Energetics and antibiotic uptake

from J. R. Saunders and Venetia A. Saunders

ALTHOUGH the modes of action of most antibiotics are well established, much less is known of the processes by which such drugs are taken up by bacteria. In a recent paper (*Antimicrobial Agents Chemother.* **12**, 163; 1977) Bryan and Van Den Elzen propose a mechanism to explain the transport of one particular group of antibiotics, the aminoglycosides.

The accumulation of streptomycin (or gentamicin) by bacteria can be divided into three phases. The initial phase is energy-independent and apparently involves ionic interaction of drug molecules with the bacterial surface. This is followed by an energy-dependent phase (EDP-I), which occurs before inhibition of protein synthesis by the antibiotic. In cells that are sensitive to streptomycin, but not those that are ribosomally resistant, this is followed by a third phase (EDP-II) which is also energy-requiring. This phase marks the onset of inhibition of protein synthesis and loss of cell viability and is characterised by a higher rate of streptomycin accumulation than EDP-I.

Bryan and Van Den Elzen have found that mutant strains of *Escherichia coli* deficient in haem production, ubiquinone production or active transport mechanisms accumulate less streptomycin or gentamicin than corresponding parental strains. In addition, such mutants show increased resistance to those and most other aminoglycosides. But they exhibit an increased susceptibility to the aminocyclitol antibiotic spectinomycin. This corresponds quite well with the fact that this drug is more effective than the aminoglycosides against anaerobic bacteria. Increased uptake of radioactive streptomycin was observed in a mutant that is unable to couple oxidative phosphorylation to electron transport (Unc^-) and is also found defective in membrane-bound ATPase. It is interesting that this strain is hypersensitive not only to aminoglycosides but also to spectinomycin.

If streptomycin is transported into bacteria by means of a specific carrier system then compounds of closely related structure might be expected to compete with it. This is apparently not the case, but accumulation of aminoglycosides in either whole bacteria or spheroplasts is antagonised in the presence of divalent cations. This could imply that these antibiotics are taken up by a carrier for such ions. Unfortunately no system capable of carrying a wide range of divalent cations has been described. A further significant finding is that calcium ions are less effective in inhibiting streptomycin uptake in a ubiquinone-deficient (*ubiD*) mutant than in the wild type. This indicates that ubiquinone has a direct role in the transport of this antibiotic. There is indeed a very good correlation between susceptibility to aminoglycosides and the possession of respiratory quinones. Thus obligate anaerobes such as *Clostridium perfringens* which have no respiratory quinones are resistant to aminoglycosides. On the other hand, aerobic organisms possessing ubiquinone or menaquinone are usually sensitive to these drugs. Furthermore, aerobically grown cells of *E. coli* are many times more sensitive to these drugs than are anaerobically grown cells. This suggests that uptake of aminoglycosides is dependent on energy derived from aerobic metabolism.

A simple explanation for the data obtained would be that aminoglycoside transport requires carriers that are dependent on trans-membrane proton motive force. However, in the absence

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How many species?

from A. Hallam

A LIVELY controversy has grown up among palaeontologists in recent years about whether marine invertebrate species numbers, or richness, increased systematically through the Phanerozoic or whether an equilibrium situation has existed, with the apparent increase through time being an artefact. The leading advocate of the first view is J. W. Valentine, who has argued for an order of magnitude increase from the early Palaeozoic to the late Cainozoic, while the steady state alternative has been propounded principally by D. M. Raup.

Raup (*Paleobiology* **2**, 289; 1976) estimated the number of species described for each of the geological periods by tabulating new species reported in the *Zoological Record*, and established a strong correlation between apparent species numbers and the present areal distribution of rocks per system. Now Sheehan (*Paleobiology* **3**, 325; 1977) has come up with another interesting finding, having made a study of those palaeontologists expressing interest in fossils of particular systems, using data from the *Directory of Palaeontologists of the World*. It turns out that there is an excellent correlation ($r = 0.94$) between the number of carefully defined 'palaeontologist interest units' and the number of described species per geological period. Sheehan concludes that the total numbers of described species do not seem to reflect meaningful estimates of the original diversity.

In his reply to Sheehan, Raup acknowledges the good correlation established between the number of species described and the number of interested palaeontologists, as well as outcrop area, but maintains that nothing very positive can be inferred from this. He prefers the view, though he cannot prove it, that geological systems with more available rock have more species and hence more species are described. In other words most palaeontologists are attracted to the most fossiliferous rocks!

Is there any way out of this impasse? Apparently there may be, provided a distinction is drawn between assemblages from different environments, which can be compared from period to period. This has been attempted by Bambach (*Paleobiology* **3**, 152; 1977), who analysed data from hundreds of fossil assemblages from three different types of environment, as inferred from the facies. The high stress, marginal marine environment always has the lowest faunal diversity and the open marine environment the highest, while the variable nearshore environment has intermediate values. Bambach's data seem to indicate that within-habitat variation in species numbers is small for long intervals of time, and that the number of species has increased by a factor of about four since the mid-Palaeozoic, with variable nearshore environments showing a less pronounced increase than the open marine, while the high stress environments show no significant change. Thus Valentine seems to be partly vindicated, but substantial problems of interpretation remain, notably the factors controlling within-habitat species richness. Bambach speculates that changes through time of availability of food resources might be the most significant, but this is clearly an area demanding much further study.

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