EDITORIAL

BACTERIAL RESISTANCE

The period 1930 – 1950 marked an important watershed in discovery of drugs generally and antibacterial agents in particular. The discovery of penicillin-G by Fleming in 1929 heralded the dawn of a new era. Among the most important antimicrobial agents discovered during this period were sulphonamides, penicillins, aminoglycosides, tetracyclines, macrolides, cephalosporins and polypeptides. Initially only one or two drugs were discovered in each of the mentioned classes. Later these original antibacterial agents were subjected to molecular modification to yield derivatives, which had improved efficacy, safety and pharmacokinetic profiles. Thus from the original cephalosporin-C we now have more than 40 cephalosporins classified as first, second, third and fourth generations. Similarly from the original penicillin-G we now have over 30 penicillins. The story is the same for macrolides, tetracyclines and aminoglycosides though the number of derivatives varies in each class of the antibacterials.

The discovery of the first effective antibacterial agent used to treat pneumonia was considered almost a miracle. Before the discovery of sulphapyridine (MB 693) in 1935 there was no cure for pneumonia. Penicillin-G was introduced into clinical use in 1940 and was followed by streptomycin in 1944. Streptomycin was the first effective tuberculostatic agent. Viewed retrospectively, it is indeed surprising that these drugs (or their derivatives) form the basis of bacterial chemotherapy 50 years later. No major discovery of an antibiotic has been reported in the last 40 years.

By 1960, effective antibiotics were available for treatment of all bacterial infections such as syphilis, gonorrhoea, urinary tract infections, plague, tuberculosis, typhoid. Indeed it appeared mankind had brought the scourge of bacterial diseases under control. It came as a rude shock when after the 1960s reports of bacterial resistance started appearing in medical journals. To counter this resistance, when one antibiotic failed to control infection, it was substituted with another one or combination of antibiotics. This continued for a while but soon it was realised that the substitution game was a stop-gap measure and could not continue for long. Even more worrying is multiresistance where a bacteria developed resistance to several antibiotics.

In the 1990s the problem of bacteria resistance was being highlighted not only in professional health journals but also in popular magazines under such headings as “Superbugs Arrive”, “Dangerous Drugs-Antibiotics Overuse is Spawning Superbugs”. One might be tempted to dismiss such headings as sensational reporting by the gutter press who rely on sensationalism to sell their magazines. A closer examination of the problem suggests otherwise. The World Health Organisation (WHO) Report on Infectious Diseases in the year 2000 states, “At the dawn of a new millennium humanity is faced with another crisis. Formerly curable diseases…. Are now arrayed in the increasingly impenetrable armour of antimicrobial resistance”. A similar problem exists with regard to antimalarials where the *Plasmodium* parasite has become resistant to commonly used drugs, notably 4-aminoquinolines and sulphonamide/pyrimethamine (SP) drugs. As for the antiviral drugs, resistance has not had a great impact as viral chemotherapy, has never been effective and immunotherapy is the rule rather than exception. Indeed it is only in the case of antiretroviral drugs used in HIV/AIDS that viral resistance has been considered significant.

The question now being asked is “Is it possible to develop an antibiotic to which bacteria will not become resistant?” Based on our present knowledge of how bacteria become resistant to antibiotic, the question is clearly rhetorical. To say that the future is bleak is probably an understatement. It has taken humanity too long to recognise the danger arising from indiscriminate use of antibiotics but the writing has been on the wall since the mid 1970s. The worst case scenario is a return to pre-antibiotic era that existed before 1930s. Frightening as it may appear, it is important to appreciate that human beings have been on this

earth for millions of years so has the bacteria. The pre-antibiotic era was marked by high morbidity and mortality especially with such diseases as plague and tuberculosis. The use of incense now common in religious rituals had its origin in medical practice, an attempt to ward off diseases!

What options do we have in dealing with the problem of bacteria resistance? A biochemical understanding of the processes involved in development of bacteria resistance might help and a lot of research is going on. Resistance is always a result of mutation in susceptible bacteria. It could involve single step or several steps. In gonococci, resistance to β-lactam antibiotics occurs in 5 steps and at least 5 chromosomal genetic loci (pen A, mrt, pen B, pem and tem) are involved. As a result of mutation, bacteria are then able to synthesise β-lactamase enzymes that destroy the β-lactam ring, an essential component of the antibiotic molecule. Different types of β-lactamase enzymes are synthesised and are classified as class A, B, C, D and E. They have different characteristics as is evidenced from the amino acid sequence. To compound the picture further, each class is made of sub-classes. For example class A β-lactam enzymes are subdivided into TEM-1 and TEM-2. The above information illustrates the complexity of the problem. Other types of resistance are even more complex and involve modification of drug receptor (aminoglycoside modifying enzymes) or an efflux mechanism which pumps out the absorbed antibiotic out of the bacteria. In other cases bacteria alter their cell wall to keep antibiotics out.

It requires a lot of optimism to speculate that the solution to bacteria resistance will be found in the near future. In the meantime, we can only make the best out of a bad situation by restricting indiscriminate use of antibiotics to which bacteria still retain susceptibility. Combination therapy where two or more antibiotics are used concurrently helps to delay onset of resistance. In the meantime the search for new antibacterial agents continues.

Editor-in-Chief