COMMENTARY

by Bernard Dixon

MICROBIOLOGY BACK TO BASICS

Bacteria may be tentatively regarded as biochemical experimenters; owing to their small size and rapid growth, variations must arise very much more frequently than in more differentiated forms of life, and they can in addition afford to occupy more precarious positions in the natural economy than larger organisms with more exacting requirements... It is impossible to exaggerate the importance of the variablity of the bacterial cell or the desirability of studying the laws regulating it."

Those monumentally far-sighted words come from the first edition of Marjory Stephenson's *Bacterial Metabolism*, which she completed in March 1929. More than any book before or since, this was the labor of love that created microbial physiology, and promised potentially limitless rewards which might accrue from the nascent discipline. As second and third editions appeared in the two decades following, *Bacterial Metabolism* both encouraged and reflected the emergence of an entirely new scientific specialty.

But while prophets, by definition, attract disciples, crucial strands in their teaching often go unheeded. Marjory Stephenson was fascinated by microbial variability and its relationship to environment. It's curious, therefore, that as the new discipline burgeoned, successive generations of applied microbiologists all but ignored this part of her message. Even as recently as 1961, at a Society for General Microbiology symposium in London, one speaker had to excoriate his fellow researchers for so neglecting one aspect of microbial behaviour that they were conducting almost worthless experiments. "There are few characteristics of microorganisms which are so directly and so markedly affected by environment as their chemical composition," said Denis Herbert from the Microbiological Research Establishment, Porton Down. "So much is this the case that it is virtually meaningless to speak of the chemical composition of a microorganism without at the same time specifying the environmental conditions that produced it."

Many biotechnologists of 1985 will feel that this is all ancient history. They may be chastened, therefore, to find Denis Herbert's words—coupled with a reminder that much the same applies to the functional properties of microoganisms—in a document published recently by the Commission of the European Communities. Entitled *Microbial Physiology and Biotechnical Innovation in the EEC Countries, Portugal and Spain*, it provides a catalog of areas in which practical applications of microbiology are being delayed not by a shortage of strategems for mobilizing genes but by a lack of insights into basic physiology.

It's now a cliche to observe that biotechnology is nothing like as unprecedented as the stock market might suggest. A Bureau of Biotechnology began operating in Leeds, England, in 1920. Pasteur's *Etudes sur la Biere*, published in 1871, could be described as a classic of the craft. And Babylonian tablets from *circa* 6000 BC show that brewing has more venerable roots still. Yet the modern, glamorous phase of the subject undoubtedly dates from the inception of recombinant DNA, gene cloning, and biotechnological man's newfound freedom to create novel workhorses by transgressing genetic barriers apparently imposed by organic evolution. What the EEC report suggests is that the new genetics has overshadowed the old physiology to such a degree that innovation is being held back through want of easily acquired data and relatively unsophisticated investigations. Produced by a working party chaired by Wim Harder of the University of Groningen, it distinguishes itself from innumerable other "state of the art" analyses by the detailed way in which it substantiates its critical conclusions.

Professor Harder and his colleagues cite, for example, the way in which genetically engineered microorganisms may not express their newly acquired information as anticipated. Thus ICI researchers were able to transfer a gene for an energy-conserving nitrogen assimilation pathway from *Escherichia coli* into their single cell protein bacterium *Methylophilus methylotrophus*. There it substituted for the original pathway, which had a similar function but consumed more energy. In laboratory experiments, this led to a significant improvement in yield. But when transplanted to large scale process conditions, the constructed organism was not stably maintained. The reason seems to have been the genetic inhomogeneity of the population, and the selection of a specific genotype better adapted to the different environment. "This example illustrates the requirement for a rigorous analysis of the performance of recombinant organisms under simulated process conditions," the report concludes. "Advances made in our knowledge of the environmentally controlled expression of constructed genotypes may well be of crucial importance for the industrial application of recombinant organisms."

Among specific areas which the EEC report identifies as significant for progress in biotechnology are the physiology of organisms from unusual environments; post-translational modification of proteins; micro-environmental regulation of the cell cycle; and microbial activities in consortia, biofilms and immobilized systems. But Harder and his group warn that the comparative neglect of microbial physiology in recent years has produced a global shortage of well-qualified specialists to tackle such questions. "There is little doubt in our minds," they say, "that this will create a bottleneck in biotechnological innovation, particularly in North America, but also to a lesser extent in Japan and Europe." Last year's report from the Office of Technology Assessment, they suggest, painted "a too-rosy picture of the role of recombinant DNA techniques in the development of new products." Time, it seems, to remember Marjory Stephenson and return to basics.

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