

COMMENTARY

Action against antibiotic resistance: no time to lose

“This enquiry has been an alarming experience.” So starts the summary of the recommendations in the report of the House of Lords Select Committee on Science and Technology on resistance to antibiotics.¹ This statement echoes the sense of foreboding that antibiotic resistance has engendered among microbiologists. There have been many calls for action to halt the well-documented rise of resistance to antimicrobials.² The current awareness of governments and the public of problems such as multidrug-resistant tuberculosis and methicillin-resistant *Staphylococcus aureus* ought to prompt action to tackle antimicrobial resistance.

The report is unique in taking into consideration all the factors influencing the development and control of antimicrobial resistance—ie, usage in human beings and animals, new agents, infection control, surveillance, vaccines, and research. Although primarily directed at the problems in the UK, the report also encompasses a global perspective.

Antimicrobial resistance genes evolve from a wide range of “house-keeping” genes. Mutations in these genes, together with DNA-exchange mechanisms such as plasmid conjugation and translocation of gene(s), and with short multiplication time, enable bacteria to change rapidly and erratically.³

One central issue is whether usage causes resistance. Although conclusive scientific evidence is largely lacking, resistance genes are extremely rare in bacterial strains preserved from the era before the widespread use of antimicrobials, but the genetic mechanisms associated with spread of antimicrobial resistance are not. Thus a reasonable assumption is that usage will encourage the development of resistance in bacterial strains, although this process and the spread of resistance genes to different species and geographical locations are not predictable. The reduction in the use of tetracycline to treat acute exacerbations of chronic bronchitis associated with *Haemophilus influenzae* infection has resulted in a fall in tetracycline resistance in that bacterium. By contrast, the virtual cessation of the use of streptomycin against Enterobacteriaceae has not lowered resistance of this family of bacteria to this drug, probably because of the maintenance of stability of the gene within a mobile genetic element called an integron.⁴

Although antibiotic resistance sometimes reduces microbial virulence rather than sensitivity to the drug, recent work with *Salmonella typhimurium* shows that avirulent antibiotic-resistant mutants rapidly accumulate compensatory mutations that restore virulence.⁵ Thus medical practitioners must make every effort to restrict antibiotic prescribing to patients known or most likely to have infections. As the committee points out, education about avoiding excessive prescribing must be provided to both medical practitioners and the public.

The committee shows that the direct and the indirect costs of managing patients infected with antibiotic-resistant bacteria are substantial. Correctly, it resists proposals to make some systemic antibacterial agents available in the UK without prescription.

Experience in human medicine has shown that long prophylactic courses of antibiotics lead to resistance. The combination of extensive prophylaxis and intensive animal husbandry, with large populations of animals in close proximity to one another, provides conditions ideal for the emergence and spread of determinants of antibiotic resistance. In the UK the use of fluoroquinolone antibiotics, such as enrofloxacin and danofloxacin, in animal husbandry has led to antibiotic resistance among the zoonotic pathogens campylobacter and salmonella.⁶

The use of antibiotics at subtherapeutic concentrations for growth-promotion has been regulated in the UK since the early 1970s under the recommendations of the Swann report.⁷ Ideally, antimicrobials for growth promotion should be those that are not or will not be used in human medicine, but they are difficult to identify. Recent studies on the molecular evolution of the vanA transposon among strains of enterococci in human beings and animals suggest that animal use of avoparcin is, at least in part, responsible for the emergence of vancomycin-resistant enterococci in human beings.⁸ Changes in husbandry and the use of probiotics could reduce the dependence on antimicrobial growth promoters.

One apparently simple solution to resistance is to replace older antimicrobial agents with structurally and mechanistically novel ones. The committee rightly commends the pharmaceutical industries for their renewed interest in producing new antimicrobials and urges the government to support the European Union's proposal for “orphan-drug” status for antimicrobials, such as antimalarials, that fulfil medical needs but that are commercially unattractive to develop. New agents are expensive to develop and there are only a finite number of molecular targets for antibiotics. The genomic approach to antimicrobial target identification will yield results only in the future and is not automatically assured of success. Furthermore, current industry and licensing protocols for new agents pay inadequate attention to the likelihood of resistance developing during use.

Although it is notoriously difficult to predict what will happen in vivo, a striking example is the emergence in the 1980s of variants of the β -lactamase genes (β laTEM and β laSHV). These genes had been prevalent in pathogenic bacteria for many years and now carry point mutations conferring resistance to extended-spectrum cephalosporins.⁹ These antibiotics had been developed specifically to withstand hydrolysis by the TEM-1 and SHV-1 enzymes. The mutations, which have given the TEM-1 enzyme cephalosporinase activity instead of penicillinase

activity, were demonstrated in vitro in 1976,¹⁰ so the resistance to cephalosporins was predictable. Information of this kind should be taken into account in drug development and licensing.

The committee sensibly goes to some length to address methods for prevention of cross-infection and surveillance of antibiotic-resistant bacteria. The UK has a strong history of good control-of-infection practices in hospitals. Nevertheless, the striking rise in reports of infection caused not only by meticillin-resistant but also by meticillin-sensitive *S aureus* in the UK suggests that some changes in medical and administrative practice have created conditions for the nosocomial spread of this bacterium. Effective cross-infection control relies on accurate and also rapid identification of antibiotic-resistant bacteria. Hope was expressed that good methods for identification of such bacteria will be developed, but technical and financial constraints mean they are unlikely to be available in the near future.

Meanwhile, quality-controlled routine antibiotic-sensitivity testing of clinical specimens in the UK's National Health Service and Public Health Laboratory Service laboratories is generating much potentially useful information on antibiotic resistance and cause of infectious diseases. However, adequate information-technology resources are required to integrate the data from these two sources. In addition, the statutory reporting of infectious diseases by disease, rather than by organism, is archaic, and microbiological data, if available, must be incorporated.

The provision of those data and future research and development activities rely on the existence of well-founded departments of clinical microbiology. Here the committee highlights the failure to direct resources, both human and financial, to correct the poor state of clinical academic microbiology.

Antibiotic-resistant bacteria have no respect for geographical boundaries, as illustrated by the importation, on several occasions, into the UK from Pakistan and India of *Escherichia coli* resistant to all β -lactam antibiotics other than carbapenems.¹¹ The committee asks the UK government to continue its support of the WHO Antimicrobial Resistance Monitoring programme and endorses the resolution to be considered at the forthcoming World Health Assembly to put the programme on a firmer financial footing. The creation of a global monitoring scheme is fundamental to the reduction of antimicrobial resistance.

Rates of resistance are lower in the UK than in many other countries. Nevertheless, the committee was not convinced that Ministers, the public, or the veterinary and agricultural community have grasped the importance of action in the short term. The health-care profession may have a better understanding of the problem, but is not provided with the resources to take action. The committee draws attention to the fact that the Swann Committee recommended the establishment of a multidisciplinary interdepartmental committee to oversee policy and research relating to antibiotic use.⁷ That was 30 years ago. We cannot afford to delay any longer the setting up of this committee.

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1 House of Lords Select Committee on Science and Technology.

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Teaching heart-failure patients how to breathe

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The pathophysiology of heart failure used to seem easy. In heart failure dyspnoea was caused by wet lungs and muscle fatigue by reduced cardiac output. The only way to make the patient better was to improve the function of the heart. Research over the past two decades has shown these tenets to be misleading. The pathophysiology underlying the symptoms of chronic heart failure is complex and poorly understood.¹ There is no single cause of cardiac dyspnoea. Increased afferent inputs from chemoreceptor, lung, and muscle receptors all play a part in this sensation. The metabolite that stimulates the drive to breathe during exercise is not known. Potassium, lactate, adenosine, and carbon dioxide have each been proposed as the major stimulus.² Given this complexity it is not surprising that treatments to relieve dyspnoea in heart failure are not uniformly effective, and that substantial limitation of everyday activities remains despite maximum modern pharmacological therapy. Treatments that do not take into account the important pathophysiological changes in the syndrome of chronic heart failure are unlikely fully to rehabilitate the heart-failure patient back to a good symptom-free quality of life. Treatments that correct the haemodynamics of heart failure do not reliably increase exercise tolerance or reduce the severity of dyspnoea because changes in endothelial, skeletal, and respiratory musculature, in lung and respiratory control mechanisms, and in whole-body metabolic and anabolic/catabolic balance may have become the factors limiting exercise capacity.

The study by Luciano Bernardi and colleagues in *The Lancet* today addresses the importance of abnormalities of the pattern of respiration in patients with heart failure. Unstable ventilatory control has long been known to occur sometimes in heart failure, and to lead commonly to