Development of Bacterial Resistance to Antibiotics
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The development of resistance to the antibiotics is a phenomenon of great theoretic interest to the bacteriologist, and it may some day become a matter of major concern to the clinician. I shall limit my discussion to penicillin and streptomycin, the two antibiotics which have been most intensively studied clinically and experimentally and about which, therefore, a good deal of information has accumulated.

One must bear in mind that susceptibility and resistance are relative terms. As customarily used, the term resistant is applied to a micro-organism when it requires more antibiotic to prevent its multiplication than most other strains of the same bacterial species.

In the case of penicillin, fortunately, few strains of the susceptible bacteria are resistant to concentrations ordinarily attainable in the blood of man. Some strains of staphylococci are comparatively resistant and a few are highly resistant. The highly resistant staphylococci owe this property to their ability to produce penicillinase, an enzyme which effectively inhibits the action of penicillin.1 These producers of penicillinase are therefore resistant to high concentrations of the drug. Some of the early reports describing 10 to 15 per cent of staphylococci as being resistant to therapeutic doses were made at a time when dosage was much smaller than it is today.

Acquired resistance—that is, the development of resistance to penicillin by previously susceptible micro-organisms—is rarely observed clinically during the treatment of infection in man. There are two reasons for this: First, bacteria acquire resistance to penicillin so slowly that most infections have been brought under control before a detectable degree of resistance has had time to develop. Second, penicillin, now that it has become so plentiful, is usually administered in doses considerably in excess of the minimum required to control the infection under treatment. Except in rare instances, therefore, this excess provides a margin of safety adequate to cover any increase in resistance which might occur.

One must be careful not to be misled into the diagnosis of acquired penicillin resistance. Not infrequently infections are thought to have become resistant because they do not respond to penicillin therapy although they were caused by penicillin-sensitive organisms. In such instances, one must be sure that the infection is being maintained by the same strain which initiated it, for secondary infection with a penicillin-resistant micro-organism often accounts for failure of the drug to control an infection rather than the actual development of penicillin resistance....

In the case of streptomycin, on the other hand, bacteria acquire resistance at a much more rapid rate. It has been noted, for instance, that susceptible bacteria in the course of only two or three transfers on culture mediums acquire resistance of such a high degree that they are able to multiply on mediums containing as much as 75,000 units per cubic centimeter.2 This finding coincides with the clinical observation that infections of the urinary tract in man must be controlled within a few days or they will become completely resistant to the maximum tolerated dosage of the drug.

In searching for an explanation of this rapid acquisition of streptomycin resistance, we have found recently that two resistant variants of Meningococcus develop which appear during the initial cultivation of a susceptible strain on mediums containing streptomycin in excess of ordinary bactericidal concentrations....

In summary then, penicillin resistance when it does develop proceeds slowly. It has not as yet become a serious clinical problem because most infections are brought under control before any appreciable degree of resistance has had time to develop and also because most patients at the present time receive doses of penicillin sufficiently in excess of the minimum required to take care of any increase in resistance which might occur during the course of their treatment.

Streptomycin resistance, on the other hand, can develop with great rapidity. This has been observed clinically as well as experimentally. It is probably due to the production by bacteria of streptomycin-resistant variants which arise by mutation. Such variants have been described for several bacterial species. In the case of Meningococcus, two streptomycin-resistant variants have been observed, one of which is remarkable in that it requires streptomycin for its growth in vitro and in vivo.

