Occasional Review

Defence against bacterial drug resistance*

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Everyone knows that acquired microbic resistance is the Achilles heel of chemotherapy. All living things can acquire some resistance to noxious agents—man to morphine, for instance. Bacteria are no exception: they can become more resistant in some degree even to ordinary germicides. But nothing in the whole of nature equals the resistance which can develop to antibiotics; it seems here as if the sharper the weapon the more completely it can be blunted. A 10-fold change can deprive an antibacterial drug of much of its usefulness, but some increases are of the order of 1000-fold or even more. Since this change is a prolific cause of treatment failure it is worth while to inquire how it can be avoided.

Origins of resistance

How does resistance arise in bacteria? One process is simply selection; treatment with an antibiotic eliminates sensitive strains and enables an originally very small minority of resistant ones to survive and spread. This is undoubtedly what happened among staphylococci in the early days of penicillin. When exposure to a drug—antibiotic or synthetic—is followed by resistance in a previously sensitive strain this is usually attributed to mutation. This is undeniable and has been conclusively proved in some instances, but when resistance increases slowly over a period of years some form of adaptation seems a more likely explanation than a long series of small genetic changes, and this hypothesis had a strong advocate in the late Sir Cyril Hinshelwood.[1] There are three mechanisms whereby genetic elements determining drug resistance, often multiple, can be transferred from one bacterial cell to another. They are transformation, the uptake of genetic material already liberated from another cell; transduction by bacteriophage, which can occur in many species; and conjugation, which occurs only between Gram-negative bacilli, although of many different genera.

Motives for discouraging resistance

The main reason for devising treatment to which resistance will not develop is to ensure the patient's recovery. But it is well to look further into the consequences of failure, which may involve other patients as well. Resistant strains of many species have an enhanced capacity for spread in a hospital, and the literature abounds with accounts of veritable epidemics caused often by staphylococci, *Pseudomonas aeruginosa*, or *Klebsiella* spp. Hence, many hospitals have "policies" for chemotherapy aimed mainly at reducing this risk. The more thoughtful and prudent will not stop there: one may have a duty to people outside a single hospital, and if the usefulness of a valuable drug is to be preserved it may be advisable to restrict its use throughout the community, or indeed the world if that were possible. An example involving a whole country was the restriction officially placed on the use of erythromycin in New Zealand in 1956.[2]

The following five bases of prescribing choice may be helpful in devising treatment which reduces the risk of bacterial resistance. The first three of them depend on classifying antibiotics according to their behaviour from this point of view.

ANTIBIOTICS TO WHICH RESISTANCE IS RARELY ACQUIRED

Other things being equal, antibiotics to which resistance is rarely acquired are naturally to be preferred. There are to my knowledge only three of them. Two, polymyxin and vancomycin, are not often indicated, but if they should be this property is one of their advantages. The third is penicillin, about which this claim needs to be qualified. Staphylococci do not acquire resistance to penicillin, unless by transduction; resistant strains arise by selection. It was believed for years that this incapacity to become resistant was a property common to all bacteria, and inherent in the nature of the antibiotic. Mercifully this has proved true of group A streptococci and apparently applies to other species, but there are two exceptions. After more than 10 years of exclusive and worldwide use of penicillin for treating gonorrhoea less sensitive strains began to be recognised, and both their frequency and the degree of their enhanced resistance have very slowly increased ever since, with the result that very much larger doses have to be given; some venereologists have also turned to alternative drugs. The second exception, more recent, is the pneumococcus. Resistant strains were first encountered in New Guinea where penicillin was being used in a seemingly not very satisfactory way for the prevention of pneumonia, to which the inhabitants are said to be peculiarly subject for climatic reasons. Two others were then detected in Australia, and later others have been reported in North America, and one causing meningitis in an infant in Oxford[3]; I am informed that two have recently been encountered in London. The degree of resistance is not great (inhibition by 0·5 instead of 0·02 μg/ml) and should be overcome by increased doses—although the Oxford case casts some doubt on this—but there must be some fear that the change will not stop there.

Rarely, other species may respond to very prolonged unsuccessful treatment by moderate increases in resistance. I recorded this in an endocarditis streptococcus 25 years ago,[4] and I have seen it also in cases of actinomycosis.

The semi-synthetic penicillins do not all share this immunity from bacterial counter-attack. Ampicillin, for instance, is a derivative to which a wide variety of bacteria may be resistant, apart from staphylococci and gonococci; they include *E coli*, *Salmonella*, and *Shigella* spp, various other enterobacteria, and *Haemophilus influenzae*. Carbenicillin is chiefly of interest for its action on *Ps aeruginosa*, and this organism may be resistant to it, either intrinsically or as the result of transference.

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ANTIBIOTICS TO WHICH RESISTANCE IS ACQUIRED RAPIDLY

At the other extreme from penicillin are two antibiotics in particular to which a high degree of resistance may develop rapidly, even over night. Streptomycin is one of these; fortunately other aminoglycosides are not so vulnerable. An illustration of this kind of behaviour may be seen in figure 1 showing the results of repeated quantitative culture of the urine of a man with a *Klebsiella* infection. Two hours after the first dose of streptomycin the bacterial count fell from 100 million almost to zero, but never reached it; next day it had risen steeply and on the following day was at the pretreatment level, and in the last two cultures the organisms were 1000 times more resistant than they had been before. I obtained some evidence that such failure can be predicted by cultivating the deposit of 10 ml of urine in a pour plate containing 1000 μg/ml of streptomycin; in this very large inoculum the presence of pre-existent resistant mutants can be detected.[4]

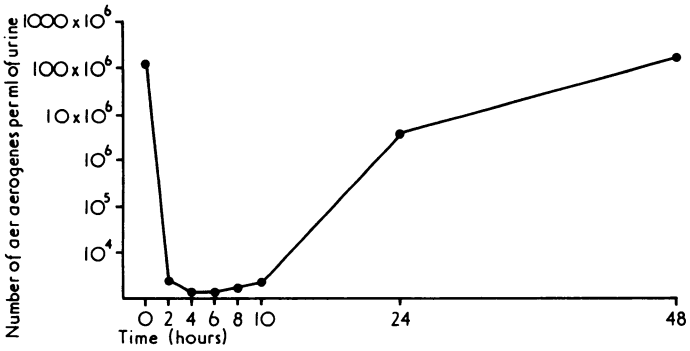

FIG 1—Effect of streptomycin (0·5 g four-hourly starting at 0 hours) on bacterial content of urine in a case in which treatment failed.

Another peculiarity in the action of streptomycin is illustrated in figure 2. This was also a culture of the urine of a patient with a *Klebsiella* infection, but he had already been treated with streptomycin. The two wells in the plate contained streptomycin solutions (serving the same purpose as the discs now used for sensitivity tests), and growth has occurred only around these. These organisms had become streptomycin-dependent, an extraordinary reversal of the role of the antibiotic from rapid killer to essential nutrient. This may be thought a happy result since stopping the treatment should effect a cure. In this case it may have, but all bacteria in an infective focus are not always affected in the same way: in tuberculosis, for instance, a lesion may contain some dependent bacilli, but others too which are just resistant or still sensitive.

In tuberculosis it is axiomatic that other drugs must be given with streptomycin to prevent resistance. Perhaps also in short-term treatment for other conditions combinations should be the rule, but, in fact, streptomycin has been largely replaced by other aminoglycosides such as gentamicin for these purposes, and resistance to these develops more slowly.

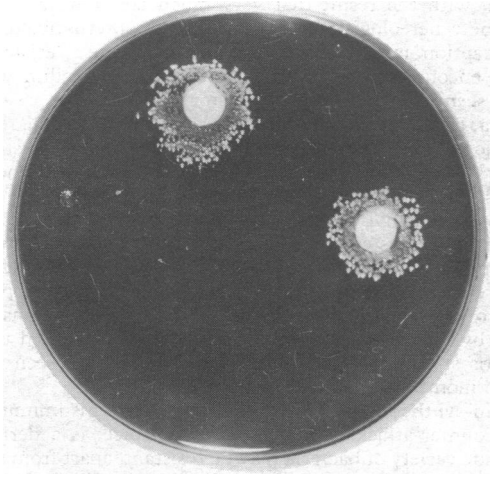

FIG 2—Plate culture of urine from a case of *Klebsiella* infection after treatment with streptomycin. Wells contain solutions of this antibiotic. Growth has occurred only around them.

Another antibiotic to which resistant mutants can appear within a few hours is rifampicin, and here again tuberculosis should never be treated with this drug alone. It is so valuable for this purpose that the advisability of restricting its use to this and no other has been seriously discussed. Occasionally it may be life-saving, as in a case of staphylococcal endocarditis in which we found that the most bactericidal combination for the resistant staphylococcus was rifampicin + erythromycin.[5] Response to this treatment was immediate and lasting. It is quite another thing to use the drug for treating meningococcus carriers,[6] and the prospects opened up by a recent study of its combined action with trimethoprim[7] are much more extensive and alarming. A moderate degree of synergy was found against a wide range of bacterial species, and possible therapeutic applications are very numerous indeed. These are largely for conditions not endangering life and susceptible to several other kinds of treatment. The benefit to be gained needs to be weighed very carefully against the risk of inducing widespread resistance to this valuable drug.

ANTIBIOTICS TO WHICH RESISTANCE IS ALREADY WIDESPREAD

It may be wise to avoid antibiotics to which resistance is already widespread simply because treatment may fail. Foremost in this category are the tetracyclines. The first of them was introduced nearly 30 years ago, and during this long therapeutic history resistance to them has increased and spread gradually until almost every important and originally sensitive species is involved to some extent. Staphylococci were involved early, although much later a tetracycline was introduced—minocycline—to which such strains remain sensitive. Haemolytic streptococci of group A are now resistant often enough to compromise the treatment of acute sore throats. Resistance in pneumococci appeared later and, although still not common, is of much higher degree than that to penicillin recently observed. Among other respiratory pathogens *H influenzae* may be resistant, although infrequently. Members of the whole large group of enterobacteria causing intestinal, urinary, and other infections show resistance with varying frequency, and this is often transmissible. Lastly, it is now unsafe to rely on tetracycline for the prophylaxis of gas gangrene. A case is on record[8] in which this was done because the patient was sensitive to penicillin and the infection developed in spite of it; the strain of *Clostridium welchii* was tetracycline-resistant.

Finland,[9] in a review article on the place of tetracyclines in antimicrobial therapy 25 years after their discovery, draws attention to the indications for their use defined in a comprehensive guide to antimicrobial therapy published by The Medical Letter Inc.[10] They are here recommended as treatment of first choice only for the diseases listed in table I. This is indeed an exotic list. Large quantities may be used in some parts of the world for cholera, trachoma and typhus, but the indications likely to be encountered in Britian are all comparative rarities. This publication lists 25 infections for which tetracyclines among other drugs are "alternatives to those of first choice," and some of these doubtless account for much of their use.

TABLE I—*Infections in which tetracyclines are drugs of first choice*[10]

Bacterial	Other
Glanders	Mycoplasma pneumonia
Melioidosis	Rickettsial infections (typhus, Q fever etc)
Brucellosis	Psittacosis
Chancroid	Lymphogranuloma venereum
Granuloma inguinale	Trachoma
Cholera	Inclusion conjunctivitis
(Relapsing fever)	

Another drawback of tetracycline is its efficacy in selecting for resistance in intestinal bacteria, revealed in a very significant study by Datta and her colleagues.[11] Women with urinary tract infections were treated with ampicillin, sulphadimidine, or tetracycline, and their intestinal flora was studied before and after treatment. The proportion of patients in whom the predominant *E coli* was found resistant underwent some increase during treatment with ampicillin and sulphadimidine, but resistance to other drugs was not significantly affected. During treatment with tetracycline not only was the predominant *E coli* resistant in every case, but there was a significant increase in the frequency of resistance to several other drugs. The relatively poor absorption of tetracycline and consequently persistent action throughout the length of the bowel may partly account for this profound effect.

Restrictions on local application

It is unwise to apply some antibiotics to an area in the body with a varied flora among which resistance may arise. An outstanding example of this is the oral administration of non-absorbed antibiotics with their consequent action on the flora of the lower bowel. At Hammersmith Hospital during the 'sixties, when neomycin was being used for preoperative bowel preparation, we frequently observed resistance in *Proteus* spp evidently resulting from this. The aminoglycoside to which it is at present most important to preserve sensitivity is gentamicin, and its manufacturers are to be commended for not supplying a formulation such as a tablet intended for this type of use. Of many other examples of local application none involves such extensive risks as this. Most treatment of the skin, for instance, whatever its merits or drawbacks, involves a limited flora including no pathogens of importance except staphylococci. An exception may be an infected varicose ulcer, since various Gram-negative bacilli may be found here, and a decision to apply gentamicin cream should not be taken lightly.

General policies for restricted or reserved use

Some large hospitals have formulated their own policies for the use of antibacterial drugs, and when these are faithfully observed they can be of great benefit. It is first assumed—and this is not an assumption but supported by ample evidence—that the more such a drug is used the more frequent will resistance to it be. Much prescribing is undoubtedly ill directed or unnecessary, and junior staff in particular need to be educated in more discriminating prescribing habits. According to some authors, notably Jawetz,[12] the field in which wasteful prescribing is as its worst is the prophylactic, and practices of this kind may need to be reconsidered and revised.

As regards the use of individual drugs, there are three possibilities. One is *restriction* to specific uses, notably for a valuable drug such as rifampicin to which resistance is readily acquired. *Rotation* is using a drug until resistance to it appears and replacing it with another, in the hope that sensitivity to the first will be restored. *Diversification*, perhaps the least hopeful policy, consists of prescribing as wide a variety of drugs as possible, no single one being used enough to provoke frequent resistance. To these may be added a fourth, the regular use of *combined* treatment, on the principle that resistance to either drug in a combination is unlikely to be acquired. This was the subject of a classical study by Barber and her colleagues[13] at Hammersmith Hospital, and although it achieved apparent success it is too costly for general adoption and presents frequent difficulties in prescribing appropriately in individual cases.

A good policy in any given hospital or group should be based on an intimate knowledge of the local flora and their drug sensitivities. These not only vary from place to place, but remain nearly constant for long period in each unit, particularly in certain fields such as urology.

Resistance derived from animal sources

A quite different question remains: how far is man at risk from drug resistance produced by medication of farm stock? Antibiotics and other antibacterial drugs are used in animals for two purposes: the treatment of infections such as enteritis and mastitis, and in much smaller doses and on a much larger scale for growth promotion, a remarkable effect which even now is not fully understood. It is beyond question that a few parts per million of certain antibiotics in animal feed has been shown to secure a substantial increase in weight gain, but another result may be an increase in resistance in the enterobacterial gut flora to the antibiotic administered. This resistance is often transferable, and the fear is that if animal bacteria colonise the human bowel their resistance may there be transferred to human pathogens, notably the typhoid bacillus.

The British attitude to this possibility has been coloured by a prolonged and extensive outbreak of *Salmonella typhimurium* enteritis in cattle in the mid-'sixties.[14 15] This strain possessed multiple transferable resistance, the original elements in which may have been due to feed supplementation, but those accruing later, notably that to ampicillin, were evidently due to treatment or attempted prophylaxis of the infection. About 500 human cases were also involved in this outbreak. The Swann Committee[16] was much influenced by this disaster, and recommended that medical antibiotics (those permitted in Great Britain being penicillin and tetracyclines) should no longer be used as feed supplements; this recommendation was implemented.

Nothing has been done to restrict the *therapeutic* use of antibiotics in animals, which had much to answer for in this outbreak. If what we fear is chloramphenicol resistance which might reach the typhoid bacillus should not the administration of this drug to animals be restricted or even prohibited? In connection particularly with the intramammary treatment of mastitis and the consequent possible presence of various antibiotics, even including chloramphenicol, in milk, I have repeatedly urged[17 18] that "the case for giving the medical profession some say in what their veterinary colleagues are permitted to do to cows is unanswerable." Whether the Department of Health has ever seriously tackled the Ministry of Agriculture on these lines I do not know, but probably a stout defence of their freedom to prescribe is common to the two professions.

Food-poisoning *Salmonella*, being pathogens in both species, are readily transmissible from animals to man, but if any large-scale transference of resistance is to occur it must be by regular commensals such as *E coli*. Can these, although non-pathogenic, also colonise the human bowel? It is widely believed that they can, and indeed in Britain seems to be an accepted doctrine. There is nevertheless some evidence to the contrary, and if this is taken into account it may be admitted at least that the question is still an open one. Proof is very difficult to obtain, because animal and human strains do not differ in their ordinary characters, and their ultimate source therefore cannot usually be identified.

My own hospital, St Bartholomew's, is next to and supplied by the largest meat market in England, and my former colleagues there have shown that meat and poultry are frequently contaminated with *E coli*,[19] sometimes possessing transferable resistance.[20] The organism was also found to be widely distributed in the kitchens, particularly on utensils and in washing-up water. *E coli* was found in 10% of dishes actually served to patients, whose faeces were repeatedly cultivated to determine whether these strains had been implanted, their identity with the food strains being verified serologically. Positive results were obtained in five cases, the sources being milk in three, semolina, and blancmange.[21] These strains and others traced in this extensive and painstaking study could not be proved to be of animal origin, although admittedly in this environment contamination from animal sources seems likely to have been more extensive than from human.

There is another approach to this problem. If slaughter house contamination of meat is an important source of drug-resistant *E coli* in man—not perhaps direct since cooking destroys them but indirectly by culinary contamination—then these organisms should be found less often in vegetarians. Apparently this is not so: in the only study of which I am aware such organisms were found just as often in the faeces of young infants and of adult vegetarians as in those of meat-eaters of two categories, in one of which indeed they were actually less frequent (table II).[22]

Drug resistance has been found to be frequent in the intestinal flora of farm workers,[23 24] and this has been attributed to transference from farm stock. There is another explanation for this. The highest frequency of resistance found has been in antibiotic production plants, but others handling antibiotics are affected in the same way, and these include not only workers in fodder plants where feeds containing antibiotic supplements are compounded, but workers on farms where these feeds are used.[25]

TABLE II—*Frequency of resistant intestinal E coli according to diet**

Subjects	Numbers	Percentage with	
		Resistant *E coli*	Strains with transmissible resistance
Meat eaters:			
Military kitchen personnel	400	38	25
Office workers	86	23	9
Non-meat eaters:			
Adult vegetarians	77	36	24
Infants <6 months	87	32	18

*From Guinée *et al*[22]

Inplantation experiments[26 27] with cultures of *E coli* recognisable by their pattern of drug resistance also lend little support to the idea that animal strains can colonise the human bowel. Swallowed *E coli* persist longer when the strain is human; bovine or other animal strains almost always disappear within a few days, in spite of the fact that the numbers administered have been thousands of times larger than those to be found in contaminated foods. This is not surprising when one considers the nutritional change involved. I once addressed a meeting on this subject in Atlantic City, where "sea food" is popular, and invited the audience to picture the plight of a bovine strain of *E coli*, fresh from a diet consisting entirely of the residues of grass, and faced with those of a meal of prawn cocktail and steamed clams. Totally unaccustomed to metabolise such materials, what chance would it have in competition with the resident flora?

It seems thus that we may have much less to fear from the animal kingdom than from the ways in which we use antibiotics on ourselves. Our best defence against bacterial drug resistance is discriminating therapeutic use, certainly involving restrictions on the prescribing of particular drugs, and possibly an overall reduction in consumption for less clearly necessary purposes.

I am indebted to the photographic department of St Bartholomew's Hospital for fig 2 and to the editor of *Medical Letter*, New York, and to Dr P A M Guinée, and the editor of *Applied Microbiology* for permission to reproduce tables I and II respectively.

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Doses of diuretics now used to treat heart failure may lower blood pressure. Is hypotension (say, a diastolic blood pressure of less than 70 mm Hg) acceptable during treatment for cardiac oedema or does such hypotension prevent the clearance of oedema by reducing renal perfusion?

Diuretics used to treat heart failure do not usually cause any damaging fall in blood pressure and usually any fall is slight in normotensive people in heart failure. Renal perfusion largely depends on the systolic pressure, and a diastolic pressure of less than 70 mm Hg would be perfectly acceptable (in aortic regurgitation the diastolic pressure may of course be much lower than this without adversely affecting renal perfusion). Renal blood flow depends on the cardiac output, and in advanced heart disease reduced renal perfusion is the instigator of the renal salt and water retention that is responsible for the clinical signs of heart failure. Modern diuretics, such as frusemide, can initiate a diuresis despite this diminished renal perfusion; indeed, they even work in renal failure when given in large doses. These powerful but short-lasting diuretics used for treating severe heart failure are not suitable as adjuvant hypotensive agents for the treatment of high blood pressure, and for this purpose milder longer acting diuretics of the thiazide group or chlorthalidone should be chosen. Diuretics may also indirectly improve renal perfusion through the beneficial effect on cardiac function achieved by reduction in left ventricular dilatation and relief of myocardial oedema.

How safe are the dichlorvos strips used as fly-killers?

Several products release small amounts of the organophosphorus compound dichlorvos from plastic strips; when placed in a room they maintain for a few months a low but insecticidal concentration of the compound in the air. Alarms have been raised periodically about possible hazards from their use, the latest being an allegation by Löfroth[1 2] that dichlorvos may be mutagenic. Since 1957 the Government has controlled the introduction on to the market of pesticides used in the kitchen and larder, as well as those used in agriculture, food storage, and the home garden through the Pesticides Safety Precautions Scheme. Under this scheme pesticide products are not marketed unless the Government, with the guidance of the independent Advisory Committee on Pesticides and Other Toxic Products, is satisfied that they can be used safely. The scheme includes provision for a review procedure if new evidence of risk becomes available. The dichlorvos strips have been through this scheme, and official recommendations, which include the precautions necessary for their safe use, have been issed by the Ministry of Agriculture, Fisheries, and Food. Reviews of new evidence have not led to any change in these recommendations. Manufacturers print the safety precautions on their labels, and if the advice is adhered to the products will present no hazard to health. One criticism of the strips has been that pesticide is given off continuously and that people are unnecessarily exposed to the compound when no insects are present. The new dichlorvos strip that can be shut off when not needed is therefore welcome.

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What is the cause of fear in childhood of flying creatures such as birds and bats?

Infants are innately fearful. Sudden, unexpected, and intense stimuli readily produce a startle reaction. This reflex reaction is quite different from the pathological anxiety of older children that is caused by genetic and environmental factors. Anxiety, it must be emphasised, can be absorbed by an almost osmosis-like process from parents, or from tense, anxiety-ridden domestic upsets. Specific fears (best described as phobias), as of flying creatures, such as birds and bats, are learnt responses that arise after single or multiple traumatic experiences, but usually in a setting of general, undirected anxiety. Some people maintain that the phobic objects are symbolic of unconscious conflicts, but this is somewhat speculative.