Grant Peterkin, head of the Skin Department at the Edinburgh Royal Infirmary, reflected that old favourites, such as Whitfield's ointment and Lassar's paste, were still second to none.[94] He noted the recent impact of nystatin on the treatment of *Candida* infections, both in topical applications and when taken orally for intestinal infection, and regretted that there had been no similar advance with tinea pedis. However, he was hopeful: 'Yet it seems possible that in the future fungus infections of the skin may be eradicated by some antibiotic given parenterally [orally].'[95] By the end of the year his hope had been fulfilled with the announcement of the oral antifungal drug – griseofulvin.[96]

Griseofulvin had been first isolated from the fungus *Penicillium griseofulvum* by Harold Raistrick at the London School of Hygiene and Tropical Medicine (LSHTM) in 1939.[97] Raistrick was Britain's leading figure in the biochemistry of fungi, having worked on industrial fermentation for the government in the First World War and then for Imperial Chemical Industries (ICI), before his appointment to the LSHTM in 1929. He had worked on penicillin in the early 1930s, following up Alexander Fleming's early publications, and his laboratory had continued to use *Penicillium* spp. as experimental models.[98] Surprisingly perhaps, griseofulvin was not screened for antibiotic properties in the early 1940s and its antifungal potential was only recognised at the end of the decade, and then in an agricultural rather than medical context.

Researchers at the Butterwick Research Laboratories of ICI found that it produced 'curling' in the hyphae of certain fungal species, inhibiting cell wall formation and cell division.[99] Further work showed it to be an effective, broad spectrum fungicide, though it had no great advantage over existing and cheaper commercial compounds. Mycologists remained interested in the compound, as did researchers at Glaxo's Sefton Park and ICI's Alderley Park Laboratories. Parallel, but separate, investigations showed that griseofulvin had a low toxicity when high doses were given to experimental animals. It also proved to be valuable as a laboratory agent for inhibiting the growth of hyphae-forming fungi, even at quite low concentrations.[100] However, its potential as an oral antifungal seemed limited because it was largely insoluble in water and, hence, could not be made available for absorption through the gut.[101]

Griseofulvin's promise as a fungicide in agriculture led Glaxo researchers to test its toxicity to humans to determine safe exposures for farm workers.[102] These trials showed few, if any, toxic effects. However, commercial development was not fast-tracked because griseofulvin was expensive to produce. In the mid-1950s, Glaxo researchers learnt that two other groups were interested in griseofulvin: Gentles through his work for the NCB, and workers at ICI who were exploring veterinary and human uses. Both Glaxo and ICI had taken out provisional patents on different aspects of the production and use of griseofulvin, and in an unusual move, signed a joint agreement in the spring of 1957 on their respective rights in all areas, from patents through to licensing. Glaxo continued to work with Gentles on animal studies, which led to a publication in *Nature* in August 1958.[103] However, work at ICI showed that griseofulvin could affect mammalian cell division and this prompted further collaboration between researchers in both companies.[104] In comparing data, it seemed that the different results were due to the particle size and that the coarser Glaxo compound was safer. Three dermatologists approached Glaxo for samples to test in patients with ringworm: Gustav Riehl in Vienna, Harvey Blank in Miami and David Williams at King's College London. The first results from these clinics were presented in late 1958.[105]

David Williams and colleagues published a report of nine patients with *T. rubrum* infection who had been successfully treated with orally administered griseofulvin, supplied by Glaxo.[106] There was great excitement about the work. Williams concluded his article with the claim that griseofulvin 'represents a fundamentally new therapeutic approach'.[107] One Cambridge dermatologist, hearing of the development, had written to the MRC claiming that the work was 'epoch making'.[108] The London trial had followed on from a report in August 1958, by Gentles, of successful oral treatment of ringworm in experimentally infected guinea pigs.[109] Gentles had rushed to publish and was similarly excited; though he went for understatement, ending with the remark that this work 'may be of some important for future progress in this hitherto unrewarding field of investigation'.[110]

Gentles and Williams spoke on griseofulvin at the annual meeting of the British Dermatological Society in July 1959.[111] Gentles reviewed the clinical literature and the growing consensus that it was effective for two reasons: first, through its deposition in keratin (the structural protein of hair and nails), and second in being fungistatic, that is, inhibiting the growth of the fungus. This meant that it was likely to be effective in deep-rooted infections of the hair follicles and in toenails. David Williams began his talk by reflecting on the reputation of dermatology within the medical profession and how this might have to change.

> Once upon a time – and thus all good stories begin – there was an old retired general practitioner who said that he could treat all skin diseases although he could diagnose none. Those were the slap happy days when local treatment was a magnificent pseudo-science – not even now do we have much understanding of how local applications work – and internal treatment was a desperate matter of letting justice seem to be done, not too critically … . But in the last fifteen years there have been remarkable advances in the chemical and antibiotic field. Treatment is becoming so specific that there is much to be said for a proper diagnosis before starting it. Penicillin has made syphilis so rare that it is easy to forget its existence. Anti-tuberculous drugs have ruined for us a fascinating, a lovely group of dermatological conditions. And now griseofulvin.[112]

Williams stated that in his clinic the 'experience so far has been so gratifying that it is difficult to be restrained about what seems to be happening'. He gave the drug a ringing endorsement, stating 'griseofulvin is a remarkable drug with minimal toxic effects and that it has come to stay, we have no doubt'.[113] Questions remained about dosage, resistance, re-infection and toxicity, yet in a call-to-arms, he concluded, 'As Montgomery must have said, the break-through has been achieved and our forces can now pour through the gap to consolidate our gains.'[114]

Harvey Blank, who worked at the University of Miami School of Medicine, had also been prompted by Gentles's article to obtain griseofulvin from Glaxo.[115] He first tried it on 'a desperate and unique case' of *T. rubrum* infection, with some success, before a more organised trial on 31 patients with various forms of ringworm. The results were 'uniformly favorable', though he cautioned that toxicity still needed to be tested with prolonged use, and that it was too early to say anything about the likelihood of relapses. Nonetheless, the drug was cleared for use in the United States in July 1959, less than a year after Gentles's paper had been published.[116] Blank organised a symposium on griseofulvin in Miami in October 1959, funded by McNeil Laboratories, a subsidiary of Johnson and Johnson, at which 37 papers were given by speakers from 11 countries, including Gentles and Williams. The rapid spread and trialling of the drug indicates the intense medical interest, across so many countries, that there was in finding oral antifungal drugs. Introducing the proceedings in *Archives of Dermatology* in May 1960, Blank reflected that the development of griseofulvin 'appears to be assuming the proportions of an historical nature'.[117] A key factor in the enthusiastic response in the United States was to explore the potential of the drug to treat persistent infection, such as fungal nail infection – onychomycosis.[118]

The St John's Hospital Dermatological Society organised a British meeting on griseofulvin in May 1960, attended by 189 doctors and scientists, with 24 papers published in a special issue of the Society's *Transactions*.[119] It was already clear that the drug was being widely used in general practice, as well as in dermatological clinics, and this despite the fact that it was expensive.[120] The introduction to the volume drew parallels between the ten-year lag in recognising the therapeutic potential of penicillin, with the 20 years taken from Raistrick's isolation of griseofulvin to its first clinical use.[121] The meeting heard a report of the first controlled clinical trial, led by Brian Russell at St John's Hospital, which was about to be published in the *Lancet*.[122] The trial showed griseofulvin was 'a striking effective remedy' and that 'In retrospect, it is questionable whether a double-blind trial was necessary.' There were 64 patients in the study: just one person of the 31 receiving the drug showed no clinical improvement, whereas 30 out 34 patients given the placebo were 'unimproved'. However, the study showed that the drug was no cure-all. There was considerable variation in the responses of individuals and even the toes of the same person! In addition, when laboratory rather than clinical assessments of cures were used, things were less positive still. Thus, after many weeks and months of treatment, over half of patients continued to harbour the fungus in the skin between their toes, and 26 of 32 patients had some abnormality in their nails. The redeeming feature was that no side-effects were reported; hence, the very long-term treatments that seemed to be necessary were felt to be safe.

Summing up at the St John's Symposium, Brian Russell stated that griseofulvin should be the treatment of choice for all forms of tinea capitis, except that due to *M. canis*, and, disappointingly, tinea pedis due to *T. rubrum*.[123] The drug was also recommended for other types of ringworm and favus, but was said to be only moderately effective against animal ringworm species. Interestingly, its value was 'doubtful or occasional' against the species that had been the main cause tinea pedis in earlier decades: *T. interdigitale*, *T. mentagophytes* and *E. floccosum*. Russell emphasised again that griseofulvin was fungistatic and not fungicidal, hence, 'clinical clearance is not synonymous with cure', while 'mycological clearance', if it could be achieved at all, took much longer. He also pointed to issues with re-infection, carriers, immunological effects, and its impact on the ecology of the body, responding to some reports that griseofulvin opened the body to *Candida* infections.

Griseofulvin became available as a prescription drug in Britain in April 1959; marketed as 'Grisovin' by Glaxo and 'Fulcin' by ICI.[124] There was no expectation within Glaxo that griseofulvin would be another penicillin in terms of sales and profit. Hector Walker, the head of research and development, observed, 'Dermatologists – at least some of them – seem a little bit disturbed that a specific treatment is now available that represents a not unsizeable part of their total practice, and there are reactionary dermatologists just as there are physicians when new treatments appear.'[125] The expectation was that topical treatments for ringworm would continue to be preferred, with griseofulvin used for persistent infection and onychomycosis. Soon, even these qualified hopes were being moderated. An editorial in *Lancet* mocked the recent meetings on the drug.

> Massed choirs met at international symposia in Miami last October and in London under the wing of the St. John's Hospital Dermatological Society on May 13 and 14 to add their paeans of praise. They sang, for doctors, in surprisingly close harmony. The main theme has been the remarkable success of griseofulvin, with pitch according to skill and experience. More recent variations have wandered a little into the more pensive, minor keys as certain problems and failures have become evident.[126]

Two years later, there was another sceptical editorial, this time responding to an epidemiological study of tinea pedis by Mary English that showed that only a small proportion of lesions of the toe-webs were fungal in origin and that there very few healthy carriers.[127]

> Griseofulvin has not lived up to expectations, and often does not eliminate fungus from the feet. In acute cases, topical fungicides often do more harm than good … For chronic cases, Whitfield's ointment is still the most usual remedy, and some difficult cases are kept symptom free by wearing sandals.[128]

However, Glaxo had been working on the drug with its American licensees and in 1962 developed fine particle form – GRISOVIN FP – for clinical trials. This was better absorbed through the gut, giving more even blood levels of the drug, even at half of the previously recommended dose. Nonetheless, results were still mixed and worries about toxicity remained.[129]

Despite the problems, in the 1960s griseofulvin became a standard treatment for susceptible forms of ringworm and joined nystatin in the new armoury of antifungal antibiotics.[130] Research on this class of drugs burgeoned in the decade, as mycological researchers in universities, government laboratories and pharmaceutical companies joined the search for natural and synthesised compounds with similar properties.[131] In the wake of the thalidomide scandal and the introduction of stricter safety regulations, much of the further work on griseofulvin was on its toxicity.[132] However, while many side effects were identified, they were all either relatively minor (headaches, gastrointestinal, photosensitivity, liver function, allergic reaction), or cleared up after treatment ended. Griseofulvin was given prophylactically to American troops in Vietnam, though this did not stop ringworm being a major cause of disability.[133] Only reduced exposure, in shorter combat rotations, affected the overall incidence of ringworm and relapses were blamed on poor compliance in prolonged treatment.[134]

Griseofulvin, as a treatment for most forms of ringworm, united athlete's foot with other sites of infection, such that tinea pedis became distanced from hygiene and fitness. This shift exemplified a trend in medicine from the late nineteenth century of moving definitions of infections based on symptoms to specific causes. Ringworm was not unified by a specific cause, because there were many fungal pathogens, but rather by a treatment – griseofulvin. The drug was a major contributor to athlete's foot and other forms of ringworm, becoming defined as types of 'dermatophytosis', a term which grew in popularity from the 1960s. It was in fact a quite general, hybrid causal-symptomatic definition, literally, skin infection with fungi.

Azoles: 'A major advance in medical mycology'[135]

The success of griseofulvin, more than the earlier nystatin for candidiasis, changed the prospects of antifungal therapy and further new drugs were anticipated.[136] In the event, a widely adopted, oral antifungal alternative to griseofulvin for dermatophytosis did not emerge for nearly 20 years, until in 1977 the Belgian company Janssen announced ketoconazole.[137] Branded as 'Nizoral', it was one of the group of synthetic compounds called 'imidazoles', or more generally 'azoles', that the company had been screening since the late 1960s. The first two widely used drugs from this work were announced in 1969: clotrimazole from Bayer and miconazole, also from Bayer, which were targeted at *Candida* infection and deep seated systemic mycoses. Ketoconazole was different. It was promoted as a broad spectrum antifungal that could be used to treat dermatophytosis as well as candidiasis, histoplasmosis and cryptococcosis.[138]

Following the precedent of griseofulvin, Janssen sponsored a meeting to review progress and spread the word. The first international symposium on ketoconazole was held in Medellin in Columbia in November 1979, linked to the Ninth Ibero-Latin American Dermatology Congress.[139] The participants concluded that they were at 'the threshold of an important new advance' and that ketoconazole was the orally administered drug that was effective for a range of conditions, from acute systemic mycosis through to the growing problem of onychomycosis, that clinicians had been looking for.[140] The drug had been developed by researchers at Janssen Laboratories from the modification of miconazole, which they made less toxic and more suitable for oral administration.[141] The new drug was effective against many of the regionally specific fungal infections discussed in the next chapter and with immunocompromised patients. The concluding address was given by William Dismukes, who worked at the University of Alabama School of Medicine in Birmingham and was a founding member of the newly formed, NIH funded, Mycoses Study Group.

He hoped that ketoconazole would be 'the first "total" antifungal agent with a broad spectrum of activity' and that very promising results *in vitro* and early clinical trials now needed to followed by longer term studies.[142]

The question with ringworm was this, was ketoconazole more effective than griseofulvin? Two reports by clinicians were presented at Medellin, one from Oregon in the United States and other Mexico. The group from Oregon reflected that,

> During more than 20 years of clinical experience with griseofulvin, the subject of failure of therapy has received scant notice. Only rarely do patients fail to respond to this drug because of either resistance of the organism or inadequate tissue levels of griseofulvin. Much more commonly, dermatophytoses respond to the drug but then either fail to clear or recur soon after discontinuance of therapy.[143]

The conclusion of the Oregon study was that ketoconazole was effective in cases that did not respond to griseofulvin, but whether it should be the first choice was left open. The second report was similarly positive. Ketoconazole was approved for clinical use and became available in 1982. The results of comparative trials with griseofulvin were published in 1985, which found they were equally effective for hair, skin and nail infection.[144] On balance, griseofulvin remained the first choice therapy because of concerns about liver toxicity of ketoconazole, which was recommended for patients who were griseofulvin-intolerant.[145] In the 1990s, two new, broad spectrum remedies that could be used topically and given orally became available for ringworm: itraconazole, another triazole developed by Janssen and marketed as Sporanox; and terbinafine developed by Novartis and marketed as Lamisil. Thus, the options available to doctors for treatment at all sites, and with all types of infection increased. However, there was some evidence of the development of drug resistance and tinea pedis increasingly presented along with the more difficult to treat, onychomycosis. Many of the azole compounds, when patent protection lapsed, became available for topical use in over-the-counter creams, competing with every other post-war antifungal back to nystatin. The development of azole drugs consolidated the remaking of athlete's foot as another type of dermatophytosis.

In this chapter, we have charted the rise and fall of athlete's foot as a disease of fitness and hygiene. It is not clear if the reported rise in incidence in the 1920s was due to the greater awareness, or presence of new pathogens in Western populations, or new conditions for ringworm fungi to spread and flourish. At the time, the majority of doctors maintained the latter and, specifically, that ringworm of the feet was a 'penalty of civilisation'. In all contexts, medical and public concern was linked to new lifestyles, new clothing, new military conditions or new working environments, the latter especially so in Britain, where coal miners rather than athletes put the condition on the map. While medical advice initially stressed prevention over treatment, proprietary medicine manufacturers turned the full weight of product development and promotion on the condition, typically selling their wares as products of medical progress. Athlete's foot was also at the forefront of the antibiotic revolution with fungal infections, through the development of griseofulvin, coincidentally a compound derived from a species of the *Penicillia*. The arrival of griseofulvin and then in the 1970s of the azoles, accelerated the redesignation of athlete's foot and other ringworm infections as dermatophytoses. They were no longer framed as 'diseases of modernity', but as fungal infections that were conquerable, if not yet fully conquered, by medical progress.

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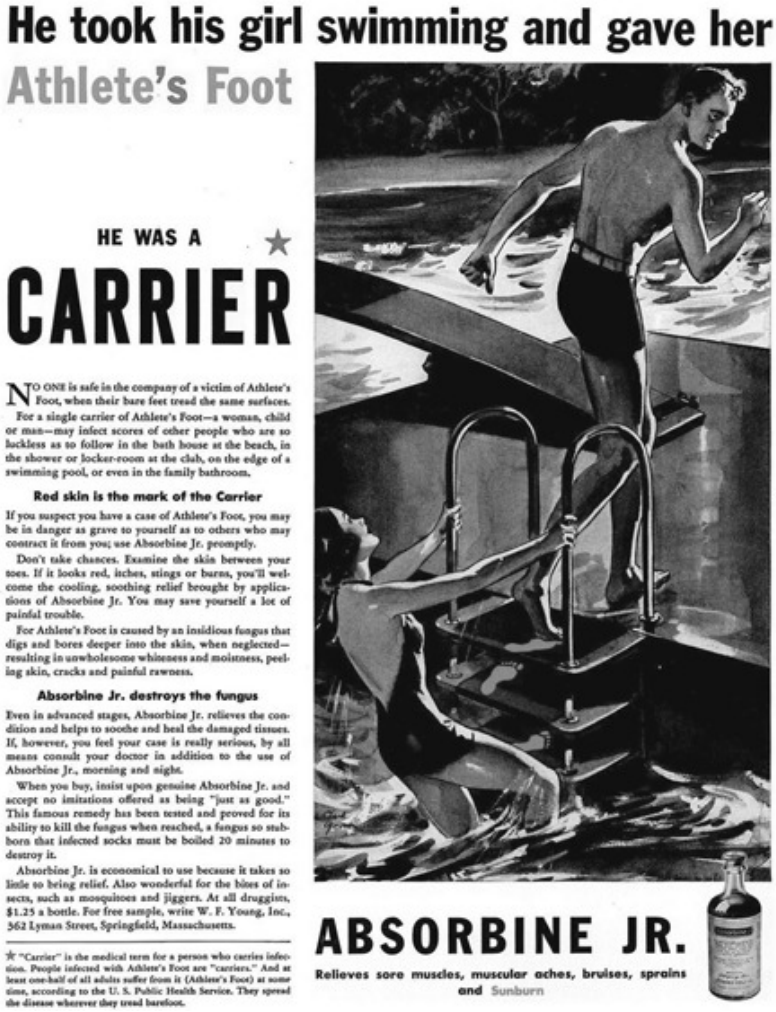
Figures



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