

Chapter 5 Fungi in medicine - antibiotics and other pharmaceuticals

We all know about penicillin. We've heard the story about it being discovered by chance when some research egghead called Fleming returned from holiday to find that his bacteria had been slaughtered by a rampaging fungus. Different versions of the story differ as to whether there and then he recognized the thing as the first antibiotic. And they also differ in the way they describe if and how Britain and the USA collaborated to produce the material that would save humanity from disease. Well, no one version of the story can be either entirely true, or entirely wrong. But I don't intend to contribute to the variety of stories, because I don't want to start here. Rather, I want to start by painting a picture of the magnitude of the change in life style which was brought about by antibiotics. Today we take antibiotics for granted. You have a mildly sore throat so you get an antibiotic; you get a slight injury so you get an antibiotic jab - 'in case of complication'. It's all become so trivial. So ordinary. But the changes created by the immediate availability of antibiotics were far from trivial. For the first time in human history they brought freedom from fear of inevitable death from 'blood poisoning' of various sorts. A death waiting for everyone for the most trifling of reasons.

In 1940 the Second World War was really beginning to get into gear. In the summer of 1940, Hitler's forces dominated Europe from the North Cape (a promontory on a northern Norwegian island which is the most northerly point of Europe) to the Pyrenees. Winston Churchill succeeded Chamberlain as British Prime Minister on May 10, and some of the darkest days of World War II followed - Dunkirk, the fall of France, and the blitz. The British army had left most of its weapons on the beaches at Dunkirk, and the U.S., after the fall of France, began the first peacetime conscription in its history. U-boats of the German Navy initiated the Battle of the Atlantic in June 1940, a conflict that would not be resolved until late 1943. But the Battle of Britain was fought in the air from August 1940 when the German Air Force launched daylight raids against ports and airfields. The new device, radar, so much increased the effectiveness of Royal Air Force fighters that the magnitude of German losses forced them to switch to night bombing at the end of September. Between then and May 1941 there were seventy-one major air-raids on London and another fifty-six on other cities. On September 17, 1940 Hitler postponed the invasion, conceding defeat in the Battle of Britain.

At secret locations in both England and Germany the first aircraft jet engines were under test. The first flight of an aircraft powered by Frank Whittle's engine took place in May 1941. In Germany, at the then secret Peenemunde site, the ram-jet powered pilotless V-1 was well advanced and work on the ballistic rocket weapon V-2 was also underway. The first of over four thousand V-2s was test-fired in 1942; two years later these ballistic missiles were exploding on their targets in England. The British had suspended the TV broadcasts which were started some years before the outbreak of war, but they were using radar arrays to detect German aircraft attacking across the English Channel and Southern North Sea. The world's first programmable digital computer was assembled by Alan Turing in Bletchley Park in England and was already in regular use decoding encrypted German military communications. And, of course, the nuclear age was being ushered in. The process of nuclear fission was explained in 1939 by the Austrian physicist Lise Meitner and her nephew, the (naturalized) British physicist Otto Frisch. So the movements that would eventually lead to establishment of the Manhattan Project in August 1942 were already underway. I mention all of these events to put the rest of the story in proper context. The time is more than 60 years ago, but many things which are now common features of our everyday life were already in use or under development - jet travel, rockets, cruise missiles, telecommunications, computers, and atomic energy. This is not the Dark Ages we are talking about, and yet ...

At the end of December 1940, a man called Albert Alexander was admitted to the Radcliffe Infirmary in Oxford, England. Albert was a police officer. He was 43 years old and had been a policeman for a long time. I have a mental picture of him, which may or may not be accurate, as a big man, confident and big-hearted; a really old-fashioned 'community cop'. He'd been injured about a month before admission to hospital, though the record does not say whether the injury was suffered in the line of duty. The injury became infected, the dreaded blood-poisoning or septicaemia. Pathogenic bacteria were spreading through the tissues of his face, head and upper body, growing faster than his immune system could cope with and causing suppurating abscesses all over his face and forehead. His eye became infected and had to be removed on February 3. Then his lungs became infected. He was close to death and was selected for experimental treatment with partially purified penicillin. On February 12 he was injected with two hundred milligrams, followed up with one hundred milligram doses at three-hourly intervals. The next day his temperature had returned to normal and he was able to sit up in bed. He continued to improve. But so little penicillin was available that it had to be re-extracted from his urine to be re-injected into his veins. Finally, all supplies were exhausted and his condition worsened rapidly. Despite the early promise of cure in what was one of the first cases to be treated with purified penicillin there was not enough of the wonder drug to save Albert Alexander. He died on March 15. Killed by an injury which had become infected. And the injury which had felled this policeman? Slashed with a knife? Downed by a gun shot? Crippled in one of the acts of war which the civilian population was then increasingly experiencing? No, none of these potentially heroic ends. Albert Alexander had been scratched by a rose thorn.

More than any other scientific advance of modern times, the 'penicillin story' is able to stir interest and imagination because this metabolic product of a common green mould is able to cure a variety of infections which yield slowly or not at all to other treatments. This one fungal product had revolutionized medicine. It cannot cure everything but penicillin can be used successfully to treat pneumonia, gangrene, and gonorrhoea. Diseases which were fatal or debilitating, and also widespread, when penicillin first came into use, diseases such as septicaemia and osteomyelitis, have been relegated to medical history. In the 1930s (and before) you didn't need a war to be in constant danger from life-threatening infection. Any injury in which the skin was broken might become infected with soil or air-borne bacteria and some of these might grow beyond the level with which the immune system could deal. When that happened the bacteria were consuming the patient and producing toxins in the blood stream which caused more widespread damage. An ordinarily-active adult might suffer scratches or minor cuts while gardening, walking, climbing. Osteomyelitis was an infection of the bone with staphylococcus which was relatively common in children - how many bloody injuries did your shins suffer when you were a child? Any man who shaved regularly might suffer infection of the inevitable nicks and cuts. This is what killed Lord Caernarfon in 1923. He who was a veteran of 19 years in Egypt before he found Tutankhamen's tomb in 1922. And it wasn't 'The Mummy's Curse' that finally saw an end to the noble Lord - it was blood poisoning, septicaemia, caused by an infected shaving cut. Less dramatic infections caused unsightly boils and abscesses all over the face as bacteria established in shaving cuts invaded otherwise healthy hair follicles. Not deadly, but painful, debilitating and above all, common. And women were even more at risk. Birth is a very messy procedure even today and before the ready availability of antibiotics an astonishing proportion of new mothers suffered, and countless died, from puerperal fever resulting from internal infection. And an equally astonishing number of new-borns were infected during birth with bacteria which were only mildly pathogenic but nevertheless caused blindness, deafness and other life-long disabilities even when the child survived. Bacteria are very successful organisms. They are widespread and adaptable. Life for humans was not easy. Penicillin contributed in a major

way to a revolutionary change in medical treatment which in turn changed the human lifestyle to such an extent that diseases which were common causes of death and disability are now rarely encountered. This dramatic change to the every-day experience of everyone on the planet is to me the most remarkable aspect of the discovery and introduction of penicillin. There are several other remarkable aspects of the penicillin story. Supply is one of them. For Albert Alexander, one of the first patients to be treated, there was little more than one gram available in the whole world and it was not enough to save his life. Today we produce enough of the totally purified material to give every human on the planet a dose of 5 grams!

Development of penicillin production on an industrial scale was a triumph in both scientific and technological terms. Penicillin was discovered, apparently accidentally in 1928, at St. Mary's Hospital in London by Alexander Fleming. There are a number of different accounts of this discovery, but the usual story is that culture dishes of the pathogenic bacterium, *Staphylococcus aureus*, which Fleming had left on his work bench became contaminated with a fungus spore. When Fleming returned from his brief holiday a fungus colony had formed and growth of the bacterium was inhibited in a zone around the fungus. Fleming identified the contaminating fungus as a species of *Penicillium* and named the unknown inhibitory substance penicillin. Fleming studied the material to some extent during the 1930s, but was unable to purify or stabilize it. He clearly recognized its potential, suggesting that penicillin might have clinical value if it could be produced on a large scale.

Penicillin was later purified by Howard Florey, Ernst Chain, Norman Heatley and other members of a team at Oxford University, which is how the antibiotic became available for experimental use at the Radcliffe Infirmary in Oxford in 1940. The Oxford team developed a purification method using the solvent ether which gave good yields of antibiotic from a meat broth medium on which Fleming's fungus had been grown. The result was a brown powder which was a remarkably potent antibacterial agent even though still not fully purified. The essence of the production process was a surface fermentation method in which the fungus was grown like a crust on the liquid medium. To produce enough penicillin-rich cultivation liquid the Oxford group used all types of readily-available bottles and dishes, but what proved to be the best of these makeshift containers were hospital bedpans! Later purpose-made ceramic or glass vessels modelled on this utensil were re-named 'penicillin flasks'.

Despite heroic efforts to scale-up production, the British fermentation industry simply lacked the knowledge and expertise to produce penicillin effectively. American academic and industrial scientists were well ahead of their counterparts in the rest of the world. They had experience of growing fungi in deep fermentation submerged culture and were expert in the selection and development of high-yielding strains. Indeed, the crucial American contribution to industrializing penicillin production grew out of the experience of American scientists during the 1930s, like Selman Waksman and Harold Raistrick, in the usefulness of fungi for industrial production of chemicals such as fumaric acid and, especially, citric acid. Transfer of penicillin development to the USA enabled the marvel of war-time antibiotic production to be achieved. By the end of World War 2, penicillin cost less to produce than the packaging in which it was distributed. It made an enormous contribution to the war effort, too. During World War 1, fifteen percent of battle casualties died of infected wounds. When penicillin became widely available in the latter half of World War 2, recovery rates from non-mortal wounds were routinely ninety-four to one hundred percent - death from infection of the wound was almost zero.

Of course, this medical/military advance was not shared with the enemy. The armies of the Axis

Powers continued to suffer the additional slaughter caused by infection of wounds. Even after the war, although transfer of American know-how in fungal fermentation enabled Britain to become self-sufficient in penicillin production by 1947, much of the rest of the world remained dependent on US production for a long time. Remember that the plot of Graham Greene's classic book and film 'The Third Man' centred around Harry Lime - a black market supplier of penicillin in post-war Vienna. Penicillin was so important (and valuable) that it was worth risking death to smuggle.

From every angle the development of penicillin is a remarkable story. The drama is heightened by its timing - right at the start of a world-wide conflict - and by the fact that this was the first time that a medically-useful fungal product was subjected to industrial level production. Not the 'first product', but the 'first medically-useful product'. Yeasts have been used since antiquity to leaven bread and to produce alcoholic drinks like beers and wines, and several traditional foods have been flavoured with fungi.

In ancient times fungi were used a great deal for their supposed curative properties, but, in the Western World at least, such use declined until interest revived in the potential applications of fungi and fungus metabolic products in medicine following the success of penicillin. Declining use of fungi, as well as plant materials, can be traced to the application of the reductionist approach of the Western scientific method which made it difficult to sustain the varied claims made for many natural products in traditional medicines. One of the writers on this topic claims that ancient writings from all civilizations refer to the use of moulds to treat infected wounds. There seems to be good evidence that our ancestors maintained cultures of therapeutic moulds or knew how to grow them selectively so they could be used to cure surface infections. The practice was revived in the early 1940s soon after penicillin was identified, but before the purified product became widely available.

Much of the traditional usage seems to have escaped formal written record although Herbalists and other medical writers of the middle ages included fungi (mainly mushrooms and toadstools) for their abilities to cure various complaints. Like most other aspects of Western science of the time, these writings owe a lot to those of the Greeks more than a thousand years before. For example, Dioscorides, writing about 200 AD, claimed that fungi could cure a great many ailments and amounted to an almost universal remedy. Extravagant claims like this are readily found also in Chinese and Japanese traditional medicine. For example Lingzhi ('fruit bodies of the fungus *Ganoderma*) is described as 'the rarest and most precious Chinese medical herb' which legend claims even to have '... the miraculous power of raising the dead to life ...'. Less extravagant claims are for Lingzhi '... preventing and mitigating a variety of clinical conditions: chronic bronchitis, asthma, neurasthenia, insomnia, amnesia, hypertension and hypotension, coronary heart disease, arrhythmia, stroke, hyperlipidemia, thrombosis, female endocrine disorder, female physiological disease, menstrual disorder, chronic hepatitis, gastric diseases and duodenal ulcer, allergic and chronic rhinitis, dysuria, arthritis, rheumatism, allergic dermatosis, cancer.' Now that quotation does not come from some ancient medical text, but from a leaflet I picked up in a departmental store in Hong Kong in April of 1999! So the material is being sold now to sophisticated and highly educated people - to the engineer who designed and built your lap-top computer, or the pilot of your next trans-Pacific flight, for example. And it's being sold on the basis of a written medical tradition which goes back more than five thousand years. That a similarly ancestral, but sadly unwritten, tradition occurred in Europe is indicated by material carried by the Alpine traveller who has become known as 'The Iceman'.

About 3200 BC a Neolithic traveller set out across the Alps. He didn't make it. Somehow he was

caught in the ice and snow, entombed and preserved in the glacier. Eventually, as a result of the glacier's slow descent of the mountains, his corpse was exposed at the edge of the ice sheet in 1991 close to the Austrian/Italian border. A well-preserved five thousand year old corpse with all of its clothes and equipment is a remarkable find by any measure. But possibly most remarkable is that there were three separate fungal products among the Iceman's equipment. One of these is easy to account for. It was a mass of fibrous material in a leather pouch together with flints and a bone tool like an awl. This fungus has been identified as one with a long history of use as a tinder, so clearly it was part of the Iceman's fire-making kit. The other two are more problematical. Both are pieces of a bracket fungus (actually called *Piptoporus betulinus*) and both are threaded onto leather thongs. One piece is essentially conical, about 5 cm in its longest dimension, and is on a simple leather thong. The other is spheroidal, about 5 cm diameter, and is on a thong which has a lobed tassel at one end. These objects were clearly carefully made and must have been important to the owner to be included as part of the kit he chose to take with him in his trek across the mountains. *Piptoporus* is known to produce (and accumulate in its fruit bodies) antiseptics and pharmacologically active substances which are claimed to reduce fatigue and sooth the mind. I can imagine that with due ceremony and additional magic, these objects may well have been seen as essential to the traveller in the mountains. The conical one could well be a sort of styptic pencil to be applied to scratches and grazes. I can understand the flattened, spheroidal one being chewed or sucked when the going got tough and the tough needed just a little help to keep going.

So our distant European ancestors held fungal products in such high esteem that they were necessary accessories for hazardous journeys. What of today, and what of the future? Today, alcohol and citric acid are the world's most important fungal metabolites in terms of production volume, although, penicillin can still lay claim to be the most important. Since the introduction of penicillin, several millions of chemicals and metabolites have been screened for antimicrobial and other pharmaceutical activities. The lesson has been well learned and chemicals screening is a major activity of the pharmaceutical and agrochemical industries around the world. Most antibiotics that we use today actually originate from bacteria, particularly the streptomycetes. Indeed streptomycin was the second significant antibiotic to be found and was largely responsible for the demise of tuberculosis as a major disease (resistance to streptomycin being a cause of the recent resurgence of tuberculosis). Antibiotics obtained from fungi which are presently of clinical use as antibacterial agents include the still-important penicillin, cephalosporin and fusidic acid (both of the latter are useful against penicillin-resistant bacteria), and the antifungal griseofulvin (used to control fungal infections of the skin, nails and hair). Obviously, antibiotics are the products which come to mind first when thinking of medically-useful fungal products, and they have dominated this chapter so far. But fungi have much more potential and some products first discovered antibiotics have subsequently been shown to possess some other potent activity in tests on mammals. For example, the increasing importance of organ transplantation in medicine focuses attention on compounds capable of suppressing the recipient's immune response so as to avoid organ rejection. The fungal product called cyclosporin is now widely used as an immunosuppressant and greatly improves the success rate of transplant operations. Another fungal product, gliotoxin, seems to regulate the immune system and may also be useful for postoperative management of transplant patients. A final example of a natural compound obtained from fungi that has great medical value is a hydroxy-acid called mevillin. This is produced by the fungus *Aspergillus terreus* and it acts as a cholesterol-lowering agent by interfering with enzymes that make cholesterol in mammals. By the mid-1990s three compounds derived from mevillin had worldwide sales that put them individually in the top ten selling pharmaceuticals by value of sales. These were Pravastatin (sales in 1995 valued at two billion US\$), Simvastatin (sales of 1.6 billion US\$) and Lovastatin (sales of 1.4 billion US\$). All of

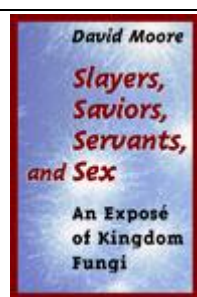
these ‘statins’ are used to reduce cholesterol levels in the body because high cholesterol levels are considered to be a risk factor in heart disease.

Fungi also produce compounds like the ergot alkaloids, steroid derivatives, antitumour agents and immunoregulators. I described the terrible effects of the ergot toxins in Chapter 1, where ergot-contaminated grain caused St Anthony’s Fire in which the sufferers experienced gangrene, cramps, convulsions and hallucinations. The toxicological effects are caused by the numerous alkaloids that ergot contains, but in low, and controlled, concentrations these are valuable drugs causing dilation of veins and a decrease in blood pressure as well as contraction of smooth muscles. They are drugs of folk-lore too, for the ancient remedy was to give ergot in childbirth to hasten contraction of the uterus. The ergot alkaloids are now produced by fermentation, similar to penicillin-fermentations. Although the alkaloids can be synthesized, strain improvement by mutation and selection of high-yielding strains has been so successful that fermentation remains the most cost-effective means of production.

Fungi don’t have to *produce* a compound to be useful because they can bring about a variety of chemical transformations of compounds, especially steroids, in a reliable and reproducible way. Most of the steroids in clinical use today are modified during manufacture in this way. The fungus is grown in the minimum amount of nutrients (this limits complications during subsequent extraction). Then the steroid to be transformed is added and about twenty to forty hours later the new steroid can be extracted. The attraction is that this relatively simple procedure may avoid anything up to twenty or thirty steps of pure chemistry. Success with steroid transformation led to similar approaches being applied to other pharmacologically active compounds, to reduce toxicity while maintaining activity or make chemical alterations to enhance activity. Using fungi in this way is a convenient and economic means of making specific compounds which would be otherwise very difficult, impossible, or just too expensive to produce by direct chemical synthesis.

Cancer would be high, if not top, on most lists of afflictions in need of a reliable cure and, consequently, a key feature of most screening programs is the search for effective, and safe, antitumour and antiviral agents. Several hundred antitumour agents have been isolated from microbes, most from bacteria. Nevertheless, many fungal products have been found to inhibit the growth of cancers in animal tests. Specificity and safety are the issues which limit the medical usefulness of most of these compounds - they may have adverse effects on the host organism as well as the tumour. The most successful antitumour agent is a polysaccharide isolated from the Shiitake mushroom. It is called lentinan and seems to work by modifying the activity of the patient’s own immune system - making it more active against the cancer cells. Lentinan has been used successfully to treat stomach cancers and is now a multi-million dollar industry. Since cancer control was one of the benefits claimed for shiitake in the ancient Chinese and Japanese medical writings, the successful development of lentinan prompts the hope that the (many) other fungi used in traditional Oriental folk medicine may also yield products useful in today’s clinical practice. The search is on. Over several thousand years an enormous number of fungal products have been recognized as having medicinal value in China, Korea and Japan. Oriental science and western science are very different. A western scientist seeks to isolate active principles from one another and to understand the parts individually and separately. Oriental science is holistic, almost anecdotal in western terms, because it seeks to understand the entire complex event. We might hope, therefore that some, at least, of the oriental remedies might yield to modern western analytical techniques so that the active principles of centuries-old medicines can be identified, purified and turned into ‘western-style’ drugs.

Of course, if you have faith in oriental wisdom you can use the traditional remedies right now. The term 'mushroom nutraceutical' is used for a new class of compounds extractable from various mushrooms. Mushroom nutraceuticals can have both nutritional and medicinal properties. Nutraceuticals extracted from medicinal mushrooms have the advantage over most pharmaceuticals that they have extraordinarily low toxicity, even at high doses. Long used as tonics in traditional oriental medicine, they are now believed to profoundly improve the quality of human health. There are claims that consumption of mushrooms as a food or the use of mushroom extracts as dietary supplements can enhance the immune response of the human body. The expectation is that this would increase resistance to disease and even have the potential to cause regression of an established disease. Several fungi have been found to produce metabolites that inhibit the multiplication of viruses in culture and in animal tests. Activity of various of these compounds against major disease-causing viruses, like poliovirus, coxsackievirus, vaccinia and various influenza viruses has been demonstrated in the laboratory, but the tricky transfer from laboratory curiosity to clinical tool has not yet been achieved. Only time and further research will tell if we can exploit the promise of the Chinese fungal remedies.



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