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DRUG RESISTANCE OF BACTERIA IN RELATION TO GENERAL BIOLOGY

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SVMMARIVM — Ex experimentis constat bacteria non solum selectione sed etiam propria uniuscuiusque aptatione posse capacitatem resistendi veneficis agentibus acquirere; haec autem aptatio non postulat, ut multi affirmare solent, Lamarkianam hereditarietatem.

Bacteria rapidly and effectively acquire what is known as « *resistance* » to various toxic agents, including the most important modern antibiotics. This phenomenon is clearly one of the greatest gravity in practical medicine: and it is also one which raises biological questions of a quite fundamental character. These questions are no less than the role of mutation and natural selection in determining changes in populations, the self-adjusting power of individual living cells, and the mechanism of transmission by heredity.

Cells become drug resistant when cultivated at gradually increased concentrations of the toxic agent, and one of the remarkable fact about the phenomenon is that the pattern of events differs widely from one drug to another. If the drug medium merely allowed a pre-existent, resistant, mutant form

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to grow and inhibited the growth of other cells, the pattern of events should be similar from case to case. Since it is not, the phenomenon is obviously more complex.

For this reason DEAN, DRABBLE and others in my laboratory in Oxford, have continued the study of the response of the bacterium *Aerobacter* to a widening range of new toxic agents. Recently terramycin, triethylene melamine and ethidium bromide have been studied. In each example the phenomenon follows a different course.

In no case is the behaviour shown with streptomycin reproduced. Here, once the cells have grown, after a long delay, at a low concentration of the drug, they will also grow without delay at a wide range of much higher concentrations. Clearly, something is selected during the first treatment, the subsequent behaviour of which does not depend on the streptomycin concentration (within limits). It is in fact what we call a first stage resistant mutant. With terramycin, on the other hand, the resistance is more or less continuously and proportionately graded to the concentration of the agent to which the cells have been exposed. This is most easily explained in terms of a direct biochemical response of the cell which adjusts its internal economy in such a way as no longer to be so much interfered with by the terramycin. The behaviour is analogous to that observed with aminoacridines and with chloramphenicol. That selection of special mutant cells is unlikely is shown by the fact that by successive transplants on plates of solid medium containing progressively increasing amounts of terramycin resistant cells can eventually be obtained although the percentage of cells forming colonies is nearly 100 per cent at each transplant.

A quite different picture is shown by the drug ethidium bromide. Here, as with the sulphonamides, the bacteria grow for a time at a low rate and then rather suddenly change over to a much more rapid rate. It looks, at first sight, as though a slow-growing group in the population start first and are pre-

sently overtaken by a faster-growing group initially present in much smaller proportion. If this were so, at the end of the operation the faster growing type would predominate and the broken curve would not be repeated in a second transfer in the drug medium. In fact it goes on being repeated for some time and is only gradually eliminated. The effect is more easily interpreted as a balance between two alternative growth modes of each cell the balance of which can be disturbed by conditions but which gradually moves in favour of the more rapid as culture in presence of the drug is prolonged.

With triethylmelamine the picture presented is quite a complex one, and I shall not describe it in detail. If the observed phenomena were to be explained by selection a very elaborate series of assumptions would have to be made about the possible mutant types and their occurrence.

In each of these widely differing examples, there is some feature which, in contrast with the streptomycin case mentioned, is much more simply explained by adaptation of individuals than by the selection of aberrant individuals from a large population.

This interpretation is strengthened by a very general consideration. Single colony isolates of cultures show properties which do not normally change their resistance in ordinary culture. Mutations and reverse mutations would presumably be in balance. Since the proportion of mutants which must be assumed to account for delays of growth in drug media is very low, the proportion of mutants is small. The reverse mutation rate must be assumed high. This would imply rapid loss of resistance on culture in absence of drug. This is not observed. The loss of resistance does indeed occur but only slowly.

I will conclude with a very general observation. Because drug resistance can be retained through many generations of a microorganism, the suggestion that it arises in the first place by a direct adaptation of individuals has been called an assertion of Lamarckian inheritance. It is in fact nothing of the

kind. Genetic factors are not the only ones determining transmission. Animal and especially human behaviour is largely influenced by what is called 'cultural inheritance' or 'cultural transmission'. This is usually of knowledge or habits, but it could be physical, as for example, when disease is transmitted from mothers to unborn offspring. Now in the case of a bacterium the so-called offspring or daughter cell shares everything absolutely in common with, and indeed is indistinguishable from the mother cell until the moment of division. Any retention of a new character bears a good deal more analogy to cultural inheritance or to the transmission of disease than it does to Lamarckian genetics. The prejudices which have been unleashed in this connexion seems to be largely unfounded.

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