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Fungi at work 1: Producing life-saving drugs

David Moore: *World of Fungi* www.davidmoore.org.uk/index.htm

Some of the wonder drugs of today come from fungi. Statins control your cholesterol level to protect you from heart disease. Cyclosporine stops rejection in transplant patients. And we still depend on penicillin – the antibiotic wonder drug of the 1940s. All these from fungi!

But there are many more reasons to be thankful; you see, the word 'drug' tends to be applied specifically to materials used to treat or prevent diseases in humans whereas fungi also provide us with compounds that treat or prevent diseases (and pests) of our crop plants. So, they are just as crucial to our agriculture as they are to our medicine.

Indeed, fungi provide us with today's most widely-used agricultural fungicides. Yes, that's right, fungi produce chemicals that kill fungi (they're called **strobilurins**); how weird is that?

Well, not so weird if you think about it from the point of view of microbial competition, because most antibiotics have evolved for just that: to help the producing organism in its ecological competition with its neighbours.

First observation of penicillin

You have probably heard the story about penicillin being discovered by chance in 1928 when Alexander Fleming returned from holiday to find that *Staphylococcus* bacteria on his culture plates had been killed by a contaminating fungus (*Penicillium notatum*). Presumably, the spores of the fungus, which are very common, floated onto Fleming's culture dishes when he was examining his bacterial colonies.

Fleming is reported to have said, some time later: "I must have had an idea that this was of some importance, for ***I preserved the original culture plate***" (Fig. 1); he was right about the importance of his observation.

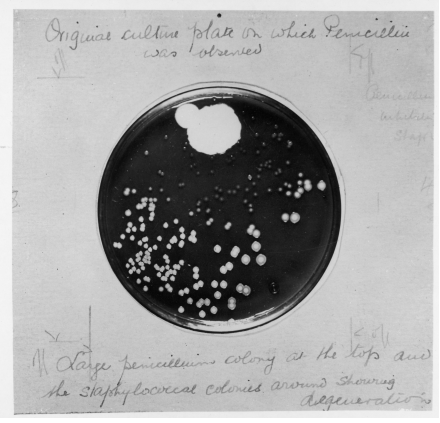

Fig. 1. The original culture plate on which Sir Alexander Fleming first observed the growth of *Penicillium notatum* in 1928. Fleming's own hand-written explanatory note beneath the culture dish reads: *'A large* Penicillium *colony at the top and the* Staphylococcal *colonies around showing degeneration'.*

Penicillin caused a revolutionary change in medical treatment which in turn changed the human lifestyle to such an extent that diseases that were common causes of death and disability before penicillin are now rarely encountered. This dramatic change to our everyday experience is the most remarkable aspect of the discovery and introduction of penicillin.

Today we take antibiotics for granted. You have a mildly sore throat, so you take an antibiotic; you have a slight injury, so you are prescribed an antibiotic jab 'in case of complications'. Indeed, in many parts of the world no doctor's prescription is necessary. It's all become so trivial, so ordinary. But the changes created by the immediate availability of antibiotics were far from trivial.

The antibiotic revolution

It could not cure everything, but penicillin was used successfully to treat pneumonia, gangrene, gonorrhoea, septicaemia and osteomyelitis, a staphylococcal infection of bone which was relatively common in children.

Diseases that were fatal and widespread when penicillin was first produced were relegated to medical history by its use. Before that time, any injury in which the skin was broken might become infected with soil-borne or air-borne bacteria. An ordinarily-active adult might suffer scratches or minor cuts while gardening, walking or climbing. Any man who shaved regularly might suffer infection of the inevitable nicks and cuts caused by an unclean razor blade.

Some of these minor injuries might become infected, the bacteria growing beyond the level with which the immune system could cope, producing toxins in the bloodstream which caused more widespread damage: the dreaded 'blood poisoning' and sepsis.

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 died from puerperal fever resulting from internal infection. An equally astonishing number of new-borns were infected during birth with bacteria that were only mildly pathogenic but nevertheless caused blindness, deafness and other life-long disabilities even when the child survived. That is the magnitude of the change in lifestyle that was brought about by the availability of antibiotics.

A matter of competition

But let's go back to Fleming's Petri dish because it illustrates something even more fundamental. Fleming's note (Fig. 1) describes an additional large *Penicillium* (mould fungus) colony. He noticed that around the margin of the mould colony there was a zone within which the pre-existing *Staphylococcus* colonies were being destroyed; and it was that point of detail that was certainly 'of some importance' and which gave rise to the whole penicillin story. So, is there something more fundamental than that? Well, there is if you ask the question: why?

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Why is the *Penicillium* mould producing a bacterial toxin? *Penicillium* and *Staphylococcus* are both common and widely-distributed microbes, and they have co-existed in the same habitats for many millions of years. Certainly, they could both grow on the nutrient agar gel in Fleming's Petri dish, but the mould goes further than mere co-existence. By producing its anti-bacterial toxin (penicillin), the fungus converts the resident bacteria into nutrition for itself; it takes control of the entire habitat. And that's the fundamental point. Microorganisms don't just grow together; all microbes actively compete with one another by challenging each other with toxic chemicals.

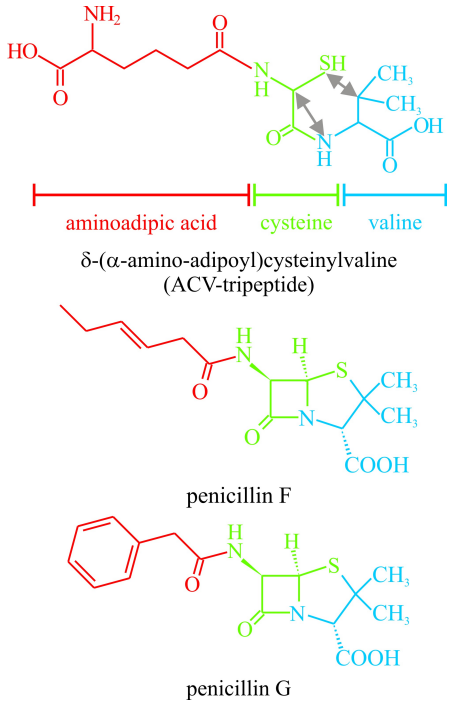

Fig. 2. Penicillin antibiotics are tripeptide derivatives. This figure shows the structural formulae of two penicillins, F & G. At the top is the precursor, δ-(α-amino-adipoyl)-cysteinylvaline. The aminoadipoyl, cysteine and valine residues of this compound are colour coded, and the double-headed arrows show the bonds that have to be made to create the penicillin nucleus.
Image © David Moore.

The fungal competition with bacteria has resulted in several clinically useful antibiotics. These include the penicillins (named this because they were originally seen to be produced by the fungus *Penicillium* - Fig. 1), and the chemically-related cephalosporins, which were originally derived from the fungus *Cephalosporium* (though this is now called *Acremonium*).

Bacteria also compete with other bacteria in the same habitat by producing antibacterials. This competition has given us some of our most widely used antibiotics for today's medicines. Commonly used antibiotics produced by bacteria are geldanamycin, erythromycin, streptomycin, tetracycline and vancomycin. Even penicillin was originally made by bacteria. When the chemistry and metabolism of penicillin synthesis in fungi was worked out (Fig. 2) it became clear that some *Streptomyces* bacteria also make exactly the same penicillin chemicals, using exactly the same enzymes to do so. During their evolution, fungi have acquired many useful genes from other organisms, particularly from bacteria. It's called horizontal gene transfer.

But fungi do not only compete with bacteria; they also interact with other organisms, and we make good use of some of the chemicals they produce as they compete. Competition with other fungi has given us the strobilurin fungicides.

The original, natural, strobilurin is produced by the pinecone fungus, *Strobilurus tenacellus*, a mushroom fungus that colonises pinecones and produces strobilurins to keep the pinecone to itself. Natural strobilurins are unstable in the light, but many synthetic analogues have been produced that are stable, and synthetic strobilurins are now the most widely-used agricultural fungicides.

Fungi also need to deter all those tiny animals in the soil that eat their hyphae. One way they do this is to produce chemicals that interfere with the synthesis of the cholesterol that the animals need to make their cell membranes. Cholesterol is not used in fungal cell membranes, which means that fungi can produce a powerful 'cholesterol inhibitor' with no risk to themselves. Some of these effective cholesterol-lowering-agents derived from fungi have been used in human medicine; they are called **statins** (Fig. 3). The two fungi used to produce statins are *Aspergillus terreus* and *Penicillium citrinum*.

Most of us appreciate that if we have too much cholesterol, the human body is not able to use up the excess and it sticks to the inside walls of our blood vessels. This build up reduces the diameter of the vessels, which restricts blood flow. If blood vessels that supply the heart become clogged, this can cause a heart attack because the heart muscle does not receive enough oxygen to function properly. To control heart disease, it is important that humans regulate their cholesterol level.

Fig. 3. A *Simvastatin* prescription. Today, statin drugs have become one of the most commonly prescribed medicines and are credited with saving 7,000 lives a year in the United Kingdom alone!
Image © David Moore.

Cyclosporine is another crucial wonder drug of today that enables long-term transplants of livers, kidneys, hearts, lungs and bone marrow; as well as auto-immune disease treatments. This compound is produced by the insect-pathogenic fungus *Tolypocladium inflatum* (Fig. 4).

Fig. 4. A *Tolypocladium* sporophore growing out of a beetle larva the fungus has parasitised.
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Cyclosporine was first identified in 1971 as a weak antibiotic. It was later found by Hartman Stähelin and Jean Francois Borel (at Sandoz Ltd, Germany) to be the first immuno-suppressive drug that allowed selective immuno-regulation of T cells without excessive toxicity. Sir Roy Calne at Addenbrooke's Hospital Cambridge established the crucial clinical role of the drug. Suppressing rejection enables the transplanted organ to continue to function.

So many contributions to our daily lives; so many reasons to be thankful for the chemical versatility of fungi!