# Antibiotic resistance: an increasing problem?

*It always has been, but there are things we can do*

Although the "antibiotic era" dates from Fleming's discovery of the effects of the fungus *Penicillium notatum* in 1928, not until 1940 could penicillin be produced in a sufficiently pure form to treat humans.[1] Ominously, a β lactamase (penicillinase) capable of inactivating penicillin was described in the previous year. Over the next few decades the production of new classes of antibiotics (derived from living organisms) and antimicrobials (synthesised chemicals) increased exponentially, and the burden of infection was lifted, especially in developed countries. In recent years concern has increased that the antibiotic era might be coming to an end—firstly, because the rate of production of new agents has diminished greatly and, secondly, because viruses, bacteria, fungi, protozoa, and parasites are showing great ingenuity in devising mechanisms for circumventing the killing activity of such agents.

So great is the concern that several committees both in the United Kingdom and elsewhere are examining different aspects of the problem. This week the House of Lords' Select Committee on Science and Technology has presented its conclusions (p 1261).[2][3] Its chairman, Lord Soulsby, an eminent veterinarian from Cambridge, said that the inquiry was an alarming experience and expressed concern that the misuse and overuse of antibiotics is undermining their effectiveness.

The report begs several questions. Firstly, is there a problem of antibiotic resistance? The answer is yes and no. Some bacteria still remain sensitive to long established treatments, including *Chlamydia trachomatis* to tetracyclines and macrolides, *Streptococcus pyogenes* to penicillin, and most anaerobes to metronidazole. (*Treponema pallidum* and penicillin used to be included in this list but the first resistant isolates have been encountered in Africa.) Against this, however, is the increasing array of resistance problems, including penicillin resistant pneumococci, multidrug resistant *Salmonella typhi*,[4] multidrug resistant Mycobacteria,[5] methicillin (and multidrug) resistant *Staphylococcus aureus* (MRSA), vancomycin insensitive MRSA (VISA),[6] and vancomycin resistant enterococci (VRE).[7] The problem is undoubtedly increasing: for example, penicillin resistant meningococci are emerging, and antiviral resistant HIV emerge even during treatment.[8]

The second question is, how does resistance arise? The first point to make is that resistance genes and mechanisms existed long before antibiotics were used. For example, antibiotic resistant bacteria have been isolated from deep within glaciers in Canada's high Arctic regions, estimated at 2000 years old.[9] The micro-organisms used to produce antibiotics must, by definition, be resistant and are thus a source of antibiotic resistance genes. Antibiotics are given not for their direct effect on humans but to kill an infecting pathogen. Unfortunately they are not so narrowly targeted and will try to kill any bacterium they encounter. The adult human composes some $10^{14}$ cells, but only 10% of these are human. The remainder are the bacteria, fungi, protozoa, worms, and even insects that make up our normal flora. Each time an antibiotic is administered the normal flora are also exposed. In addition, many antibiotics are excreted in an active form and thus environmental bacteria are exposed. Under optimal conditions bacteria double in number every 20 minutes; Britons, with our 2.4 children, have a doubling time of 60 years.

Bacteria thus have infinitely expandable and mutable populations to throw in waves at the barrier of antibiotics. Thus in the presence of antibiotics, resistant mutants have a selective advantage. Not only can the resistance be passed vertically from generation to generation; methods of horizontal gene transfer—for example, plasmids—have also evolved, and resistance can be passed to other species and genera. Furthermore, large plasmids encoding multidrug resistance can be as assembled by sequential addition of other mobile genetic elements (integrons and transposons). Examples of resistance genes originating in commensal or environmental bacteria and transferring to pathogens include tetracycline resistance from enterococci to pneumococci and gonococci, and erythromycin resistance from *Bacillus sphaericus* to *Bacteroides fragilis*.[10]

The next question is, who's fault is it? The report recognises that antibiotics are overused and misused in human and veterinary medicine, farming (growth promoters), aquaculture, and plant culture. It is fruitless to apportion blame. A more productive route is for all to recognise the problem and agree strategies to slow down the loss of important drugs from our therapeutic armamentarium.

The final and most important question is, what can we do to achieve this aim? The report makes several recommendations. These include encouraging the prudent use of antimicrobials by educating the public, increasing the emphasis on infection and antimicrobials in undergraduate and postgraduate medical curriculums, developing surveillance systems for antimicrobial resistance, and developing and applying evidence based guidelines on antibiotic use and

prescribing. In veterinary medicine the use of growth promoters such as virginiamycin, which belong to classes of antimicrobials likely to be used in human medicine, should be phased out. The veterinary use of antimicrobials such as fluoroquinolones, which are so important in treating human infection, should be used only in strictly defined circumstances. The report recognises that control of infection by proper hospital hygiene and vaccines will play a part in decreasing the use of antibiotics. It emphasises that we have insufficient information on the development, sources, mechanisms, and prevalence of resistance and recommends that this should be urgently addressed. It also

recommends that the government should develop an overall strategy (and allocate the necessary resources) for safeguarding the effectiveness of antimicrobials.

Finally, we must not neglect international aspects. It is no use the United Kingdom or the European Union acting alone. Bacteria do not recognise international boundaries, and intercontinental spread of resistant bacteria is well described.[11] [12]

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# Drugs in British prisons

*Policies need outside scrutiny if they are to do more good than harm*

The prison service seems to be losing its own "war on drugs." Blood borne virus transmission[1] continues despite improved access to harm reduction measures: another HIV seroconversion in a Scottish jail occurred in 1997. Moreover, the prison service has failed to meet its 1996-7 key performance indicator on drugs,[2] which was for the rate of positive results from random mandatory drugs tests to be lower in the fourth quarter than in the first (in the first quarter 3269/13 594 (24.0%) of tests yielded positive results, in the fourth 24.2%). Yet the prisons' key performance indicator on drugs was always misguided, because it avoided real targets,[3] such as reducing the use of opiates inside, reducing the prevalence of injecting inside, and increasing the proportion of accommodation given over to drugs free wings. The main problem is that research inside prisons is not done to outside standards and new policies are not evaluated.

Scotland, and Glasgow in particular, has an injecting culture, including in prisons. At Barlinnie Prison in Glasgow, Scotland's largest prison, 15% of those tested in the first eight months of random mandatory drugs testing tested positive for opiates.[4] This implies that 22-45% of inmates are using heroin inside the prison.[5] Because of heroin's short urinary half life and the relative infrequency of inside injecting—on average, six injections in four weeks—random mandatory drugs testing seriously underestimates the percentage of prisoners who are using opiates.[5] Willing anonymous salivary HIV (WASH) studies are an internationally recognised

method of estimating without bias the prevalence of HIV and injecting risk behaviours in prisons.[6]

Extrapolating from the percentage positive for opiates in random testing to the higher proportion who are inside users of heroin requires information from prisoners. Data from interviews in 1994-5 with 1009 prisoners in England and Wales about the impact of imprisonment on their use of injectable drugs (opiates or stimulants) were given their first public airing this winter by John Strang at a meeting in Glasgow. Strang identified the tenacity of opiate use in prison. In English prisons use of injectable drugs was often by non-injection routes, but when injection did occur it was high risk. A third of prisoners (324/1009) reported lifetime use of opiates; 22% had injected but only 2% (24) reported injecting in prison, much lower than in Scotland.[5] Overall, however, Strang found 184 users of injectable drugs in prison, and 149 (15% of interviewees) had taken opiates. Parliamentary questions have revealed the rate of opiate positive results on random testing in April to September 1997 in those prisons where Strang interviewed prisoners to be 5.4%. Against the prisoners' self reported inside use of opiates of 15%, the opiate positive rate underestimates it by nearly threefold if no major change in behaviour has occurred.

Prisons need to have the same general policies as drug treatment services on the outside; they should give priority to getting prisoners "off injecting" before getting them "off drugs" and to rehabilitation of inside users of opiates. Underestimating the numbers taking

opiates through random mandatory drugs testing risks serious under-resourcing of prisoners' health care.[5] Moreover, the policy of random mandatory drugs testing is not delivering reductions in opiate use. Worse, forewarned that such testing would create a new market for heroin in prisons—because heroin has a shorter half life than cannabis and thus is less likely to be detected by random testing[3]—what steps has the prison service taken to estimate the incidence of initiation into heroin use, and addiction, in prisons as a result of the policy? The answer "none" is not acceptable. Audit—prisoner surveys—could be.

Only four out of l9 prisons inspected in England and Wales in 1996-7 were conducting internal audit on any aspect of health care in prison.[7] It took external audit to document that only 5% of prisoners had been offered vaccination against hepatitis B—in or out of prison[5]—and that only 15 out of 276 of Glasgow's incarcerated methadone clients had their prescription continued in prison.[8] This issue, together with the frequency of inside injecting, was to have been followed up in Europe wide study of willing anonymous salivary HIV studies in 1997. HM Inspectorate of Prisons is also set to expand its use of prisoner completed questionnaires.[7] Outside standards should apply[7] in the commissioning[9] and publication of prison based research. An initiative by the Chief Medical Officer for Scotland and the Scottish Prison Service for an independent working party under his chairmanship on public health issues in prisons heralds those outside standards and is good news.

The "big idea" of Keith Helliwell, Britain's drugs Tsar, is to concentrate resources on drug users who regularly resort to crime—which is sensible—and for courts to take them out of the penal system through compulsory treatment orders—which is unproved. A court based randomised trial of this approach for proof of efficacy, safety, and quality would be truly innovative.[10] The brief could be: once convicted, individuals who have been assessed as eligible for a treatment order or prison are asked for informed consent to randomisation. Those who agree are duly randomised; those who withhold consent have their case determined by the judge. All are followed up—whether randomised or not—to compare recidivism and health related outcomes. Good research informs. The new British drugs strategy—in prisons and outside—needs academic credibility,[10] not credulousness or political spin.[9]

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# Leukotriene modifiers in the treatment of asthma

*Look promising across the board of asthma severity*

Leukotriene modifiers are an entirely new class of asthma treatment, which have entered clinical practice in 1996-7 in several countries including Britain, Japan, and the United States. Their development is an example of rational drug design following the elucidation of leukotriene structures in 1979-80 and the subsequent confirmation of their pathophysiological role as inflammatory mediators in asthma.[1]

There are two types of leukotriene modifier: leukotriene synthesis inhibitors and cysteinyl leukotriene receptor antagonists.[2] Both are used to block the bronchoconstrictor and pro-inflammatory activity of cysteinyl leukotrienes within the asthmatic airway. Cysteinyl leukotrienes ($LTC_4$, $LTD_4$, and $LTE_4$) were originally identified as long lasting smooth muscle spasmogens and collectively termed "slow reacting substance of anaphylaxis" (SRS-A). They are now known to be metabolites of arachidonic acid formed by the 5-lipoxygenase pathway[1] and are produced almost exclusively by inflammatory leucocytes, especially mast cells, basophils, and eosinophils. The leukotriene receptor antagonists block the activity of cysteinyl leukotrienes at their receptors ($CysLT_1$) on bronchial smooth muscle and elsewhere, while the leukotriene synthesis inhibitors block the synthesis of all leukotrienes by interrupting the 5-lipoxygenase pathway.[2]

Cysteinyl leukotrienes are among the most potent constrictors of human bronchial smooth muscle known, being 10-5000 times more potent in vitro than other bronchoconstrictor agents such as histamine, prostanoids, or platelet activating factor.[3] [4] When inhaled by normal or asthmatic subjects, they cause sustained bronchoconstriction lasting 30-45 minutes. Asthmatic patients are hyperresponsive to the bronchoconstrictor effects of cysteinyl leukotrienes, especially $LTE_4$. Their ability to impair airflow is augmented by airway oedema, mucus hypersecretion, and reduced mucociliary clearance. After a single dose, inhaled cysteinyl leukotrienes induce non-specific bronchial hyperresponsiveness for up to one week.[3] They have been detected in the fluid from bronchoalveolar lavage and urine of asthmatic subjects after inhaled allergen challenge and in the urine after acute spontaneous exacerbations.[5] [6] Cysteinyl leukotrienes are potent and

selective chemoattractants for human eosinophils[4 7] and may also be involved in airway remodelling in asthma, causing hyperplasia of bronchial smooth muscle and airway epithelium.[4]

The important contributions of cysteinyl leukotrienes to airway dysfunction and eosinophilia in asthma have been confirmed by clinical trials of leukotriene modifying agents.[2 8 9] Although first generation compounds such as FPL 55712 lacked potency and were toxic, the second generation antagonists such as montelukast, pranlukast, and zafirlukast show much greater potency against inhaled leukotrienes, while the synthesis inhibitors such as zileuton and BAYx1005 can reduce leukotriene synthesis to negligible levels.

Most early clinical trials of leukotriene modifiers in asthmatic subjects have used the inhaled allergen challenge model to assess their effect on the early bronchoconstrictor response and on the late bronchoconstrictor response, which is associated with leucocyte influx and increased bronchial responsiveness.[10] Both types of leukotriene modifier block the early response by 70-80%, showing that cysteinyl leukotrienes released from mast cells are the most important mediators of acute allergic bronchoconstriction.[2 8 9] More surprisingly, they also consistently block up to 70% of the late response, showing that late bronchoconstriction is mostly due to cysteinyl leukotriene release, probably from infiltrating eosinophils. The eosinophilia itself is inhibited by leukotriene modifiers, suggesting that eosinophil influx is partly induced by the chemoattractant activity of leukotrienes released during the early response.

In patients with asthma, leukotriene modifiers improve baseline lung function and reduce bronchial hyperresponsiveness for several months.[11–14] Treatment with oral montelukast, zafirlukast, or zileuton significantly improves many clinical outcome measures, including night time awakenings, daytime symptom scores, and use of $\beta_2$ agonists.[11–13] The size of these effects is similar to that seen in patients treated with 400-500 μg of inhaled beclomethasone daily. An anti-inflammatory effect is also suggested by significant reductions in eosinophil counts in the sputum and blood of asthmatic patients treated with montelukast or zileuton, and by significant reductions in the use of corticosteroids.[9 11]

Present evidence suggests that these drugs may be especially useful in defined patient populations.[8] They are effective in blocking bronchoconstriction after challenge of susceptible asthmatic patients with exercise or cold, dry air, with a particularly dramatic effect on shortening recovery time. They are also effective in blocking adverse reactions to aspirin and other non-steroidal anti-inflammatory drugs in susceptible asthmatic patients.[15] Even in the absence of exposure to non-steroidal anti-inflammatory drugs, persistent severe asthma in patients sensitive to aspirin is associated with chronic overproduction of cysteinyl leukotrienes, which may be caused by a genetic anomaly in the luekotriene synthetic pathway.[16 17] Conversely, a subgroup of patients in whom leukotrienes may play relatively little role in asthma pathophysiology has been identified, reinforcing the need to target leukotriene modifiers to appropriate patient groups for maximal benefit.[18]

Although most trials have been performed in patients with mild or moderate asthma, some evidence suggests that leukotriene modifiers may also be useful in more severe asthma, as their effects are additive to those achieved with moderate or high doses of inhaled corticosteroids.[8] The corticosteroid sparing effects of these drugs may prove to be important in reducing the side effects of chronic treatment with oral corticosteroids. Although their anti-inflammatory effects are likely to be less pronounced than those of high dose corticosteroids, their excellent side effect profile and their availability as oral drugs are likely to ensure that compliance with treatment is substantially better than for inhaled corticosteroids.

While interrupting the leukotriene pathway offers a new opportunity for treating asthma, the position of such drugs in the asthma armamentarium has not yet been firmly established. Further effectiveness studies are needed to determine the true value of this oral anti-asthma treatment. From the available data, leukotriene modifiers seem to act across the whole spectrum of asthma severity, although it will be important to distinguish responders from non-responders.

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# Functional neurosurgery for Parkinson's disease

*Has come a long way, though much remains experimental*

Acquired brain lesions have long been known to modify the symptoms and signs of Parkinson's disease. After many false starts, in which various surgical lesions abolished tremor only at the expense of a hemiplegia, and with the advent of stereotactic techniques, neurosurgeons found that discrete lesions of the globus pallidus or thalamus could improve features of parkinsonism without (usually) causing a hemiplegia. Tremor appeared most responsive to thalamotomy, so this procedure became widely applied in the 1950s and 60s. Despite often permanent relief of tremor and rigidity, thalamotomy had no effect on akinesia, the core disabling feature of Parkinson's disease. Also, although unilateral surgery in this disease, which classically presents unilaterally or asymmetrically, was associated with low morbidity, as the disease progressed a second, contralateral, lesion was often made but with an unacceptably high (25%) incidence of pseudobulbar speech and swallowing difficulties. After the introduction of levodopa in 1967, the first treatment that dramatically alleviated akinesia, surgery took a dive until the mid-1980s, since when surgical approaches to treating Parkinson's disease have experienced a renaissance.

While using a stimulating electrode to guide lesion placement for Vim thalamotomy, Benabid's group in Grenoble found that high frequency discharges could abolish tremor.[1] Why not, therefore, simply insert a chronic stimulating electrode without making a destructive lesion? This technique of deep brain stimulation provided excellent control of tremor in patients with both Parkinson's disease and essential tremor.[1] The mechanism underlying this effect is still debated, but since deep brain stimulation mimics the effects of a lesion, the functional result of the high frequencies used is probably inhibition, rather than stimulation, of the neurons surrounding the electrode tip. Importantly, bilateral stimulation could be applied, or stimulation applied on the second side after a previous destructive lesion, without the high morbidity previously associated with bilateral destructive lesions. Akinesia, however, was still not alleviated.

Current models of striatal output pathways, supported by in vivo recording and lesioning studies in primates with parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), indicate that both the subthalamic nucleus and the internal pallidum are overactive in parkinsonism.[2] In 1982 Laitinen et al reported that selective posteroventral pallidotomy produced major improvements in akinesia, rigidity, tremor, freezing, falls, speech, and also levodopa induced involuntary movements (dyskinesias).[3] Many centres have since investigated pallidotomy in Parkinson's disease. Some use only imaging and stimulation with the lesioning electrode to determine lesion location, while others argue that the optimal site can be properly delineated only by additional microelectrode recordings, a debate that remains unresolved.

Generally unilateral pallidotomy dramatically reduces contralateral, and mildly reduces ipsilateral, levodopa induced dyskinesias (incidentally, the opposite of what existing, and therefore inadequate, models would predict). The degree of benefit to off period parkinsonian features is usually much more modest, about 20-30%.[4-6] Some centres have reported negligible morbidity, but others have experienced occasional deaths or stroke or other unwanted sequelae secondary to haemorrhage, infarct, or misplaced lesions. Some have reported low morbidity after bilateral (sometimes simultaneous) lesions, but others have experienced a high rate of neuropsychological (abulia) or pseudobulbar sequelae.

Might pallidal stimulation produce equivalent benefits with lower morbidity, especially when applied bilaterally, or contralateral to a prior destructive lesion? In this rapidly evolving field, few full peer reviewed papers have yet appeared. Unilateral or bilateral pallidal stimulation also appears to reduce levodopa induced dyskinesias. However, the stimulation site giving maximal suppression of dyskinesias may be associated with worsening of akinesia, whereas electrode settings that improve akinesia are less helpful for dyskinesias.[7] Rigidity seems to be improved whatever the setting, but freezing of gait may appear for the first time, or worsen. This focal effect of stimulation within the internal pallidum may limit the efficacy of this technique.

Since the smaller subthalamic nucleus is also overactive in Parkinson's disease some centres have explored the effects of bilateral stimulation of the subthalamic nucleus (since spontaneous lesions in or near the subthalamic nucleus may cause hemiballism, surgeons have been understandably reluctant to create lesions in this structure). Such stimulation has a much greater effect on underlying parkinsonism,[8] including tremor[9] and freezing of gait, but usually neither improves nor worsens levodopa induced dyskinesias. Nevertheless, the antiparkinsonian effect is so striking that, in contrast to pallidotomy, levodopa dosage can be dramatically reduced, with consequent reduction of dyskinesias as well.[10] Also, at least three centres, one of them in Britain,[11] have made subthalamic lesions with major benefit to parkinsonism, usually without increasing dyskinesias. Most of these procedures must still be considered experimental, and many questions remain unanswered. How, therefore, should clinicians looking after patients with Parkinson's disease view their current status?

No definitive answer is yet available. However, for severe drug resistant unilateral parkinsonian tremor a unilateral thalamotomy might still be appropriate, although several years down the line, when akinesia and dyskinesias are prominent, one may wish one had done a pallidotomy or subthalamic procedure. Prominent tremor on the second side may indicate a thalamic stimulator. Disabling dyskinesias despite optimal adjustment of medication may be helped by a unilateral pallidotomy, although the underlying off period

parkinsonism may improve only moderately. For the second side, it is uncertain whether a stimulator or a second lesion is the best course. The most effective intervention seems to be a bilateral subthalamic procedure. Most experience has been gained with stimulation, but bilateral lesions can undoubtedly be effective.

One problem in comparing these techniques is that some centres only use stimulation and others only make lesions. In all centres there is an inevitable learning curve. Lesions have the advantage that, once produced, the effect is permanent, but the morbidity might be greater than for deep brain stimulation, particularly with bilateral procedures. However, deep brain stimulation may be less effective in the pallidum. Stimulation also usually requires multiple postoperative visits to vary the choice of electrode settings, pulse width, amplitude, and frequency. There is always the (low) risk of infection and ulceration of wires through the skin, and the initial procedure entails an additional operation to implant the stimulator. Moreover, the equipment implanted in unilateral deep brain stimulation costs about £5000, £4000 of it for the pulse generator, which has to be replaced after four or five years; bilateral stimulation doubles the price. Use of stimulators is also to some degree commercially driven, whereas lesioning is not.

Functional neurosurgery for Parkinson's disease is therefore in its second childhood. We still need to establish what targets and what techniques are indicated for what clinical pictures, but a bilateral subthalamic nucleus procedure appears potentially the most effective. Moreover, the long term efficacy of these lesioning or stimulation procedures needs to be compared with the best results from fetal nigral cell grafts and optimal medical treatment such as continuous parenteral administration of apomorphine.

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# Developing the *BMJ*'s coverage of basic science

*We are introducing science commentaries*

The *BMJ* wants to do a better job of informing readers about developments in basic science. One of several ways in which we are trying to do this is by including with some research papers a brief commentary on the science underlying the clinical phenomenon described in the paper. The first of these science commentaries, on peanut allergy, appears on p 1275.[1]

In the next 20 years basic science is likely to transform medical practice. The new genetics will produce greater understanding of disease processes; new treatments, diagnostic tests, and prognostic markers; and a greatly increased ability to predict people's risks of particular diseases. Some visionaries predict a revolution akin to the appearance of antibiotics. Other developments in science—for example, in imaging—are also likely to have profound effects.

So ordinary doctors should be paying attention to basic science. Ideally, they should also be excited by it. Creativity in science can be just as compelling as creativity in music, painting, or film making—if it is presented in the right way. Sadly our research tells us that many practising doctors feel unequal to the task of keeping up with basic science. They find it hard to understand and often put anything labelled science on one side to read later, often not reading it at all.

We have been trying—particularly with our well received series on science, medicine, and the future—to present science in ways that will be attractive to readers. But our research and our advisers tell us we must go further. We are thus introducing the science commentaries in the expectation that some readers will prefer their basic science in small, bite sized chunks. Importantly, they will be written by a science journalist, using the journalistic skill of presenting complex material in an easily understood and attractive way. In addition we will continue to increase our coverage of basic science in news, editorials, and other parts of the journal. Rather than blinding with science, we hope to offer illumination.

Abi Berger   *Science editor, BMJ*
Richard Smith   *Editor, BMJ*

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