GLIDING BACTERIA AND ADHERENT ANTIBIOTICS

One of my clearest memories from the first scientific meeting I ever attended is of a conversation about the horrendous difficulty of growing myxobacteria in the laboratory. London's Royal Institution was the venue, and the occasion the Society for General Microbiology's April 1961 symposium on Microbial Reaction to Environment. With, as I recall, the sole dissenting voice of Edward Cantino from Michigan State University, there was general, muttered agreement that these and the other so-called gliding bacteria had such exotic requirements that only a fool or an innocent would try to make practical use of them. Everyone shook their heads dismissively when Cantino, experienced in the elusive ways of his beloved water mold *Blastocladiella emersonii,* argued that it couldn't be *that* difficult. Clearly, a belief had taken root. So, despite suspicions as early as the 1940s that gliding bacteria might be valuable providers of antibiotics, this likely lode was long neglected. Until a few years ago, when Hans Reichenbach and his colleagues at the Gesellschaft für Biotechnologische Forschung, Braunschweig, West Germany, resolved to screen gliders from genera such as *Lysobacter, Cytophaga,* and *Myxococcus.* They soon began to realize that while a few of the filamentous types proliferated less spectacularly *in vitro* than the yeasts and *E. coli* favored by biotechnologists, most unicellular species could be persuaded to grow vigorously in artificial media. Not only that, Dr. Reichenbach has now discovered that an "astonishing" number of strains also produce potent and indeed unusual antibacterial substances.

Reichenbach and his colleagues twice used the adjective "astonishing," rare in scientific communications, during a report presented to the Third European Congress of Biotechnology held recently in Munich. Hot on the heels of a paper in BIOTECHNOLOGY (**2:**796, 1984) by researchers at Tel Aviv University, their comprehensive survey of approaching a thousand strains strongly suggests that the Israelis' finding of antibiotic TA made by *Myxococcus xanthus* is not a flash in the pan. Creeping along interfaces, Gram-negative gliders seem to generate antibiotics even more diverse than the taxonomic groups from which they themselves are drawn.

The Braunschweig team grew some 850 organisms, all newly isolated, using liquid cultures in a rotating incubator, and then tested both cell mass and culture fluid on paper discs against Gram-positive and Gram-negative bacteria, yeasts and molds. Myxobacteria in particular were richly rewarding, with 55 per cent of strains delivering antibiotics. Dr. Reichenbach and his coworkers believe this is related to the intricate biochemistry of organisms whose complex life cycle embraces free gliders, fruiting bodies and myxospores. The diversity of substances analysed so far supports that idea. A few relatively simple structures turned up, such as 3-formyl indole and 5-nitro resorcinol. But most were more complex, and while compounds arising from acetate, propionate and amino acid metabolism predominated, their structural variety reflected a diversity of secondary metabolism.

Many of the antibiotics seemed to work by inhibiting bacterial respiration. But here too there was heterogeneity, with mechanisms of action ranging from impaired RNA synthesis to interference in the production of cell wall polymers. Several isolates manufactured more than one antibiotic. *Stigmatella aurantiaca* strain Sq a15, for example, synthesized stigmatellin, myxalamid and quinoline N-oxide. As reported in a paper to appear shortly in the *Journal of Antibiotics,* these substances are, chemically and biosynthetically, completely different, yet they all act on the respiratory chain.

As yet, low yields are the main obstacle to the practical exploitation of gliding bacteria. Given today's almost total ignorance of their physiology, however, this may be seen not as an unbreachable barrier but as an opportunity to evolve media and cultural conditions encouraging antibiotic production. Hans Reichenbach and his group are already making considerable progress in this direction, and indicate in their forthcoming paper methods of using supplements such as skimmed milk and soy flour for the large scale cultivation of myxobacteria.

A second biotechnology group represented at the Munich conference highlighted another route through which greater productivity might be secured from gliding microbes—genetic manipulation. Dr. A. M. Breton and colleagues at the Université de Technologie de Compiègne in France are not primarily interested in antibiotic production. They have been attracted towards *Myxococcus xanthus* because of its uncommon capacity to secrete proteins into the extracellular growth medium, and see it as an excellent candidate for the industrial manufacture of protein products. But this has led them to develop a system in which the broad host range plasmid RP2 can be employed as a vector. As described recently in *FEMS Microbiology Letters* (**22:**85, 1984) they have also shown that a simple copy of transposon Tn5 allows a 10-fold resistance to kanamycin in *Myxococcus* as compared to *E. coli* and the expression of streptomycin resistance at a high level. Genes for secreted proteins having been cloned in several laboratories, Dr. Breton and his colleagues believe they are on the verge of putting this genetically amenable organism to work.

So, if gliders can be tailor-made for protein production, there is every reason to hope that similar techniques will help us boost their capacity to turn out the secondary metabolites we humans label as antibiotics. Those SGM skeptics, 23 years ago, were correct in one sense. As Hans Reichenbach has confirmed, gliding bacteria *are* an exotic group. But Edward Cantino was right too. Biological exotica are not objects to be rejected in favour of the familiar. They are just waiting to be investigated for the far more exciting fruits they may bear.

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