

SUPERBUG

Nature's revenge

Why antibiotics can breed disease

Geoffrey Cannon

The Virgin logo, featuring the word "Virgin" in a stylized, cursive script font.

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5 The Trouble with Antibiotics

SUPERINFECTIONS

Naturally enough, the more powerful the dose of any drug, the more problems it can cause. The more courses you take, and the more broad spectrum the formulation, the more likely you are to suffer ill-effects from antibiotics; but just one course can sometimes make you ill. Simple cause and effect is easy to understand. If you take a course of antibiotics and immediately suffer, say, diarrhoea or shock, you or your doctor are likely to guess that the drug is involved.

The trouble with antibiotics, though, is not so much their acute ill-effects as the long-term damage they can do to individual patients and to the community, by a relatively complex process of cause and ill-effect generally better understood by microbiologists than physicians. Antibiotics often are effective short-term treatments for infection but, in the longer term, can be the underlying cause of the same or other infections. That is to say, in curing disease antibiotics may cause more disease. This is partly because of a phenomenon known as *superinfection*.

When you take antibiotics, the drug kills vast numbers of bacteria in your gut and elsewhere, on and in your body, but countless millions remain. The bacteria that survive include species unaffected by the drug, or else (initially rare) drug-resistant variants of a vulnerable species. Non-bacterial micro-organisms such as fungi also survive, unless the drug is specifically formulated against them. After a number of courses of antibiotics, these surviving micro-organisms are liable to multiply and to fill the space created by the drug.

The bacterial species that are normally dominant on and in our bodies are the friendly flora that have evolved in harmony with us. These species are usually resilient. A course of antibiotics may devastate them, but is unlikely to wipe them out totally; and afterwards they are liable to become re-established in the right relationship with each other, especially in normally healthy adults.

But not always. Antibiotics can start a sequence of events in which the naturally protective populations of bacteria are overwhelmed by superinfection with different species of bacteria and other micro-organisms. Professor Marc Lappé of the University of Illinois, explains¹³:

When antibiotics kill or inhibit harmful bacteria, they also eliminate vast numbers of relatively benign or even beneficial bacteria. When these more benevolent counterparts die off, they leave behind a wasteland of vacant organ and tissue. These sites previously occupied with normal bacteria, are now free to be colonized by new ones. Some of these new ones have caused serious and previously unrecognized diseases.

The people most likely to suffer this malign process include the very young, the old, the weak and the generally ill, as well as those whose immunity to illness has been weakened for other reasons. After courses of antibiotics, our friendly flora in effect have to fight to re-establish themselves as the dominant species. The more drugs we take, and the generally more vulnerable we are, the greater the chance that they will lose this fight against superinfection by other species of micro-organisms liable to cause disease.

The bacteria and other micro-organisms that are liable to be superinfectious can be subdivided into three types. The first normally live harmlessly in profusion on or in the body, notably in the gut, and are capable of harm only when their natural balance with the normally dominant friendly flora is destroyed. The *E. coli* bacillus is an example: it is a menace usually only when it multiplies out of control throughout the gut, or else when it is able to invade other parts of the body, such as the urinary tract, whose opening is normally shielded by friendly bacterial flora.

The second type of potentially superinfectious micro-organism may also live in or on the healthy body, but in small numbers, normally kept down by the dominant friendly flora. These have no known useful function in the healthy body, and, like the normally more common species such as *E. coli*, can be a menace when they multiply. Examples are the *Clostridium difficile* bacillus that can cause a severe and even deadly 'pseudomembranous' colitis, and the *Candida albicans* fungus that can cause thrush after antibiotic therapy. (More of these later in the book.)

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The third type of micro-organism does not live in the normal healthy body, and is kept out by the body's natural defences of which friendly flora are an integral part. When these flora are devastated by antibiotics, we become more vulnerable to these foreign bacterial species. Among very many examples are the shigella family of bacilli that are the microbiological cause of dysentery, the *Vibrio cholerae* bacillus that causes cholera, and the *Treponema pallidum* spirochaete that causes syphilis.

Superinfections can usually be checked by further courses of antibiotics formulated for this purpose. Doctors in Europe, North America and other privileged parts of the world, with access to well-stocked pharmacies, can usually check superinfections, although they may not be able to cure them. People in Africa and Asia and other less privileged parts of the world are more likely to succumb, simply because of a lack of appropriate drugs.

Ironically, superinfections have the effect of enhancing the reputation of antibiotics as wonder drugs. If you become ill with thrush, say, or severe diarrhoea, and do not realise that your illness may well be a superinfection caused by a previous course of antibiotics, you will turn to antimicrobial drugs again and, once you recover, will be all the more likely to turn to these drugs once again in future.

THE CHEMICAL TREADMILL

Soon after antibiotics were first used, microbiologists became aware of superinfection. So did industry. Many antibiotics are specifically formulated to treat superinfections caused by other antibiotics. On the one hand, antibiotics are effective against bacterial infection; on the other, more and more antibiotics are used every year. Why? This paradox is partly explained by superinfection: the more antibiotics are used, the more they *have* to be used. This is the drug treadmill.

If you are surprised by the phenomenon of bacterial superinfection, consider its parallel on the land. When farmers use insecticides and other biocides, they disrupt the balance of nature. Sometimes this does no harm (unless, that is, you are concerned not just about pests but also about all the other species of animals, birds and insects that are killed). At other times, though, just as in the case of the ladybirds and the aphids mentioned earlier, biocides may have the effect of turning previously harmless insects into major pests. In

the worst cases, new pests created by the use of biocides may cause vast damage. The distinguished entomologist the late Professor Robert van den Bosch explains¹⁴:

When applied to a crop, a biocide kills not only pests but also other species in the insect community, including the natural enemies that restrain noxious species . . . Insecticide spraying frequently creates a virtual biotic vacuum in which the surviving or reinvading pests, free of significant natural-enemy attack, explode. Such post-spraying pest explosions are often double-barrelled, in that they involve not only the resurgence of target pests but also the eruption of previously minor species, which had been fully suppressed by natural enemies. The frequent outcome is a raging multiple-pest outbreak, more damaging than that for which the original pest-control measure was undertaken.

A pesticide that kills ladybirds is liable to provoke a plague of aphids. An antibiotic that kills *S. viridans* and other friendly flora found on or in the body is liable to provoke an outbreak of superinfection. Indeed, 'provoke' is really the wrong word. Potentially superinfectious bacterial species are relatively harmless in the healthy body. When antibiotics are a link in the chain leading on to disease, it is really the drug, just as much as the bug, that is the cause of superinfection.

Dr van den Bosch concludes:

This is the genesis of the insecticide treadmill . . . [which] is magnified and prolonged by genetic selection for insecticide resistance in the repeatedly treated pests . . . Insects become resistant to pesticides, and the more intensive and widespread the poisonous blanket, the more rapid the selection for resistance in the pests. With insecticide resistance plugged into the formula, the treadmill whirrs at full tilt, and the consequences can be awesome.

The phenomenon of resistance is the second parallel between biocides and antibiotics. The fact that, after chemical attack, agricultural pests evolve mutant strains invulnerable to the insecticides formulated to destroy them has been known since 1914.¹⁵ Pesticide-resistant creatures spread; during the 1950s, as the use of agrichemicals multiplied, scientists and farmers found that more and more pests were resisting

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more and more of the biocides hurled at them. In 1979 in Britain, the Royal Commission on Environmental Pollution¹⁶ reported: 'Resistance to insecticides and fungicides is a matter of serious concern.'

Worse still was the discovery that insects carrying micro-organisms that cause human disease were also evolving mutant strains resistant to biocides. DDT (dichloro-diphenyl-trichloroethane) was identified as an insecticide in 1939 by the Swiss scientist Dr Paul Müller, who won a Nobel price for his discovery, which had proved effective against the malaria mosquito. In 1955, the World Health Organisation announced a \$1.3 billion programme for the global elimination of malaria to be achieved by spraying the mosquito's habitat, including houses, with DDT and dieldrin, another insecticide.

Thus the 1950s were the 'golden age' of biocides as well as of antibiotics. Scientists believed that all human diseases borne by insects or animals – including yellow fever, typhus and plague as well as malaria – could be eliminated forever by chemical means. But mosquito resistance to DDT was observed as early as 1950, and to dieldrin, in 1954. Other very toxic insecticides such as malathion and lindane were substituted. These worked, but only for a while, and colossal epidemics of malaria carried by insecticide-resistant mosquitoes broke out all over Asia in the 1970s. Professor Robert Metcalf of the Department of Entomology at the University of Illinois reported¹⁵:

some countries have recorded 30–40 fold increases in the case of malaria from 1968 to 1976 . . . By 1986 resistance had been reported in 58 *Anopheles* [mosquito species] recorded as vectors of human malaria and multiple resistance was widespread in more than 30, with 8 species showing resistance to all the five classes of insecticides available for residual house spraying.

The World Health Organisation programme to eliminate malaria was abandoned in 1976. The disease is now uncommon in Europe and North America but has surged once again as a vast epidemic elsewhere in the world. Worse, not only are the mosquitoes that carry the malaria parasite often resistant to insecticides, but now *Plasmodium falciparum*, the species of protozoa that causes the most vicious form of malaria, is also often resistant to chloroquine, otherwise the first-choice anti-malarial drug.¹⁷

Those suffering from chloroquine-resistant malaria can, if they happen to live in Europe, North America or elsewhere in the prosperous parts of the world, usually be successfully treated after returning home. But insecticide-resistant malaria mosquitoes carrying drug-resistant malaria bugs amount to a public health catastrophe in Africa and Asia, and the cost of biocides and antibiotics – all of which are liable eventually to become useless as pests and bugs develop resistance – is crippling the economies of some already impoverished tropical countries.

In 1989, Professor Metcalf wrote¹⁵:

The past 40 years have seen insect resistance to insecticides develop from a scientific curiosity to an immense practical problem that threatens man's ability to control not only the insect pests of agriculture but also the insect vectors that transmit major human and animal diseases.

In the same year, his address to the annual meeting of the American Association for the Advancement of Science resulted in the following headline in the (London) *Independent*: 'MONSTER BUGS THRIVE AS CHEMICAL ARSENAL FAILS:' 'Some strains of insects and microbes have appeared that are resistant to nearly everything in our chemical arsenal,' stated Professor Metcalf, and he warned that 'the world may be returning to the agricultural and medical dark age that existed before the discovery of modern insecticides and antibiotics.'¹⁸

Superpests, invulnerable to at least some forms of chemical treatment, have emerged and may become epidemic as a result of the use of biocides. Similarly superbugs – which is to say bacteria and other micro-organisms that resist treatment with one, some or even all available drugs – are a new health hazard created by the use of antibiotics; which is why in effect, antibiotics are pesticides used on people.

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What antibiotics do, in a phrase used by microbiologists, is to exert 'selective pressure' on bacteria. This distorts and accelerates their evolution, so that previously vulnerable species become drug-resistant. To some extent, this is simply the result of Darwinian

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chance mutation. When any bacterial species is attacked by antibiotics, only the fittest survive. However, in a population of many millions of bacteria, there will be some chance mutants, maybe one in a million, that just happen to be invulnerable to the drug that kills all the others. These previously insignificant mutants survive, multiply and colonise the space left by the destruction of all the other bacteria in the species that were previously vulnerable to the drug. So in future the drug doesn't work.

The creation of superbugs is not just a matter of chance mutation, however. Although microscopic, bacteria are very complex and adaptable living organisms. Their genetic organisation includes structures that probably evolved in order to resist naturally occurring chemicals contained in rival living things, just as plants, insects, birds, animals and, indeed, we humans have evolved means to resist predators.¹⁹

These structures – rings of genetic material contained within the bacterial cell wall in addition to the chromosome – are called *plasmids*. I mention them now briefly (more of these later) so that you can see why antibiotics, like biocides, can have such an explosive effect. The codes for bacterial resistance to antibiotics are contained in plasmids. Under selective pressure from drugs, these codes – also known as 'R' (for 'resistance') factors – can be transferred not only within bacteria of the same species, but also from one species to others. And there is more! Plasmids may contain codes for resistance not just to one but to a number of antibiotics. Under pressure from a course of one antibiotic, bacteria may therefore transfer multiple drug resistance within and between species.

What this means is that, as a result of taking antibiotics, you could end up with a gut full of bugs against which any number of future courses of antibiotics will be useless. And drug-resistant bacteria may themselves be the microbiological cause of unpleasant or even deadly infectious disease. If you take antibiotics, such disease may spread from you to me. If I take antibiotics, such disease may spread from me to you. You cannot avoid superbugs by avoiding antibiotics. Superbugs are everywhere.

CAULDRONS OF CONTAGION

So far, superbugs can usually be successfully treated by one or more of the antibiotics in any well-stocked pharmacy. Nevertheless, there

are four reasons why they are frightening. First, the next antibiotic you take may be for an infection caused by the last antibiotic you took, which has made you vulnerable to superinfection, so that you get more infections that make you more ill, so that you take more antibiotics . . . and so on and so on, round and round the drug treadmill.

Second, the antibiotic you take, say, for a mild infection, can breed superbugs that may transfer their drug-resistance to more dangerous bacterial species, making you vulnerable to invasive and even deadly infections. In the West, these usually can be treated, but sometimes only with drugs that are expensive, powerful, relatively more toxic and unpredictable in their effects.

Third, it is possible that, one day, antibiotics will breed a superbug that is the microbiological cause of a deadly epidemic infection that resists treatment with all antibiotics. Outside the West, this is now effectively happening countless times, simply because the drugs that can be used against serious infections are not available, or because the victim cannot be reached by a doctor. In the West, this doomsday superbug, everything-resistant enterococci, are now causing disease outbreaks in Western hospitals, and are killing people, but are not yet epidemic^{19,20}.

Fourth, you may never take antibiotics and yet be vulnerable to disease caused by a superbug, from any chance encounter with somebody themselves infected. The intestines of people who take antibiotics are factories producing drug-resistant bacteria. The next course of antibiotics you take may be for an infection caused by the last course of antibiotics taken by somebody else, which has made them more vulnerable to infection; so then you become more vulnerable and thus suffer another infection, so then you and they take more courses of antibiotics . . . and so on and so on, multiplied countless times across communities, countries and continents.

Overcrowded living conditions, infectious surroundings and constant dosing with antibiotics create ideal breeding-grounds for superbugs. Five examples of such cauldrons of contagion are: factory-farmed animals; hospital patients, including mothers and their babies; school children, especially at nursery school; people with many sexual partners; and countless millions of people living in slums throughout the world. In the August 1992 issue of *Science* magazine, an article on this subject²⁰ concluded:

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Those who believed a plague could not happen in this century have already seen the beginning of one in the AIDS crisis, but the drug-resistant strains [of bacteria], which can be transmitted by casual contact in movie theaters, hospitals, and shopping centers, are likely to be even more terrifying.

Superbugs are everywhere in the world. 'Each time an antimicrobial agent is used, there is potential for a significant effect on world microbial ecology' – this is Professor Calvin Kunin in an address to his colleagues of the Infectious Disease Society of America in 1984. He continued:

Most of the world's population is located in the so-called under-developed parts of the world. The greatest proportion of this population live under conditions of poverty, inadequate medical care, and poor sanitation and nutrition . . . These conditions, abetted by often irrational self-administration of antibiotics, have become a fertile ground for resistant micro-organisms . . . Travel is so extensive today that these organisms have gained entry and spread rapidly in Western countries.

In this address and in a report to the World Health Organisation in 1990²¹, Professor Kunin gives examples of some of the many strains of drug-resistant diseases that have spread like brushfire internationally or globally. These include: meningitis, 'which spread rapidly throughout the world'; pneumonia in and from South Africa and Spain; and the global epidemic of drug-resistant gonorrhoea that 'appears to have originated in southeast Asia and Africa'.

In a cover feature, 'The end of antibiotics', published in March 1994²², *Newsweek* magazine stated: 'Every disease-causing bacterium now has versions that resist at least one of medicine's 100-plus antibiotics . . . Already patients are suffering and dying from illnesses that science predicted 40 years ago would be wiped off the face of the earth. The scientists were wrong. Before science catches up with the microbes, many more people will die.'

6 Gold in Them Thar Pills

SULPHONAMIDES: WEAPONS OF WAR

The antibacterial era began in the 1930s, not in the UK with penicillin, but in Germany with sulphonamides. In 1935, the German firm I. G. Farben began manufacturing and marketing Prontosil, the first sulphonamide drug. It had been discovered by Dr Gerhard Domagk, Farben's research director, who was awarded the Nobel prize for medicine.²³

Sulphonamides were the wonder drug of the 1930s, medically and commercially.²⁴ By 1941 over 2000 tons had been manufactured and used to treat puerperal fever, pneumonia, meningitis and infections of the gut and urinary tract. Sulpha drugs (as they are known) were vital to the war effort in the late 1930s and throughout World War II. They were used by the American military authorities to treat gonorrhoea among their troops, and by the Japanese to treat their soldiers' dysentery. Ironically, given its German origin, Winston Churchill recovered from pneumonia in North Africa towards the end of the war after treatment with a sulpha drug.

Prontosil was protected by patents, and its success helped to make Farben a vast chemical conglomerate. After World War II, the firm was broken up into three: BASF, now also well known in the plastics industry; and two chemical manufacturers, Hoechst and Bayer, which are today two of the three biggest drug companies in Europe, each with sales in 1993 totalling over £4 billion.²⁵

Sulphonamides turned out not to be magic bullets. Some of their ill-effects have already been mentioned. Allergic reactions and diarrhoea are quite common. Less frequently they can also sometimes cause sore gums or tongue, loss of appetite, nausea and vomiting, gut pain, headache, need to sleep, inability to sleep, dizziness and vertigo, numbness and tingling, hallucinations, depression, nervousness, apathy, confusion, nightmares, painful joints and muscles. Rare ill-effects include kidney failure, severe hepatitis, liver damage,

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severe anaemia, Stevens-Johnson syndrome (which can cause permanent eye damage) and Lyell's syndrome, in which the skin peels off in sheets.²⁶

Even in the 1930s, doctors found that sulphonamides increasingly did not work in cases of gonorrhoea: gonococci bacteria were becoming drug-resistant. In those days, drug resistance was a mystery. By the 1950s, around half of all meningococci, bacteria that cause meningitis, were resistant to sulphonamides, as were the *E. coli* that cause urinary tract infections. An analysis carried out in London between 1974 and 1978 found that three quarters of all strains of *Shigella dysenteriae*, the bacterial cause of dysentery, were sulphamide resistant.²⁷

Professor Thomas O'Brien of the Department of Medicine at Brigham and Women's Hospital, Boston, Massachusetts, is a leading authority on antibiotic resistance. I went to Boston to see him, and asked him how bacteria become resistant to sulphonamides. Initially, he explained, the drug works by blocking a bacterial enzyme involved in the synthesis of folic acid. However, in time, the bacteria simply get another enzyme to do the job. 'It's like in a factory – if the lights go out, somebody turns on the emergency generator.'

Because of their toxicity and because they often don't work, sulphonamides (with one exception) are now not much prescribed in Europe and North America, except for meningitis and urinary tract infections. The exception is co-trimoxazole, the combination of a sulpha drug with trimethoprim. As already mentioned, although it has the ill-effects of other sulphonamides, co-trimoxazole is a popular drug, prescribed for many common conditions including bronchitis and other respiratory tract infections, children's middle ear infections, and gonorrhoea, as well as cystitis and more serious infections such as typhoid fever.²⁶

SAFE SEX WITH PENICILLIN

Alexander Fleming first noticed the antibacterial power of penicillin in 1928, but he did not take his research far enough to make his discovery useful. This work was done by a team of scientists in Oxford led by Professor Howard Florey and Dr Ernst Chain, who became motivated by the imperative need for drugs for Allied troops in the war against Hitler's Germany.

In early 1940 Florey and Chain used up all the penicillin then manufactured in an attempt to save the life of an Oxford policeman who had developed septicaemia after cutting himself shaving. Despite recycling the drug from the patient's urine, the supply ran out, and he died. Yet within a few years penicillin replaced sulpho-namides as the general-purpose antimicrobial drug of choice, for two reasons. First, penicillins (in the original and also later forms) are relatively safe drugs, with fewer and milder ill-effects than sulpho-namides. Second, while Florey and Chain did not attempt to take out patents on penicillin, seeing it as a wonderful natural healer, American and then British pharmaceutical firms made it very profitable by patenting the manufacturing processes of as many varieties as they could devise.

Early on, penicillins became the drugs of choice for puerperal fever, bacterial pneumonia and meningitis, and bacterial sexually transmitted diseases. Professor O'Brien explained to me how penicillins work. 'Bacteria are tiny little organisms in a hostile world, that need to be protected,' he told me. 'They have a cell wall around them that protects them against trauma and shock. This is their home. They would swell and rupture without their protective cell wall. Penicillins sabotage the synthesis of the cell wall; so they pop – like popcorn.' All antibiotics in the very large betalactam family, including all penicillins and cephalosporins, work like this.

In the 1960s, women were liberated sexually by the contraceptive pill. Penicillin gave men sexual licence as from the 1940s. Production of penicillin was given a priority in the USA after its entry into World War II, second only to production of the atom bomb. In 1943 a total of 29 pounds of penicillin was manufactured. Ten years later the figure had risen by a factor of around 30,000, to just under 400 tons.

Healthy servicemen were given hefty doses of penicillin as protection against gonorrhoea and syphilis during the later years of World War II, and then later in Korea, Vietnam and wherever else in the world they have been based. Prostitutes were also dosed. Antibiotics thus became used rather like vaccination, prophylactically as a guard against an infection that a healthy person has not got, but might get. American GIs loved penicillin. Safe sex! British troops were pleased, too. In 1943, Churchill was faced with a problem. He was asked whether penicillin, then scarce, should be used to treat venereal diseases or battle wounds. His careful reply was: 'This valuable drug must on no account be wasted. It must be put to the best military use.'

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So preference was given to troops with VD who could most quickly be made fit to fight.

Penicillins are still often effective against a range of bacteria that are the microbiological cause of a variety of common childhood infections of the ear, nose, throat and lower respiratory tract, including streptococcal, staphylococcal and pneumococcal species. Paediatricians, the physicians who specialise in childhood medicine, took to penicillins in a big way from the start. In 1950, the British journal *The Practitioner* published a book in which various distinguished doctors contributed their 'Favourite Prescriptions'. The chapter on children was by Dr Philip Evans, then consultant at the Hospital for Sick Children at Great Ormond Street in London. He wrote: 'The most popular prescriptions in paediatrics are of antibiotics, because children so often suffer from acute infections . . . Penicillin is the standby, perhaps because one cannot give an overdose.' After specifying a recommended dose, he added: 'But in babies this amount is usually and harmlessly exceeded.'

In these early years, treatment with antibiotics was an event in the family. In 1950, I was ten years old and, in a letter to my father, wrote: 'I am just recovering from an attack of tonsillitis, and am hoping to be back at school by Monday. The doctor prescribed penicillin lozenges and M&B [a sulpha drug made by May and Baker, hence the 'M&B'] and as you realise, I wasn't exactly looking forward to them. Still, it turned out that the penicillin at least, did the trick.' (Or so I and the doctor thought at the time; later my tonsils, now known to be part of the body's immune defences against disease, were removed. Tonsillitis is usually not a bacterial but a viral infection. Oh, well . . .)

The first penicillins were 'natural', derived from moulds. These include benzyl penicillin (also known as penicillin G) and phenoxymethyl penicillin (penicillin V), both of which are still used, including for common infections of children. But as early as the 1940s, doctors were faced with a growing problem: penicillins increasingly simply did not work. Bacteria had evolved a weapon, known as betalactamase or penicillase, which attacks the drug itself, cutting its betalactam ring. Professor O'Brien explained: 'It's like a Patriot missile. The incoming Scud antibiotic molecules are intercepted.'

By the 1950s, various bacterial species were resistant to penicillin. The most fearful was *Staphylococcus aureus*, which can cause acute

and sometimes dangerous sepsis on or in the body, in the blood (septicaemia) and in vital organs.²⁸ Penicillin-resistant *S. aureus* made open-body surgery once again a hazardous procedure. 'I had a medical student classmate who died of staphylococcal sepsis in the 1950s because it was multi-resistant,' Professor O'Brien told me.

Since the 1950s, drug companies have formulated successive generations of penicillins in an attempt to keep one step ahead of resistant bacteria. 'This vast and very profitable market has been driven by resistance,' says Dr O'Brien. In the late 1950s, the British firm Beecham, not until then a drug company, devised synthetic penicillin specifically designed to combat betalactamase, of which methicillin, cloxacillin and flucloxacillin are still on the market. In due course, though, *Staphylococcus aureus* evolved a new resistance mechanism, and developed into what is known as 'MRSA' (methicillin-resistant *S. aureus*). This superbug is now a major menace, for penicillins of any type now rarely work against it. '*Staph. aureus* that are sensitive to penicillin are collectors' items,' stated a 1990 review.²⁹

Other bacteria whose danger to humans is increased by frequent resistance to penicillins include those that cause pneumonia and meningitis, as well as invasive hospital infections. One group of drugs, the carboxypenicillins, have been devised specifically against *Pseudomonas aeruginosa*, now a troublesome hospital pathogen.

The story of the development of penicillins, and of the other betalactam drugs, notably the cephalosporins, is a story of science and industry wrestling with ever-evolving nature. The most popular antibiotics devised for use in general practice are the aminopenicillin family, including amoxycillin and ampicillin. Like other penicillins, these occasionally cause sickness, diarrhoea and allergic reactions²⁴ but usually work against a variety of bacterial infections. In 1989, the world's top-selling antibiotic was reckoned to be SmithKline Beecham's Amoxil, an amoxycillin, with an annual market value then of US\$368,500,000.³⁰ In the UK, successive generations of cephalosporins, which are increasingly expensive, are mostly reserved for use in hospitals before surgery, and for invasive infections. In the USA, cephalosporins are vigorously promoted by industry for use in general practice.

From the point of view of the general practitioner and the patient in the community, penicillin of one type or another is usually effective treatment. It is true that if you take regular courses of

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penicillin, in childhood or as an adult, you are sooner or later likely to suffer allergic reactions as your body loses its ability to absorb the poison of the drug, so that the drug becomes unusable. It is also true that 'safer' antibiotics such as penicillin are all the more likely to be prescribed, and this increases the risk of breeding superinfections and superbugs in your gut, which may cause serious untreatable infections. In general practice, penicillins are also often prescribed for illnesses that are not infectious, for infections that are not bacterial, and for bacterial infections better treated with milder remedies, or best left to clear up by themselves.

The use of any antibiotic puts selective pressure on any bacteria to evolve drug resistance. Routine dosing with penicillin of vast numbers of men whose sexual behaviour put them at high risk of sexually transmitted diseases has turned out to have had disastrous consequences, originally unforeseen. In the mid-1970s, drug-resistant *Neisseria gonorrhoeae* spread all over the world. One source was the Philippines, where during the Vietnam war US servicemen and local prostitutes had been routinely given heavy doses of penicillin as protection against gonorrhoea. As a result, the gonococci evolved and acquired a betalactamase that was – and is – resistant to any dose of penicillin. Karma! By the mid-1980s, between one third and one half of all gonococci in many countries had become resistant to penicillin.

In any case gonorrhoea remains a worldwide epidemic and the disease is flaring up within inner-city areas in the United States. A report in *Scientific American* published in 1991³¹ states:

The re-emergence of bacterial sexually transmitted diseases (STDs) in young, black and Hispanic inner-city poor populations, coupled with the rising incidence of AIDS and other viral STDs, has created a demand for public health care and preventive interventions that exceeds the capacity of many systems to provide diagnostic and treatment services.

In plainer language, this means that the environments of inner cities now are such as to create new cauldrons of uncontrollable bacterial contagion. Reports in the 1990s have identified gonococci in Britain, as elsewhere in the world, that are resistant not only to penicillin but also to cephalosporins, tetracyclines, the aminoglycoside spectinomycin, and even to quinolones.^{32,33} Widespread multi drug-

resistant gonorrhoea, now threatened, would be a public health catastrophe.

Penicillins remain far and away the most commonly used antibiotics. In 1987, a study carried out for the US National Institutes of Health estimated that world production of all penicillin for human and animal use in 1980 was 17,000 tons, almost two-thirds of the 25,000 tons of all types of antibiotic manufactured in that year.³⁴

STREPTOMYCIN: PAYDIRT

Back in the USA in the 1940s, streptomycin was the first all-American antibiotic. It was identified at the University of New Jersey at Rutgers by Professor Selman Waksman, a soil biologist, who deduced that micro-organisms with antimicrobial properties would be found in earth. After a meticulous search with a team funded by the local drug firm, Merck of Rahway, Waksman and his collaborators isolated streptomycin in 1944.

Streptomycin, an aminoglycoside antibiotic, was an immediate sensation because, as well as working against a number of bacteria, it can kill *Mycobacterium tuberculosis*. The fortunes of Merck were founded on streptomycin. In 1948, penicillin and streptomycin alone accounted for more than half of the drug industry's total income from the sale of patented drugs, and in that year of the \$191 million export sales for all drugs from the USA, almost half came from antibiotics, mostly streptomycin and penicillin.³⁵ Now merged as Merck Sharp and Dohme, this American-based multinational was in 1994 the biggest drug firm in the world, with annual sales in 1993 of \$8,822,000,000.^{25,30}

Tuberculosis was identified as a bacterial infection by the German bacteriologist Robert Koch in 1882. This knowledge created over half a century of paranoia: the invisible germ that causes tuberculosis seemed invincible, even though the rates of suffering and death from the disease steadily decreased during the twentieth century. The first scientist to discover a drug that really worked against tuberculosis could expect the tumultuous acclaim that would now be enjoyed by a scientist who found a successful treatment for AIDS. So it proved: Waksman was awarded a Nobel prize in 1952 for streptomycin, following Fleming, Florey and Chain, who had shared one in 1945 for penicillin. Waksman

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became rich on the royalties from streptomycin, and a massive Waksman Institute was built at Rutgers.

First impressions are often lasting impressions. The first animal and human trials of streptomycin cleared it as a safe drug, and it was acclaimed as the answer to tuberculosis. Nevertheless, streptomycin and other aminoglycosides turned out to be unusually toxic.

As already mentioned, streptomycin can damage the ear, on rare occasions causing progressive and sometimes permanent deafness and the loss of the sense of balance. Other more common ill-effects include nausea, fever, numbness, kidney damage, and allergic reactions. Moreover, bacteria soon developed shields against aminoglycosides; resistant strains of *Mycobacterium tuberculosis* were first reported as early as 1946.

Because of its toxicity and also because it is now often ineffective, streptomycin is no longer much prescribed in developed countries. Once used to treat a multitude of diseases³⁶ it is now recommended only as one of a combination of drugs or else as a fall-back option for tuberculosis and a few other serious bacterial infections such as brucellosis and bubonic plague.¹⁰

In the Third World, however, streptomycin is a popular drug, sold over the counter and in markets as a remedy for colds and coughs, and prescribed for trivial bacterial infections. As reported by Dianna Melrose of Oxfam³⁷, the Indian doctor Mira Shiva has stated that the use of streptomycin, in combination with penicillin and chloramphenicol,

for ordinary infections is creating increasing problems for developing countries like ours. Primary resistance of tuberculosis to streptomycin which is one of the first-line drugs is a calamity. We can't afford expensive second-line drugs. Further infection of individuals with resistant tuberculosis mycobacteria helps in making the situation worse.

THE CHLORAMPHENICOL GUSHER

After streptomycin, two further types of antibiotic were first developed in the United States in the late 1940s. First was chloramphenicol in 1947, discovered by scientists at Yale University. The research was funded by Parke-Davis, who still market the drug under

the brand name Chloromycetin. Next were the first tetracyclines, developed and still marketed by Lederle and Pfizer with the brand names Aureomycin and Terramycin. All these drugs work against bacteria in similar ways to streptomycin, and can be effective against a great range of bacterial species, including some unaffected by penicillins.

In the late 1940s, American drug firms managed to persuade the US Patents Office that antibiotics, even those that are products of nature, could be patented as authentic inventions. This is why there are now such a vast array of antibiotics on the market: every firm wants to own a slice of the action. With the patent rights on chloramphenicol secured, Parke-Davis had capped a drug gusher. The firm went from nowhere in particular to No. 1 in the US market in 1951, with sales of \$52 million in that year from Chloromycetin. Sales steadily increased throughout the decade. Physicians loved chloramphenicol – it worked. It can be effective against a great range of bacteria, including those that are the microbiological cause of whooping cough, diphtheria, gastroenteritis, dysentery, meningitis, gonorrhoea, cholera, anthrax, and infections in the body and blood.

But what the original clinical trials had not picked up is that chloramphenicol has a snag. As well as some of the usual ill-effects of antibiotics, it can sometimes kill people. In 1952, alerted by reports from observant physicians, the US Food and Drug Administration, together with the National Research Council, confirmed that chloramphenicol can have a deadly effect on bone marrow. It is now known that anything between one in 10,000 and one in 40,000 people given the drug, develop a severe irreversible 'aplastic' anaemia, caused by suppression of blood-cell formation in bone marrow.²⁴ A standard textbook states: 'It can appear during treatment, but it often appears long after treatment has ended. It is not related to the dose of the drug. The prognosis is very poor, with a high percentage of fatalities.'¹⁰

Chloramphenicol is especially dangerous for babies.²⁴ In the 1950s, hospital doctors were worried by 'grey baby syndrome': occasionally, premature babies were turning grey, going into shock and dying. At first nobody knew why. Then researchers had an idea. In those days – a time of great enthusiasm for antibiotics – premature babies were commonly given 'prophylactic cover' just in case they fell victim to a hospital infection. Initially, it was assumed that the infants were well protected, the thinking being rather like that of

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enthusiastic growers who spray seedlings with insecticides to keep off pests. But could it be that the antibiotics were killing the grey babies?

The answer was yes. In 1959, the *New England Journal of Medicine*³⁸ reported a survey in which a total of 126 premature babies were allotted to four treatment groups. Half were given penicillin and streptomycin or else no drug treatment: less than a fifth died. Half were given chloramphenicol alone or with other antibiotics: more than three-fifths died. The findings of the survey were agreed to be conclusive, and babies were taken off chloramphenicol.

The *British Medical Journal* published an editorial in 1952³⁸ stating, of chloramphenicol, that 'The only absolute and imperative indication for its use is typhoid fever.' In 1961 another editorial³⁸ written with reference to the 'grey baby' syndrome cited work questioning whether it is possible to define a safe dose of chloramphenicol, and concluded that deaths from aplastic anaemia caused by the drug had probably been under-recorded.

The patent on chloramphenicol has now run out; any drug firm can market it. The data sheets circulated by the pharmaceutical industry to general practitioners in Britain now include an explicit warning³⁹:

Chloramphenicol is a potent therapeutic agent and should not be used for trivial infections. It should be administered according to the instructions of a medical practitioner. It is recommended that chloramphenicol should be reserved for use in typhoid fever, *Haemophilus influenzae* meningitis, serious chest infections and situations where . . . no other antibiotic would suffice.

So in Europe and North America, chloramphenicol is now not much used. Physicians do still prescribe it from time to time, though, for an ironic reason that applies to all antibiotics. If an antibiotic is cheap and relatively safe, like penicillin, it will be used a lot. The result is that drug-resistant superbugs become epidemic and so the drug is liable to become progressively useless. On the other hand, if an antibiotic is expensive, or relatively hazardous like chloramphenicol, and its dangers are well known to physicians with access to safer alternatives, it will be used only occasionally. The result is that bacteria are less likely to develop resistance to this drug, and so it is most likely to work against infection. Antibiotic chemotherapy

obeys a version of Sod's Law: as time goes by, safe drugs don't work, and the drugs that do work may well be dangerous. Sometimes the drug that is most likely to damage you is most likely to damage bugs.

By contrast with Western countries, chloramphenicol is still a common drug in the Third World, where typhoid is endemic, and it is marketed by many manufacturers, foreign and local. Dianna Melrose reported that in 1981 she was offered the drug in Yemen for uncomplicated diarrhoea. A World Health Organisation worker in Ethiopia noted in 1977 that a hundred people attending one health station got through 5000 capsules and vials of tetracycline, streptomycin and penicillin, and 2000 capsules of chloramphenicol, in three months. A VSO worker in Nepal, also quoted by Dianna Melrose, reported in 1979 that it was commonplace to see people buying capsules of tetracycline and chloramphenicol for children with fever or diarrhoea. In the 1990s chloramphenicol remained a common drug in Africa and Asia.

The consequences have been disastrous. The shigella and *Salmonella typhi* bacilli that are the microbiological causes of dysentery and typhoid have developed superbug versions resistant to chloramphenicol and other antibiotics all over the world. Dysentery, a major worldwide epidemic killer in the nineteenth century, faded and had become uncommon by the 1920s, but starting in the 1960s, explosive outbreaks caused by drug-resistant superbugs have killed tens of thousands of people in Central America, Asia and Africa. In 1988, the World Health Organisation reported in its *Guidelines for the control of epidemics due to Shigella dysenteriae*⁴⁰: 'As resistance to sulfonamides, streptomycin, tetracyclines and chloramphenicol is common, these drugs should never be used until strains have been demonstrated to be susceptible to them.' In developing countries, dysentery is now often close to untreatable with any available antibiotics.

TETRACYCLINES: THE MAGIC BOMB

Throughout the 1940s, research scientists in America and Europe searched for the superdrug: an antibiotic active against the greatest number of bacterial species. Imagine! A drug that kills all known germs, dead! The quest for the ultimate germicide was initially rewarded with chlortetracycline, isolated in the USA like streptomycin and chloramphenicol from soil samples. The successful team who

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struck the drug equivalent of oil this time was led by Professor Benjamin Duggar, working for Lederle. Chlortetracycline, first marketed in 1948, and then later tetracyclines, proved to be the broadest spectrum antibiotics yet identified and accepted by regulators as safe in use.

From the start, physicians loved tetracycline, using it not so much as a magic bullet as a magic bomb. Marketed as the most powerful and effective antibiotics, which indeed they can be as treatment of many bacterial infections, tetracyclines are now second in world sales only to penicillins. They remain commonly prescribed for ear, nose and throat, gut, urinary tract and sexually transmitted bacterial infections, and also for acne. The 5000 tons of tetracyclines manufactured worldwide in 1990, for use as human medicine and also for use on animals and on plants, is expected to double to 10,000 tons by the year 2000.³⁴ In the UK over 20 branded tetracyclines as well as generic versions are on the market.

In his remarkable book *The Prize*,⁴¹ Daniel Yergin argues that more than any other resource, oil has, for better or worse, shaped the modern world and our place in it. A similar claim can be made for antibiotics. Certainly, the vision of the American industrialists responsible for the commercial exploitation of antibiotics in the 'golden years' beginning in the late 1940s, was as focused as that of the oilmen of the previous century.

Antibiotics are treasure that is consumed. Like other treasure such as gold and art, the value of drugs is maximised by control of supply. Like other consumer goods such as cars and computers, the value of drugs is sustained by obsolescence. In the case of drugs, ownership and control involves patenting and branding, and obsolescence enables the development of successive new patented branded products. The pioneers of the modern pharmaceutical industry believed with reason that this could be the realisation of their dreams, the secret of their success.

In 1948 Cyanamid/Lederle owned chlortetracycline, branded as Aureomycin (which is still on the market). In 1949 Pfizer developed a new tetracycline, oxytetracycline, owned and branded as Terramycin (also still on the market).

From the start, Pfizer marketed Terramycin with phenomenal energy.

In 1935 the firm's total sales had been \$5 million. By 1953 it was the market leader in the UK. In 1957 its total sales were \$200 million,

with profits of \$23,900,000, almost all from broad-spectrum antibiotics.⁴² In 1990 Pfizer was the twelfth biggest pharmaceutical company in the world, with annual sales of over \$3.5 billion.³⁰ The fortunes of Cyanamid/Lederle similarly depended on tetracycline: in the early 1950s their profits were entirely from broad-spectrum antibiotics, whose sales between 1954 and 1961 totalled over \$300 million.⁴²

The tetracycline story became more complex and dramatic in the 1950s. The race was on to develop new versions of tetracycline that could be protected by patent.

In 1952 scientists working for Pfizer isolated tetracycline itself by removing the chlorine atom from chlortetracycline, and applied for this new formulation to be patented. In 1953 Cyanamid and two other companies, Heyden and Bristol, also claimed patent rights on tetracycline. Industry had reason to fear that the US Patent Office would insist that tetracycline was unpatentable, on the grounds that it was not sufficiently different from chlortetracycline, in which case the profits of the initial market leaders would be liable to collapse. In the event, the Patent Office upheld industry's ownership of tetracycline.

As long as tetracycline in its various forms was protected by patent its branded versions were immensely profitable. However, in 1961 the UK business was disturbed by a new company, DDSA Pharmaceuticals, who marketed what was in effect a generic version of the drug with the apt name Econamycin, at a tenth of the price charged to the National Health Service by companies owning other branded versions.

Enoch Powell, then UK Minister of Health, gave DDSA a contract to supply hospitals. Pfizer challenged the UK government; the case eventually went to the House of Lords, then the ultimate court of appeal in the UK, where in an extraordinary decision the government's right to override a drug patent in the national interest was upheld.

In the early 1970s the patents on tetracyclines expired; they are now cheap drugs, in branded as well as generic versions.

Unfortunately though, like other early antibiotics, tetracyclines have turned out to be troublesome drugs. Apart from their ill-effects on teeth and bones, which make them inappropriate for pregnant women and children, they can affect kidney function, as well as causing nausea, diarrhoea and allergic reactions in common with

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many types of antibiotic. Other ill-effects include sore tongue, difficulty in swallowing, sore anus, and green/yellow faeces.²⁴ The immediate toxicity of tetracyclines is less problematic than their longer-term ill-effects. Because they are so very broad spectrum and penetrative, they can devastate gut flora, and superinfections with invasive bacteria or fungi such as *Candida albicans*, are common consequences of tetracycline treatment.

While tetracyclines check or kill bacteria in much the same way as aminoglycosides like streptomycin or chloramphenicol, the mechanism by which bacteria develop resistance to tetracyclines is different. 'It's like a bilge pump,' Professor O'Brien explained to me. 'The bacteria develop this marvellous ability: the bacterium expels the drug right out of the cell again.' What this means is that, when bacteria become resistant to tetracyclines, the drug is not absorbed and degraded, but is ejected into the outside environment.

Because of their ill-effects, tetracyclines are now not so often used in many European countries and in North America. However, they are massively used by farmers, to prevent and treat bacterial infection in intensively reared animals, and also as growth promoters. They are also used in horticulture. In addition, and in common with all potent antibiotics that are out of patent and therefore cheap, tetracyclines are used in massive amounts throughout the developing world. Thus, every year, an unknown fraction of some thousands of tons of tetracycline is being pumped out of humans and animals into the environment, in biologically active form. What effect this is having on us and the planet is also unknown.

THE GOLDEN AGE FADES

After tetracycline, other antibiotics, mentioned briefly earlier in this book, were identified and marketed. Erythromycin, in the macrolide group, remains a valuable drug. The relative toxicity and high cost of vancomycin has given it a clinical advantage: it still works against the *Staphylococcus aureus* superbug. Hospital doctors in Europe and North America usually now hold some antibiotics in reserve, specifically for use against dangerous superbugs, which is lucky for hospital patients in rich countries.

The lincosamides, including clindamycin and lincomycin, gained a bad reputation after the discovery that they can (rarely) cause

potentially deadly pseudomembranous colitis which in rare cases kills people, but other antibiotics can also cause this vicious infection.²⁵

And in the late 1950s the first antifungal, nystatin, was marketed.⁹

QUINOLONES: GENE GENIES

With one exception, since the 1960s no new group of antibiotics has been marketed. As the patents on older products have expired, much of the commercial thrill of the golden age, when antibiotics dominated drug sales, has gone. Now, the top-selling drugs are for non-infectious diseases. But antibiotics still have a big share of the world drug market: 11 percent of all drug sales in 1980, projected to rise to 15 percent in the year 2000 as the vast new markets in the developing world are thoroughly penetrated.³⁴

Quinolones are the one new family of antibiotics. These synthetic drugs include nalidixic acid, ciprofloxacin and norfloxacin. In the 1980s and 1990s they have been and are vigorously promoted for use against a great variety of bacterial infections. Quinolones work by wrecking the integrity of the bacterial chromosome. Scientists are generally confident that, while quinolones attack the DNA of bacteria, they have no effect on human DNA. If they did, the consequences would be extremely serious, because damage to DNA, the building blocks of life, in one generation will cause deformities in the next. So far, though, the argument that quinolones may be mutagenic is only theoretical.

The main agreed use of quinolones is for urinary tract infections. But industry has argued for them to be used for other common 'indications' (which is to say diseases). Interviewed in Bristol for this book, microbiologist Professor David Reeves, chairman of the working party on antibiotic use of the British Society for Antimicrobial Chemotherapy, said that industry 'has pushed quinolones very hard'. He explained that, 'with any new drug, the companies want to realise the return on their investment in the shortest possible time. So they will go for the widest range of indications.' In his opinion, 'Many quinolones are marginal antibiotics for treating respiratory infections. Yet the drug companies were keen to get respiratory infections as an indication, because if they were confined to urinary tract infections, you would be looking at a far smaller market.'

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Accepted uses for quinolones now include, as well as urinary and respiratory tract infections, those of the skin, soft tissue, bones, joints, gut, eyes, ears, nose and throat, and gonorrhoea. A recent indication being argued for is travellers' diarrhoea.

Industry and many scientists were at first very enthusiastic about the safety of using quinolones, but as so often happens with drugs, in time reports of ill-effects on patients have accumulated. While quinolones seem not to be particularly toxic, they do have a number of occasional ill-effects, including nausea, diarrhoea, stomach pain, skin reactions, headache, disorientation, visual disturbances, hallucinations, fits and, rarely, psychosis.^{10,43}

Methods now used to regulate and monitor the safety of drugs cannot be perfect. In 1991 a new quinolone, temafloxacin, was licensed for use in the UK, and around 20,000 prescriptions were issued for its branded version, Teflox, between October 1991 and June 1992.⁴⁴ In September 1991, the journal *Hospital Doctor*⁴⁵ had reported that: 'A tough new generation of quinolone antimicrobials is about to emerge in the UK . . . Much hope is being pinned on the first of the arrivals, temafloxacin, already licensed elsewhere in Europe.' Indications for use included urinary and respiratory tract infections (including pneumonia) and drug-resistant hospital bugs.

Then, on 6 June 1992, Dr Christina Carnegie, medical director of Abbott Laboratories, wrote to all physicians in the UK stating that Teflox had been withdrawn worldwide 'as a result of reported serious adverse reactions'.⁴⁶ These included blood disorders, liver and kidney problems, anaphylactic shock, and death. 'Although the reports of these serious adverse events are rare,' wrote Dr Carnegie, 'you should discontinue treatment in any patient currently receiving temafloxacin and replace it with an alternative therapy.' So happily, this unusually toxic quinolone is now off the market.

The main worries about quinolones are not, however, concerned with their toxicity. Could they conceivably be mutagenic in humans? It seems utterly unlikely; but as Professor Richard Lacey puts it⁴⁷, 'the question of mutagenicity is not resolved.' Conservative microbiologists such as Dr Lacey feel some unease about any drug that works by interfering with bacterial DNA, particularly when, as with quinolones, the drug is synthetic, with no analogy in nature. Although it is accepted by virtually all microbiologists that damage to bacterial DNA has no bearing on the integrity of human or any other eukaryotic cell structures, nature is still capable of nasty surprises.

Second, quinolones are similar to tetracyclines in two respects. First, the drug is not fully absorbed; some is excreted unchanged into the environment. Second, bacteria evolve resistance to quinolones by means of the 'bilge-pump' mechanism that expels or 'spits out' the drug. So what happens to the quinolones? Dr Tore Midtvedt is worried about this question. Writing in *Lancet* in 1989⁴⁸ he said:

More than ten million patients [have already] received ciprofloxacin, just one quinolone. Some of these drugs are used in veterinary medicine and in fish farming. The worldwide production of quinolones is not available but it seems reasonable to suppose that it runs into several thousands of kilograms.

It is astonishing that so little is known about their fate . . . If not broken down, quinolones must end up somewhere, but I know of no studies of their ultimate fate. I am surprised that drug registration authorities have allowed introduction of such potent drugs . . . without asking this question. The potential hazardous biological effects of quinolones should not be underestimated.

Talking to Dr Midtvedt in his laboratory at the Karolinska Institute in Stockholm, I asked him to elaborate. 'We now have drugs that are not broken down by any microbial enzymes – I'm talking about the quinolones,' he told me. The coastal fish farms in his native Norway are the most extensive in the world, and by the time of my visit in 1992, he had established that between 10,000 and 20,000 kilograms (11–22 tons) of quinolones had already been used to prevent or treat the infectious diseases inevitable when fish or any other creatures (humans included) are grossly overcrowded. 'In all environments in which it has been investigated, the quinolones will stay active in the water, just below the surface, for months and for years,' he told me. 'They will stay partly inside the wreck of the microbes they have inactivated and partly outside.' With what effect on marine life? And on human health? He couldn't say.

Dr Midtvedt was equally concerned about the use of quinolones to prevent and treat travellers' diarrhoea. Although quinolones work against diarrhoea, prophylactically and therapeutically, as already stated, taking any kind of antibiotic for simple diarrhoea is usually a bad idea: the condition, while often intensely unpleasant, is best left to resolve itself, or if severe, treated by rehydration. And the after-effects of antibiotics, quinolones especially, could be troublesome.

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'Now, about a hundred million people travel north to south every year,' said Dr Midtvedt. In many countries, quinolones are available without prescription. 'All those people going north to south will produce quite a lot of faeces down there, and they are not bringing their faeces back with them. And in the faeces you will have a substantial amount of quinolones. And the development of resistance will start in the south. And it has started. There are now many reports of resistance to some quinolone anti-diarrhoeal agents in those countries. Because the mechanism of resistance to quinolones is efflux – spitting out the active drug, like tetracycline – the drug will go from one microbial species to others.' The result is that quinolones are becoming ineffective against serious bacterial diseases. How many people in the African and Asian countries visited by those tourists who were anxious to settle their stomachs will suffer from infections made drug-resistant by quinolones imported into their environment? There is no way of knowing.

Like other antibiotics before them, quinolones may cause superinfections, in which normally friendly or harmless bacteria become dangerous by spreading into parts of the body where they normally have no place. A short report to this effect, from the Public Health Laboratory Service in Portsmouth, appeared in the *Lancet* in April 1992.⁴⁹ Lactobacilli, normally friendly flora that live in profusion in and around the vagina, and which protect women against invasion by potentially dangerous bacteria, were turning up in the blood of severely ill hospital patients. Because quinolones are regarded as unusually safe drugs, they are now often used extensively on hospital patients. They have a very broad spectrum, and wipe out many friendly and harmless bacterial species – but not lactobacilli, which happen to be invulnerable to quinolones. So, in the opinion of Dr Rosalind Maskell, consultant at St Mary's Hospital, Portsmouth, and an authority on urinary tract infections: 'The nearly uniform resistance to the quinolones suggests that the lactobacilli in the commensal [friendly or harmless] flora of patients treated with these agents, to which most other commensal species are sensitive, may multiply and assume a pathogenic role.' In other words, quinolones can turn women's most intimately friendly flora into enemies.

Dr Midtvedt regularly contributes the chapters on antibiotics to the annual *Side Effects of Drugs* edited by Professor Graham Dukes, lately of the World Health Organisation European region office in Copenhagen (who kindly wrote the Preface to this book).⁵⁰ I asked

him this question: 'As now used, do antibiotics do more harm than good?' He thought for a while, and then said: 'If you are taking the whole consumption – humans, animals, fish farming and so on – they are doing more harm than good.' I asked him when he himself used antibiotics. 'I have used them seldom: I have good health,' he said. 'Once in my lifetime I had a urinary tract infection. I took antibiotics for three days. I took the cheapest and the most narrow-spectrum one. It worked.' And for the future? 'The way we are using antibiotics, we are increasing our problems. We must reduce total consumption, and we must reduce the drugs that most promote resistance. And we have to find other treatments for infectious diseases.'

DOSING EVERYBODY ON THE PLANET

From industry's point of view, antibiotics are not now the most promising class of drug. But the market for antibacterial drugs continues to expand worldwide. The annual market value for antibiotics for human and also for animal use worldwide, was estimated by an expert group convened in 1984 by the US National Institutes of Health at US\$8,250 million in 1980 and US\$18,000 million in 1990, with a projected figure of US\$40,500 million in the year 2000.⁵¹

Annual production of antibiotics for human use worldwide has been estimated at around 25,000 tons in 1980 and 35,000 tons in 1990, with a projected figure of 50,000 tons in the year 2000.⁵²

The amount of drug in different courses of antibiotics varies. But given a rough average of seven grams for an average seven-day course, 35,000 tons a year works out at five billion courses of antibiotics every year: enough for one course every year for everybody on earth in the year 1990. Indeed, it was stated in 1982 of penicillin alone that: 'Today there is sufficient fermentation and production capacity worldwide to provide every individual on this planet with sufficient penicillin for one therapeutic treatment each year.'⁵³

People living in developed countries may have the impression that doctors are more cautious in their use of antibiotics nowadays. In general though, the trend is upwards. In England, the total number of prescriptions issued by general practitioners for antibiotics in 1980 was just over 43 million, which averages out at just under a course per person per year. Eleven years later the figure had increased

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remarkably, to just under 70 million, or close to one and a half courses per person per year.⁵⁴

At this rate, and given a 75 year lifespan, everybody in the UK will on average be taking antibiotics for around 750 days or over two years, during their lives. And this excludes antibiotics prescribed in hospital and by dentists, and any purchased over the counter in other countries.

These remarkable statistics of production and consumption would be testimony of unqualified benefit to humanity, if antibiotics were harmless, or at least almost always appropriately prescribed. But they are not.