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INFECTION CONTROL

EDITORIAL

Antibiotic Resistance

Treatment of bacterial infections in the hospital and community has been altered drastically over the past decade with the emergence of pathogenic organisms that are no longer susceptible to our most commonly prescribed antibiotics. Not only are hospital stays prolonged, but medical expenses have increased because of the need to use the newer, more costly antibiotics. Additional expense is often incurred by the need for two or more drugs, where formerly one would have sufficed. Despite the best efforts, deaths occur from multiply-resistant, unresponsive bacterial infections. Alongside the widely recognized multiply-resistant enteric organisms have now appeared new strains of enterococci which are resistant to all antibiotics currently available, even the most recently developed cephalosporins.

While there is general recognition among medical personnel that the problem of antibiotic resistance exists, there is also apathy and/or hopelessness in changing the situation. Any concern seems too often placated by an optimism that "we have new and more effective antibiotics." But is this a valid assessment of the situation?

While it is true that new antibiotics are being developed to treat resistant bacteria, patients (especially those who are immunocompromised), are still failing therapy because of multiple resistance in common organisms such as *E. coli, Hemophilus, Klebsiella,* and *Staphylococcus,* and the newer drugs bring problems of their own. The aminoglycosides, while often life-saving in the therapy of gram-negative infections, produce side effects which not only limit their use, but also cause irreversible tissue damage. The newer penicillinase-resistant cephalosporins induce chromosomal beta-lactamases which have now become important new determinants of resistance. Previously susceptible organisms have obtained genetic determinants which allow them to resist the very antibiotics which were developed to treat them. It does appear that species resistant to the newer drugs are emerging at faster rates than before, perhaps since the environment has been "primed" or contaminated with antibiotics.

Antibiotic resistance in most species of bacteria is carried on small, often transferable extrachromosomal DNA elements called R plasmids or R factors. Plasmids have the unique ability to transfer among species which do not normally exchange chromosomal DNA. In the late 1950s, when Japanese medical scientists initially described multiply-resistant *E. coli* and *Shigella* and demonstrated that this resistance could be transferred among different coliform bacteria, the news was received with great alarm. Confirmation of their findings came from workers in other countries. These R factors, while ubiquitous, were not as frequent then as they are now. Their emergence can be seen as a phenomenon of this century. Studies in areas of the world where antibiotics had not yet been introduced, have shown that they existed before antibiotic usage, but in low numbers.[1,2] Analyses of stored strains of *Enterobacteriaceae* isolated in the early to mid-1900s, before the use of antibiotics, showed an almost complete absence of resistant strains. Among 433 different bacteria tested, resistance was found only in nine isolates of *Proteus* (with tetracycline resistance) and in two other bacteria (with ampicillin resistance), all non-transferable.[3] Of great interest was the finding that many of these strains did contain plasmids, but not R factors. Plasmids, as we can surmise, have long been present in bacteria where they offer presumably some advantage to their host bacteria, but originally they were not encoding multiple resistance to antibiotics. We recently examined antibiotic sensitivity of coliforms recovered from the feces of two groups of baboons living in the wild and compared these findings to

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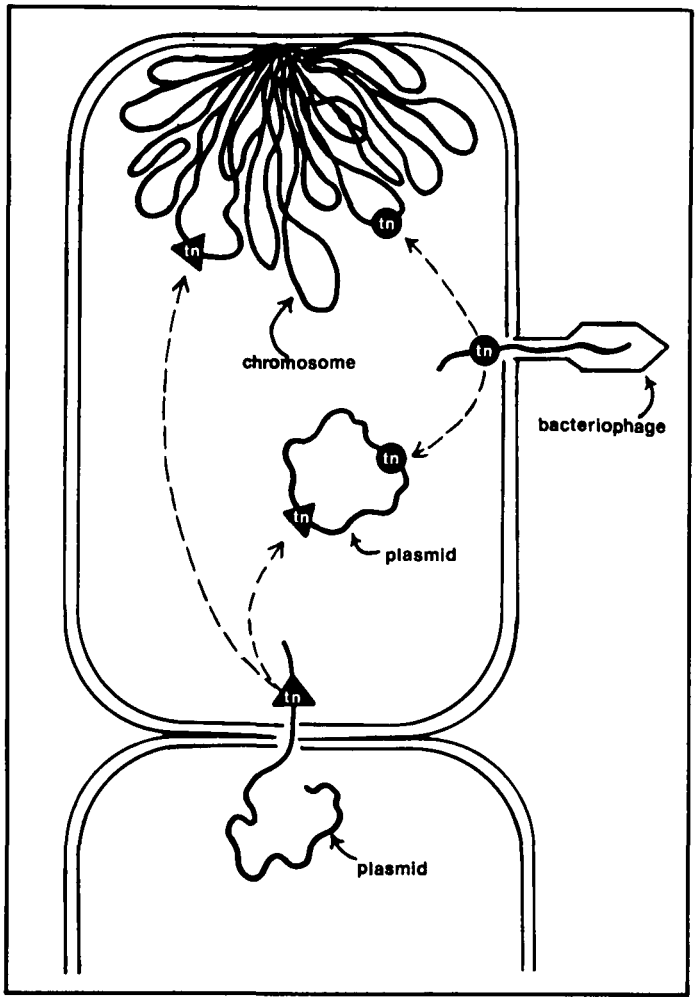

Figure. This figure illustrates the genetic exchange of antibiotic resistance determinants. Antibiotic resistance determinants are often located on transposons (tn) which are carried on different DNA vehicles (chromosome, bacteriophage, plasmid). Plasmid DNA enters the cell during cell to cell mating. The bacteriophage injects its DNA upon infection of the cell. Transfer of transposons can occur among any DNAs present in the cell.

a group living in proximity to humans and human garbage. Only the latter group showed a high frequency of multiply-resistant organisms (unpublished data, 1983). It is therefore apparent that present-day resistance has resulted from the increased production and distribution of antibiotics which have led to the creation of multiple resistance plasmids by the accumulation of resistance determinants on already existing plasmids.

Interspecies transfer of resistance has been vividly realized clinically with the emergence of resistant *Hemophilus* and *Neisseria* bearing the same genes which specify resistance to penicillins and tetracyclines in *E. coli* and other coliform bacteria. While the complete plasmid vector for these resistance genes is not necessarily identical in the new species, the genetic determinants of resistance are.[4] In fact, one of the important findings of this decade was the discovery that the majority of antibiotic resistance genes, in both gram-negative and gram-positive bacteria, reside on elements called "transposons" or "jumping genes" which can "transpose" from one DNA vehicle (plasmid, bacteriophage) to another, including the chromosome; and the donor still retains a copy of the transposon (Figure). Thus, copies of resistance determinants can readily spread and increase while residing on other replicating DNA vectors. Presumably it is in this way that a copy of the transposon-borne tetracycline resistance has come into *Hemophilus*. Even at the lower frequencies (10^{-6}-10^{-8}) characteristic of most transposons, when this kind of genetic exchange occurs, it is easily selected by the antibiotics in use.

The prevalence of resistance is a direct consequence of antibiotic use in man, animals and cultured plants. It is, therefore, not surprising that from Mexico and South America come reports of trimethoprim-sulfamethoxazole resistant *E. coli, Shigella* and *Salmonella,* found on transposons, which have emerged in concert with increasing amounts of this drug combination being sold over-the-counter and being used in hospitals and outpatient clinics.[5-7] It is important to recognize that now, even in community hospitals, penicillin-resistant staphylococci and *Hemophilus* have emerged in such great numbers that penicillin is no longer guaranteed effective in therapy. Of equally important concern are the rising numbers of other multiply-resistant pathogens in the community hospitals and outpatient clinics. Ten years ago this problem was generally limited to the larger city hospitals.

There is another factor involved in the antibiotic resistance problem—*the transportation of resistant strains* among nations and among populations. Venereal diseases, such as gonorrhea, spread among individuals as do the penicillinase-producing *Neisseria* that have now emerged. Local spread begets international spread; the strain which emerged in Southeast Asia was soon delivered to Singapore, the United Kingdom and America. These penicillin-resistant strains have been found in over 50 countries of the world and are still moving. In some regions as many as 60% of the isolates are now penicillin-resistant.

Upon reviewing human consumption of antibiotics, observers have documented misuse in offices and hospitals. There are clear examples of physician-written prescriptions for antibiotics where even a low suspicion of bacterial infection is lacking. One study used a medical student with simulated illness to demonstrate this point.[8] Another analysis of antibiotic usage in 20 randomly-selected general hospitals in Pennsylvania showed that in surgical prophylaxis alone, 20% to 25% of antibiotic usage could have been eliminated.[9] Clearly, prescriptions for the penicillins, tetracyclines and erythromycins occur with great regularity as the demand of the patient or the expediency of the physician presents itself. It is only by raising concern at the level of all individuals that this over-utilization of antibiotics can be eliminated and the re-establishment of an environment low in resistance genes can be realized.

What has been done about this problem? Many articles and reports have been written over the past 20 years describing the problem and its relation to antibiotic use. Largely these were confined to the medical literature. More recently, at a January 1981 conference in Santo Domingo, representatives from 30 countries presented

https://doi.org/10.1017/S0195941700058215 Published online by Cambridge University Press

evidence that many different species of multiply-resistant bacteria, particularly pathogens, had emerged as major public health problems in their countries. Following that meeting, 150 physicians and medical scientists issued a public statement in press conferences in four different countries (United States, Brazil, Dominican Republic, and Mexico) to bring attention to consequences of worldwide antibiotic misuse which now plagues the public health arena. An international response to this worldwide appeal helped launch the Alliance for the Prudent Use of Antibiotics,* a union of interested individuals and international groups whose aims are to propagate information toward educating users of antibiotics on the proper handling of these drugs. The Alliance's activities are guided by a Board of Directors and an internationally-representative 30-member Scientific Advisory Board. The Alliance has contact now with individuals and groups working in over 60 countries of the world on the antibiotic resistance problem. APUA supports each national effort with information, materials and implements necessary to help achieve the goals of that country. Each country may be dealing with a different priority in the overall resistance problem. Thus help is given to individual groups in these countries to work toward improving antibiotic use in that country. A portion of APUA's efforts also goes into supporting small research projects directed toward improving understanding of antibiotic resistance. A major aim of the organization is to evaluate and update the problem as it exists in different parts of the world and dispense this information in newsletters and other means of correspondence, as well as sponsored lectures and seminars.

In November of 1981, the World Health Organization convened a Scientific Working Group on Antibiotic Resistance to address the worldwide economic and medical concerns of the problem. This 18-member group of medical and research specialists from different countries wrote a 28-page document outlining the problems of resistance, and making recommendations for more judicious and careful prescription and utilization of these drugs in all countries. The group suggested that by being aware of the kinds of resistance genes, particularly among the reservoir bacteria (coliforms and staphylococci), medical personnel may be better able to predict the efficacy of certain antibiotics in a particular environment. This knowledge would certainly be helpful in deciding on treatment of infections caused by *Salmonella, Hemophilus, Neisseria* and *Streptococcus pneumoniae*.

If we are to reverse the ever-increasing frequency of antibiotic-resistant organisms, and to eliminate the spread of resistant bacteria from nation to nation, some concern about utilization of antibiotics in the world's population is required. By reducing the ineffective usage in all areas, we can expect to see reduction in resistance genes as these selective pressures are removed. This has been clearly shown in hospital, farm and large geographic settings. The issue is not only to save the older drugs, but also to protect the newer antibiotics from a similar demise. The need to spend millions of dollars on new antibiotics to treat these multi-resistant organisms can be diminished. It is even possible that some of the first-line antibiotics will again become effective in the treatment of common diseases. The concern among many of us is that the same indiscriminate use seen in previous utilization of antibiotics will be perpetrated in the use of newer ones.

The Alliance for the Prudent Use of Antibiotics seeks to promulgate the best uses of antibiotics and to provide data relevant to effective and ineffective usage. The Alliance intends to serve in an advisory capacity to all who deal with antibiotics so as to achieve well-founded, sound usage of these drugs. APUA seeks the support of all (medical personnel, scientists, and the public) in pursuing the safeguarding of these drugs as a mainstay in our continued struggle with microbial infections.

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