ADVANCES IN BIOTECHNOLOGY

Volume I

Scientific and Engineering Principles

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GUEST EDITORIAL I

BIOCHEMICAL ENGINEERING: WHERE HAS IT BEEN AND WHERE IS IT GOING?

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"Biochemical engineering" has been with us for more than three decades. The term first appeared publicly in the May, 1947, issue of Chemical Engineering magazine (Kirkpatrick, 1947a) in an editorial entitled "The Case for Biochemical Engineering." In essence this was a proposal for the establishment of formal educational opportunities that would permit at least some chemical engineers to become more familiar with the biological sciences, especially biochemistry and microbiology.

Later in the same year this initial suggestion was reinforced. The 1947 "Award for Chemical Engineering Achievement" was given to Merck & Co. for "successful pioneering in the large-scale production of...streptomycin." The article accompanying the announcement was entitled "A Case Study in Biochemical Engineering," (Kirkpatrick, 1947b). In it, Chemical Engineering's editor argued forcefully and, in view of subsequent developments, successfully, for recognition of "biochemical engineering" as a legitimate and needed activity.

The American academic community was quick to respond to this invitation. In fact, the University of Wisconsin had apparently anticipated it. A separate undergraduate degree program was approved there in 1946, although no students were enrolled until a year later (Hougen, 1947). Wisconsin's pioneering effort was followed closely by others and several "biochemical engineering" curricula were established over the next few years, most of them as options in conventional undergraduate chemical engineering programs (anon, 1951). Two of these were differently structured, however: MIT's program was set up in what was then the Department of Food Technology (now Nutrition and Food Science) while that at Columbia was restricted to the graduate level on the grounds that such a degree of undergraduate specialization was ill advised. By the mid-1950's academic enterprises labeled "biochemical engineering" had appeared in England and Japan. Others followed later in continental Europe, India, and Latin America.

As we look back at the genesis of biochemical engineering a number of points are worthy of special note. They provide useful insights into the evolution of biochemical engineering and also offer valuable guidance for evaluating its future prospects.

First, we should note that even though the term "biochemical engineering" may have been an editorial invention, the field was not. Chemical and civil ("sanitary") engineers had long dealt with processes based on biologically catalyzed chemical change. Indeed, the 1947 Chemical Engineering Achievement Award, cited above,

specifically acknowledged the achievements of one group of chemical engineers who had overcome the unique constraints and problems associated with large-scale antibiotic production by aerobic organisms. Many other industrial and governmental groups enjoyed equal success in similar technological developments and all did so without the imprimatur of "biochemical engineering." Few of the individuals involved had had the benefit of educational preparation such as that provided by even the pioneering curricula of the late 40's and early 50's.

Next we should recognize that biochemical engineering arose as a general response to specific technological needs. An industry already existed and this industry was encountering problems for which the available knowledge base was inadequate. Biochemical engineering developed, informally at first and later formally, to provide this knowledge. Professor Shuichi Aiba (1980) recently made exactly this point when he pointed out that most early biochemical engineering research was concerned with establishing, through external control, an environment for the organism which the biochemist/microbiologist deemed to be desirable. Analysis and measurement of oxygen transfer by aeration, design of reliable air and medium sterilization processes, and the development of pH control methods are examples of these very significant achievements. Furthermore, all of them illustrate a phenomenon which I shall call "technology-pull." This will be more fully described later on.

Biochemical engineering was then the issue of a "marriage of convenience" between biotechnology and a rapidly evolving fundamental approach to chemical process analysis and design. During the 1930's chemical engineers were moving steadily away from their industrial chemical origins. Generalized concepts for dealing with rate processes had been formulated and successfully applied to a variety of situations. These concepts and the methods for applying them were precisely the tools needed to deal with the first generation of biochemical engineering problems --aeration and oxygen supply for example. Large-scale production of penicillin and streptomycin introduced the biotechnologist to problems for which their previous, largely anaerobic, experience offered little guidance. The new generation of chemical engineers were simply in the right place at the right time.

Finally, examination of its origins convincingly demonstrates that biochemical engineering was largely an academic invention. This conclusion is, incidentally, as valid for England and Japan as it is for the United States. Society's needs would have been met, as they were prior to 1947, by chemical engineers working more or less harmoniously with biochemists and microbiologists even if no one had conceived of the term and no academic programs had been invented.

This does not mean that sound academic programs in biochemical engineering are unnecessary. On the contrary, these programs have contributed much to biotechnology. They provide graduates who are better prepared to cope effectively with the vagaries of bioprocesses and their research activities have given rise to methods for the solution of many generic problems associated with these processes.

Despite its earlier contributions, the influence of the academic biochemical engineering community has been significantly eroded over the last decade. Although most clearly evident in North America, the same trend can be recognized elsewhere. In what remains of this paper I would like to analyze more fully the current state of biochemical engineering and offer some suggestions for its future. Before doing so, however, I would like to look for a moment at the driving forces which generate technological development.

"TECHNOLOGY-PULL" AND "SCIENCE-PUSH"

Earlier I used the term "technology-pull" for the driving force behind biochemical

engineering's early achievements. "Technology-pull" means simply that an industry --an organized technology--already exists and provides the stimulus for basic engineering research. This research is carried out to make the existing technology more effective. Its objectives may be to better understand the phenomena which underly existing practices, to rationalize and improve design methods, to improve reliability and reduce uncertainties and, in general, to sweep out empiricism.

In contrast to "technology-pull" we have "science-push." Here achievements in basic science, independent of existing industrial technologies, provide the driving force for engineering research and development. Some outstanding examples are nylon, solid state devices and the microprocessors which use them, and, in biotechnology, immobilized enzymes. There is little doubt that recombinant DNA techniques will constitute the most potent "science-push" ever to be felt in our field.

CURRENT STATE OF BIOCHEMICAL ENGINEERING

Earlier I suggested that biochemical engineering was primarily an academic invention and that its early efflorescence was in large measure a result of the effectiveness of academic research in addressing the real problems of an existing industry--that is, "technology-pull." I also expressed my belief that the influence of the academic biochemical engineering community is declining. If this is a valid assertion, then what are the reasons?

A major factor contributing to this situation has been the limited growth of biotechnology--and hence employment opportunities for biochemical engineers-- during the late 60's and 70's. Furthermore, many industries and research centers regularly fill "biochemical engineering" positions with chemical engineers and others who have no special academic preparation in the field. These individuals may then obtain added background through the many continuing education opportunities which exist--university evening courses, special short courses, etc.

An even more significant reason for the fading influence of academic biochemical engineering is, in my opinion, the increasing failure of its research activities to address problems which "matter"--that is, to respond to "technology-pull." There is a growing monasticism in the academic community. Young faculty members enter it with little or no experience in the field. Pressed to publish by tenure rules and practices and supported by government grants given in response to proposals evaluated by other faculty members, they all too often invent hypothetical problems which can be solved rather than attacking real problems which ought to be solved.

This alienation of the academic research community from its external constituencies is, I submit, real. Furthermore, it appears to be on the increase, at least in North America. Recently, Dr. Herbert Fusfeld, Director of New York University's Center for Science and Technology, offered the following observation (Fusfeld, 1980):

> "Federal funds for university research from 1950 to 1970...did strengthen our foundation of science, our university research capabilities, the training of graduates, and hence the infrastructure for future industrial growth. But the bridge between university and industry, although neither completely broken nor abandoned, fell into disuse. Research objectives evolved from government goals and funding.... While industrial research became stronger internally, the university research community leaned toward its new and generous patron."

Another critical factor in the American biochemical engineering experience has been the diversion, ever more rapid since the mid-50's, of the basic science community away from biotechnology. Most of the financial support for biochemical and microbiological research in American universities over the last two decades has come from health-related sources. As faculty members interested and experienced in the technological applications of biological systems have retired, they have generally been replaced by persons whose interests lie elsewhere.

One important result of this trend has been a marked decline in "science-push" stimuli for biochemical engineering research. This situation has been further exacerbated by the relative failure of the few "science-push" developments in biotechnology which did appear during the last two decades--single-cell protein production from hydrocarbons and immobilized enzyme techniques--to find major application. Although recent funding support for basic research on renewable energy sources has drawn some life scientists back to biotechnology, it is still only a trickle.

A secondary result of the massive change in orientation of the life sciences is less obvious but no less important. To fill the university void in basic science support for biotechnology, a few persons educated as engineers have reeducated themselves to carry out research in biochemistry and biology. Although some individual accomplishments have been striking, this approach requires both special dedication and extreme effort. Less happily, it can become an obstacle to advancement in the purely engineering academic domain.

So far, these problems have been most evident in North America and, to a lesser extent, in the United Kingdom. Continental Europe and Japan, with strongly established traditions of cooperation between universities, industry, and public agencies, have fared much better. Another significant difference is found within the academic establishments themselves. In the United States, Canada, and the United Kingdom biochemical engineering activities have been almost exclusively a province of chemical engineering departments. (The MIT program is a notable exception.) This practice is in accord with the traditional university structure in these countries, where engineering education is separated by rather rigid barriers from education in the sciences. Furthermore, it reflects their historical experience. When formal educational programs in biochemical engineering were first launched, there were proposals that this field be treated as a "new engineering discipline" (anon, 1951). The reaction to these suggestions was increasingly negative, so as biochemical engineering programs developed they were held tightly in the embrace of chemical engineering educators. An unfortunate result of this approach was increasing isolation from the basic life sciences.

In contrast, the European pattern has been to treat biotechnology in a more unified manner. Basic science and engineering are more closely associated, often in a single organization structure--university institute, academy of science, etc. The European "technical university," combining in one structure all aspects of technology--mathematics, science, and engineering--has, of course, facilitated this approach.

SOME SUGGESTIONS AND PROPOSALS

Biotechnology may be said to comprise all aspects of the exploitation and control of biological systems for technological ends. Biochemical engineering is its engineering component and as such its fortunes are and will continue to be inexorably linked to those of the broader field. There have been no significant new developments in biotechnology over the last decade so it has been a frustrating time for biochemical engineering. Still biochemical engineering research activity has continued to expand--at least that part of it which is visible through

publication, hence primarily work from universities and research institutes. Much of this research has, however, been remote from the needs of practice.

There are now about us many indications that we may be on the threshold of a new era of expansion in biotechnology. If academic biochemical engineering is to contribute to this new phase as it did so effectively in the 1940's and 50's, then it must become more responsive to the needs of its external constituencies. It is essential that we maintain and reinforce the bridge between university and industry where it remains strong and restore it where it has fallen into disuse. To do so may well require changed attitudes on the part of biochemical engineers in universities and in the organizations which employ them.

It is especially important for younger members of the university community to establish effective contact with the "world of practice." University people must get out and ask what the problems are. Consultation is one approach but I am not convinced that it is the best. It tends to tie one to a single viewpoint and, for younger people with limited experience, this may tend to narrow rather than broaden.

Perhaps those of us who are older have simply failed to communicate the real pleasure which can be derived from contributing to the solution of "real" problems. Peter Medawar, the British biologist and Nobel Laureate, has recently published an inspiring little book entitled Advice to the Young Scientist (Medawar, 1979). In it he asserts that to make important discoveries a scientist - and I would add "engineer" - must work on important problems. The results must matter; there must be someone - a group of people or an entire segment of society - who already need and want the results of the research in which one is engaged.

On the other side of the coin, industry must overcome its frequently excessive concern for security. In fairness, I must say that I have personally never found this to be as great an obstacle as is often claimed. But there is no question that industry, fearful of losing its "secrets", has often shut out those who ought to constitute a singular resource - the academic community.

In summary, future prospects for biotechnology are bright. If biochemical engineering is to take its proper place in this new age it must strengthen or, where they are lacking, establish mechanisms for identifying the generic research needs of biotechnology and for responding to them effectively.

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GUEST EDITORIAL II

GENETICS AND INDUSTRIAL MICROBIOLOGY: STILL FURTHER HORIZONS

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The program committee challenged me to aggregate some of my own thoughts on the strategies of further development in recombinant DNA technology. My focus will be on some rather manifest elements in the logic of the existing science and technology. This is moving so rapidly that we are contemplating a time horizon with a median of perhaps five, or at most ten years for further developments. There will be some vexing exceptions; it is not always possible to anticipate in advance just how hard a given problem is going to be: a number of things can be foreseen with some confidence as being on the agenda of the next symposium of this kind within the next few years. There will be exceptions; twenty years ago, many of us believed we would soon advance from the cloning of a frog from somatic cell into the egg, to the cloning of a mammal. That has so far proved not to be feasible.[1] Perhaps fundamental biological distinctions between frogs and mammals, of which we are still not fully aware, impede those kinds of developments. Similar pitfalls may affect the extrapolation of DNA technology. However, if we look at the recent past, if anything the pace of events in the last five years has exceeded most people's prognostications, even my own. One loses one's breath trying to keep up with the pace, not only in scientific, but in technological developments in this field.

May I take a few things as given for this discussion, without depreciating the enormous ingenuity and diligence, insight and imagination that are involved in the development of the techniques? They are also very great fun, and I don't want to deprive anybody of the opportunity to engage in those details, even though I am going to leap-frog over all of them just now. My stipulation is that our appreciation of the structure of DNA and of a few of the enzymes (I think we have far from exhausted them) that are involved in its replication, in recombination, in repair, in splicing and so forth, and in the regulatory factors that control those, permits us to plan the manipulation of DNA as if it presents difficult but surmountable technical problems. It is very difficult for me to visualize an objective in DNA design for which we cannot outline a plausible research program.

Our strategic challenge, almost unique in the history of technology, is less "how" than "what"! Many techniques other than DNA-splicing and implantation into an appropriate vector are crucial for useful applications. They include the systematic fractionation of DNA, particularly from eukaryotes with large genomes, the isolation of particular components with the best ways of expanding them; modifying those sequences in ways that open up new lines of experimentation with respect to the end products that one is going to see, the confrontation of products in a

variety of metabolic pathways with one another, techniques for sequencing both in an analytical and in a synthetic sense the desired intermediate and end products. However, I repeat, those are today fairly manifest technical problems for which answers are being found every day. We can conclude that we have a very thorough repertoire of procedures, either in hand, or very shortly to be in hand, to do whatever is socially, technically and economically feasible and desirable in those spheres.

As we work our way through these problems, we find, for example, ways in which we can assure fairly consistent expression of a sequence, even at very low levels. We can, of course, then use the most sensitive, or selective procedures to isolate the rare progeny we seek. We are already much further along today than we were two or three years ago in this methodological infrastructure.

How then do we manage the development of this technology? Our orientation should not be confined to products themselves, but also how these can be introduced, marketed and integrated into our science, technology and economy. These issues deserve at least a small percentage of the time that is now occupied with the technological feasibility of specific ventures. Please recall, too, that DNA splicing is just one of a host of techniques for doing genetic experimentation, which began in a systematic way about 115 years ago with Mendel. Hybridization is still the bedrock of genetic analysis in all organisms; recombining DNA in the way that nature had evolved will still play a very large part in all that we do in this field in a very wide variety of organisms. Still other technologies have to be thought about: the development of chimeric or mosaic embryos, organisms which contain no admixtures of DNA within a single nucleus but the allophenic mice that Beatrice Mintz is making, where the embryos are constituted from zygotes of a variety of origins. This opens up another modality of "genetic engineering"; it begins to breach the boundary between the somatic and the germ line in a given animal and permits the introduction of genetic innovations into a germ line that would not otherwise be feasible. This can go on over a wide variety of other ontogenetic technologies.

The one development that I would neither advocate nor foresee in any practical way is the direct application of gene modification to human beings. There has been an enormous amount of nonsense about that, at the levels both of technical feasibility and of moral, political and practical and common-sense feasibility. One has to stop and think what one would have to do to validate a procedure that one would wish to advocate for the rectification of genetic disease in an already existing individual suffering from a genetic defect. I think one sees immediately the impossibility of the situation. How would you ever set up a clinical trial that would enable you to demonstrate that injecting DNA or any other such material into, say, a child with sickle cell disease or cystic fibrosis or phenylketonuria was an efficacious and safe procedure, particularly in the face of competing techniques that have a higher degree of predictability and assurance and reliability - and I refer here particularly to pre-natal diagnosis and pre-emptive abortion? I think the moral imperative to prevent the birth of defective children by our insight into the inevitability of genetic disease in certain confrontations, in our ability to monitor those pregnancies with more and more specific and reliable methods for knowing just what the outcome of a particular gestation is going to be, is an ethical categorical that overrides the possibility of the clinical trials for the rectification of disease, once established.

On the other hand we are going to learn a great deal about diagnostic human genetics, the understanding of the way in which gene alterations result developmentally and physiologically in a defective line, and how these can be mitigated by therapeutic measures as well as by the pre-emptive ones that I have just indicated. Diagnosis will be the main role of DNA technology applied to humans.

Even more than the products we surely will make, the applications to industrial microbiology, insight into the genome, particularly in human beings but also in

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