REVIEW ARTICLE

Resistance to antimicrobial agents: a personal view

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Problems of antimicrobial drug resistance are presently serious, but not yet desperate. The principal areas of concern are two-fold: multiresistant opportunist bacteria that affect vulnerable patients in high dependency areas of hospitals (the most pressing problem for developed countries); and multidrug resistance among classic pathogens like *Mycobacterium tuberculosis*, *Salmonella typhi*, *Shigella* spp., *Neisseria gonorrhoeae* and *Plasmodium falciparum* (mainly, although not exclusively, a problem for developing countries). The first type can be contained to a large extent by good infection control practices and careful prescribing based on agreed policies of antimicrobial drug use. The input of infection control nurses and laboratory-based clinical microbiologists is crucial and these services deserve full support. The second type additionally requires co-ordinated action to regulate more effectively the manufacture, availability, promotion and use of antimicrobial drugs. In this case the input of governments, international agencies and pharmaceutical companies is essential. Prescription-only status for antimicrobial drugs used in man and animals should be the norm. The number of drugs available for the treatment of viral, fungal and parasitic infections is comparatively small and much less is known about resistance. More research in these areas would be welcome. Teaching good prescribing habits to medical students is presently haphazard and needs to be formalised. Surveillance needs to be improved. The second half of the 20th century has been a golden age of antibiotics, but the outlook is uncertain. If antimicrobial chemotherapy is to have a secure future, prescribers must learn to use these powerful tools with greater discretion and their use worldwide must be regulated effectively.

The problem of resistance

Microbes are remarkably adaptable and amazingly versatile. Through the course of evolution they have developed sophisticated mechanisms for preserving genetic information and disseminating it efficiently in the interests of survival. They recognise no boundaries. Resistance developing in one part of the country, or, indeed, of the world, can be disseminated readily. Similarly, non-human use of antimicrobial agents is a potential source of resistance in man; for example, resistant micro-organisms developing as a result of the use of antibiotics in animal husbandry may reach man through direct contact with those animals or through the food chain.

Bacteria

Because we have so many antibacterial agents (at least 200 different drugs are on the world market for the

systemic treatment of infection [1], of which about 85 are available in the UK [2]) the treatment of bacterial infection in the community at large is relatively secure. However, the apparent richness of available resources must be judged alongside the ability of micro-organisms to acquire the capacity for multi-drug resistance: certain mechanisms of resistance can negate the therapeutic efficacy of a whole family of antimicrobial agents, e.g., methicillin-resistant *Staphylococcus aureus* (MRSA) strains are resistant to all penicillins, cephalosporins and related β -lactam antibiotics; and the genetic information for unrelated resistance mechanisms, affecting numerous agents, can be assembled on transmissible genetic elements. Special problems may arise with infections caused by micro-organisms for which therapeutic options are, for particular reasons, already narrow – tuberculosis and typhoid fever are good examples.

Of course, in many countries of the world therapeutic choice is already severely restricted for economic reasons. It is partly because of the restricted availability of affordable antimicrobial drugs (but also

because poverty provides the conditions in which infectious diseases flourish) that many of the most acute problems of resistance are borne by communities in the poorer nations.

For countries with advanced health care systems the major area of concern is the treatment of vulnerable patients in high dependency areas of hospitals [3]. Here, patients become colonised or infected with opportunist microbes, some of which are already intrinsically resistant to many antibacterial agents, or have developed multiple resistance through the selective pressure of intensive drug use. Often, these problem organisms are indigenous to particular units, although the opportunity for spread may (and does) occur as patients are transferred to other wards or between institutions. Such multiresistant opportunist pathogens are not usually a threat to the general community, because they are mostly of low intrinsic virulence. However, multiresistant *S. aureus* may represent an exception, as staphylococcal infection is fairly common in domiciliary practice and some of these infections require antimicrobial therapy.

Viruses, fungi and parasites

In contrast to the profusion of agents available for the treatment of bacterial infection, the number of chemotherapeutic drugs for diseases caused by viruses, fungi, protozoa and helminths is relatively small. Moreover, such agents as are available often belong to closely related groups of compounds, so that the possibility of cross-resistance may exacerbate the potential problem of drug resistance (e.g., most antifungal agents are either azole derivatives or polyenes). Resistance to antimalarial drugs in *Plasmodium falciparum*, the species of malaria parasite that is estimated to be responsible for 1.5–2.7 million deaths each year, is causing particularly severe problems [4].

A fair amount of research is presently directed towards understanding aspects of resistance to antifungal and antiviral agents, but more needs to be done. Mechanisms of resistance to chemotherapeutic agents directed against protozoa [5] and helminths [6], and the epidemiology of such resistance, are poorly characterised. The only real exception is malaria, where a considerable amount of work has been done. The lack of interest in antiparasitic agents is largely due to the fact that much protozoal infection and most helminthic infection in man is borne by the poorer countries of the 'Third World'. However, concerns about parasitic infection also impinge on the developed world: millions of people travel each year to areas in which malaria is endemic; some cosmopolitan protozoal diseases – like cryptosporidiosis – are presently untreatable; others – like trichomoniasis – are virtually untreatable in the event (at present fortunately rare) of nitroimidazole resistance.

Despite the fact that >1.25 billion people harbour intestinal worms, and many millions suffer from the effects of systemic worm infections, most research on drug resistance (and drug development) in helminths has centred on parasites of animals [6, 7]. Yet therapeutic choice in serious conditions such as schistosomiasis and filariasis is severely restricted; in the case of hydatid disease (which occurs in the UK), it is virtually non-existent.

Frequency of resistance

We still do not understand the factors that govern how resistance develops, even in bacteria, which have been extensively studied. Twenty-five years after the introduction of penicillin into widespread use, 90% of strains of *S. aureus* encountered in hospitals were resistant to the drug, but this is not the norm. In the same period, all other micro-organisms within the spectrum of penicillin retained full susceptibility, and many have remained sensitive to this day. Among organisms responsible for infections for which antibiotics are commonly prescribed in domiciliary practice (e.g., urinary tract infection), the level of resistance to the drugs used generally seems to stabilise at between 20 and 40%. Different selective processes are at work with different drugs and micro-organisms. So-called 'infectious drug resistance' disseminated by well-characterised genetic transfer mechanisms is important in many cases; in others a slow, step-wise process (e.g., penicillin resistance in pneumococci), or both (e.g., penicillin resistance in gonococci), may operate.

A great deal of work has been done in this area [8, 9], particularly the molecular epidemiological aspects, but many practical questions remain unanswered. In particular, the conditions of drug use that favour the emergence of resistance are poorly understood. Similarly, more needs to be learnt about the effects of reduced selective pressure on the prevalence of resistance. Reductions in drug usage have been found to be associated with a decline in the prevalence of resistance in some cases [10], but there is also evidence, at least *in vitro*, that resistance may not always confer a disadvantage when selection pressure is removed [11].

Education

Control of antimicrobial drug resistance pre-supposes careful, informed prescribing. Use of antimicrobial agents appears deceptively simple, but rational prescribing requires a good deal of thought and knowledge. Quite apart from the vast number of different agents (often with confusingly similar names) with which the prescribers have to cope, they need to be familiar with the pharmacological properties of the drugs, the formulations available, potential side-effects, special needs of children, the elderly and other groups,

and the benefits and limitations of antimicrobial intervention in individual infective conditions [12].

In addition, there are a number of problems peculiar to these drugs. Prescribing antimicrobial agents differs from the use of other formulary compounds in two ways. 1. Unlike drugs that are designed to influence a physiological system in the patient, antimicrobial agents are intended to target selectively a living micro-organism, that is inhabiting a variably accessible location within the host and has triggered a complex immunological response. Ideally, antimicrobial therapy should be selective in the sense not only of avoiding unwanted side-effects, but also in supporting the immune response and leaving the normal microbial flora intact. 2. Use of antimicrobial agents, unlike other treatments, always has implications beyond the welfare of the patient receiving the drugs, as it adds to the pressure for the development of resistance. Although failure of therapy because of the development of resistance in the infecting micro-organism during treatment is unusual – except with certain drugs for which the selection of pre-existent resistant mutants may occur – resistance among other micro-organisms of the patient's normal flora may be promoted and alter the balance within the general bacterial ecology.

At present, teaching on antimicrobial chemotherapy in the UK (and elsewhere) is spasmodic [13]. Nottingham may be unique in offering a 2-week module on antimicrobial therapy for third year medical students about to start their clinical training. Generally, knowledge of antimicrobial agents is gleaned from a few lectures within the general microbiology or pharmacology teaching, while it is intended that practical prescribing should be learnt at the bedside. Equally little is done at the postgraduate level, while the pharmaceutical industry is very active in promoting its products. Publications like *Drug and Therapeutics Bulletin* and *Prescribers' Journal* help, but are inadequate of themselves.

A thorough knowledge of the properties of antimicrobial drugs and an understanding of what they will, and will not do, is essential in the control of antimicrobial drug resistance. The use of antibiotics for conditions in which bacteria are unlikely to be involved (such as viral respiratory infection) or in which antimicrobial drug therapy offers only limited benefit (e.g., most diarrhoeal illness; acute recurrences of herpes simplex) should be discouraged during the prescribers' formative training. The subject of antimicrobial chemotherapy needs to be given a much higher profile in the medical curriculum and at the postgraduate level.

Role of infection control and clinical microbiology services

Hospitals in the UK are fortunate in that they usually have excellent on-site laboratory facilities, with well-

trained technical staff and medically qualified consultants who act at the interface between the laboratory and the wards to give expert advice on the diagnosis and management of infection. Most large centres also have clinical infectious disease specialists. The supportive reference and epidemiological monitoring functions of the Public Health Laboratory Service (PHLS), with its network of peripheral laboratories that carry out the diagnostic service work in many hospitals, are also first-rate. In addition, the UK has pioneered the development of control of infection teams (often led by a consultant microbiologist) who formulate and monitor policies of hospital infection control, co-ordinate the response to problems of infection and perform an important educational role. It is hard to quantify the benefits that accrue from these activities, as they are largely indefinable (infection prevented, unnecessary use of drugs pre-empted, expensive ward closures avoided, etc.), and the educational role is often carried out through informal conversation. However, in the context of antimicrobial drug resistance, it is hard to escape the conclusion that the generally successful containment of major resistance problems in the UK owes a great deal to these activities.

In recent years an increasing squeeze on resources has put a great deal of strain on these services and morale has suffered. Well-equipped and well-staffed laboratories, with good clinical liaison are essential to the fight against antimicrobial drug resistance [14]. Adequate support needs to be provided for clinical microbiology laboratories, infectious disease units and control of infection teams.

Surveillance

National surveillance

The surveillance of antimicrobial drug resistance in the UK (and elsewhere) is presently unco-ordinated, although the PHLS and the British Society for Antimicrobial Chemotherapy have recently initiated a collaborative venture to formulate standard procedures that should lead to better information in the future. There are several pitfalls that must be avoided if useful information is to be obtained: surveillance must be tailored to different circumstances so as to answer specific questions. Thus, surveillance of the prevalence of resistance among organisms causing urinary tract infection in the community obviously requires a different approach to that needed to monitor the development and spread of resistance within an institution, where the problems may be inherent to that institution, or even be unit-based within it. Another problem is that of obtaining reliable denominator data. For example, simply examining organisms routinely isolated from specimens submitted to the laboratory from general practice is liable to introduce bias because of the likelihood that resistant organisms from patients who have failed empirical therapy will be over-represented.

International surveillance

Although carefully targeted local and national surveillance is most important in defining and addressing many problems of antimicrobial drug resistance, there is also a need to monitor developments internationally. The World Health Organization is attempting to co-ordinate such information through its Antimicrobial Resistance Monitoring Programme [15] (with the associated WHO Network scheme [16]). This is an important step forward and deserves full support.

Regulation*Availability of antimicrobial drugs*

Procedures for the licensing of drugs and the control of advertising in the UK are generally good. However, one area of concern is the question of over-the-counter availability of drugs. Whatever the pros and cons of wider availability for other prescription drugs, the trend towards relaxing prescription-only status for antimicrobial agents [17, 18] must be resisted. Self-medication is likely to lead to suboptimal use of these agents with a concomitantly greater risk of the development of resistance [19]. It is a matter of considerable anxiety that two of the agents presently available over the counter, aciclovir and fluconazole, represent important therapeutic drugs that belong to groups of antimicrobial agents (antiviral and antifungal agents, respectively) that are far from plentiful. The development of widespread resistance to these agents would have serious consequences, yet the impact of general availability on the development of resistance is not being systematically monitored.

Genetically modified products

The use of antibiotic resistance genes as selective markers in genetically modified products is not likely to pose a threat to the use of antibiotics in man, as mobilisation of these genetic elements seems unlikely to occur and the resistance markers used are, in any case, already common in environmental bacteria. Nevertheless, the use of these markers is unnecessary and, for this reason, it would seem prudent to avoid such use.

Non-human use of antimicrobial agents

The overall contribution to resistance of the use of antimicrobial agents in agriculture is a matter of dispute, although it seems clear that antibiotic-resistant enteric bacteria, including salmonellae, are reaching man from animal sources. This issue has been examined before in the Netherthorpe Report (1962) [20] and the Swann Report (1969) [21], but the time is probably ripe to revisit the matter. The question of whether use of antibiotics as growth promoters is still effective in the light of modern methods of animal husbandry needs to be examined. Little is known about the impact, if any, of other non-human uses of antimicrobial agents.

Regulation as a global problem

Regulation of the manufacture, distribution, advertising and use of drugs, including antimicrobial drugs, in many countries outside the UK, notably nations of the developing world, is an area of great concern. Poor quality products, inadequate storage, improper usage (often encouraged by unscrupulous advertising of inappropriate formulations and drug combinations), open availability, inadequate dosage and illicit marketing abound [22–25]. Governments, international agencies and voluntary organisations do what they can, but more co-ordinated action is necessary [26] and more pressure needs to be put on the pharmaceutical companies to regulate their own activities in areas of the world in which abuses are common.

Prospects for new antimicrobial agents*Antibacterial agents*

In the half-century from 1945 to 1995 a steady flow of new antibacterial agents became available. Most of the major antibacterial drug families had been discovered by 1960. Since then efforts have focused on developing derivatives of these compounds with improved properties, especially compounds specifically aimed at overcoming resistance mechanisms that were making the older drugs unreliable. For the rich resources now available we are indebted to the pharmaceutical industry, notably in Europe (including the UK), Japan and the USA, which carried out nearly all the research and development needed to maintain the flow of new compounds. It is unlikely that this situation will continue for several reasons: the cost of research and development is extremely expensive; the market for antibacterial agents is crowded; the returns are uncertain; and a number of compounds that have been marketed have not proved sufficiently profitable. It has been claimed that the process of drug development from discovery to marketing takes about 12 years and costs c. \$359 million; only one in 6000 starter compounds reaches the market, and only 30% of products that do survive actually yield a profit [27]. None the less, there is still some interest in antibacterial agents within the pharmaceutical industry and new techniques of molecular modelling, combinatorial chemistry, etc., are expected to yield compounds that might be progressed if a market need is identified [28].

Agents active against other types of infection

In contrast to antibacterial compounds, the search for antiviral and, to a lesser extent, antifungal agents is still being pursued energetically. The potential market, especially for effective, non-toxic drugs for viral diseases, is huge. All the major pharmaceutical companies are actively looking at these areas. The possibility of stimulating or otherwise modifying the host response to infection by modulating natural

biological mechanisms is also being actively investigated, but has so far met with only modest success. Research into antiparasitic agents is largely confined to those of potential use in animal husbandry. Occasionally, this yields compounds that prove to be of value in human medicine, as with ivermectin and the anthelmintic benzimidazole compounds.

Vaccines

Vaccination has been spectacularly successful in the control of many infectious diseases. In the case of smallpox total eradication has been achieved. Prospects that poliomyelitis may also be eradicated are good, and the WHO's Expanded Programme on Immunisation has been very successful. Much good work continues in this area, boosted by the recent success of *Haemophilus influenzae* type b conjugate vaccines. However, vaccines are unlikely to be the answer for the generality of infective conditions. In parasitic diseases, notably malaria, efforts to produce an effective vaccine have been continually frustrated. Moreover, vaccines have their own problems, not least those of cost and the logistics of distribution. The risk of side-effects, however rare, is a barrier to acceptance by the general public and a disincentive to manufacturers because of the possibility of costly litigation.

The ability of the drug houses to come up with ever more potent antibacterial agents has, until now, blunted the impact of bacterial resistance. The necessity to husband the rich resources available for treatment of infection by careful and circumscribed use has not been seen as a high priority. Such wastefulness can no longer be afforded.

This review is essentially the text of a personal submission to the House of Lords Select Committee on Resistance to Antibiotics and other Antimicrobial Agents and is also published with the evidence to the Committee (London, The Stationery Office, HL Paper 81-II, Session 1997-98).

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