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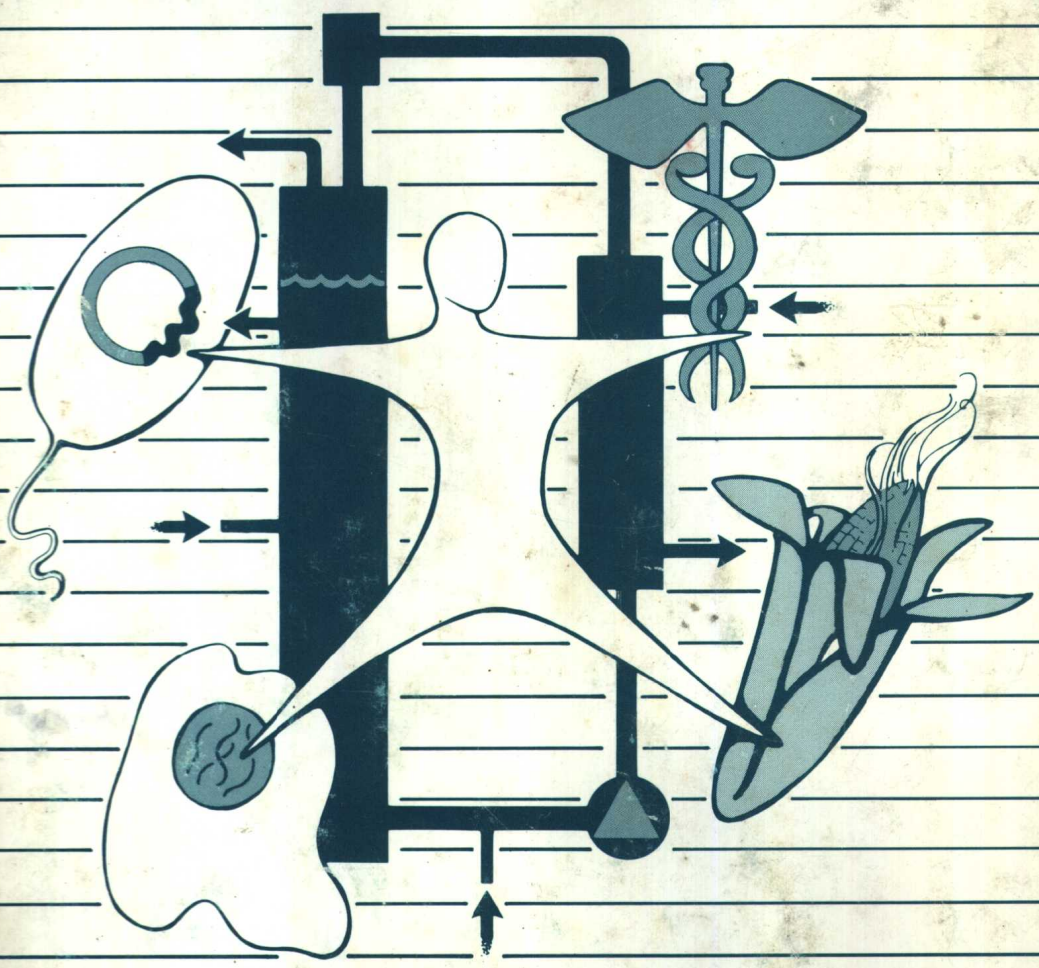
Basic Biology of New Developments in Biotechnology



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Basic Biology of New Developments in Biotechnology

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Most significant were the conception, imagination, and planning efforts for the conference lead by our symposium organizer, Allen Laskin and supported by our Scientific Advisory Committee, consisting of Victor Bloomfield, Stanley Dagley, Richard Hanson, Harry Hogenkamp, and Alexander Hollaender. We appreciatively acknowledge the valuable consultation and expertise of the Local Organizing Committee and the Office of Continuing Medical Education.

This symposium forms the third in a series of conferences including "Trends in the Biology of Fermentations for Fuels and Chemicals" held in December, 1980, and "Genetic Engineering of Microorganisms for Chemicals" held in May, 1981; both of which have also been published by Plenum Publishing Corp., New York. Taken together, these three volumes describe the interfacing of basic knowledge of genetics, biochemistry, and microbiology with the new advances in fermentation technology, drug design, agricultural plant development, and medicine, that will assist in opening new directions in the biotechnology of the future.

I express thanks to my fellow associate editors, Allen Laskin and Alexander Hollaender assisted by our editorial team of Stanley Dagley, Richard Hanson, Larry McKay, and Joachim Messing. We appreciate the conscientious and exceptionally competent job of our Technical Editor, Claire M. Wilson and her associates in assembling the manuscripts.

Most importantly, the success of this symposium rested squarely upon the creativity, vitality, and cooperation of the speakers, conveners, and authors whose efforts we enthusiastically acknowledge in composing this fine volume.

Palmer Rogers

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INTRODUCTION

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I was contacted in the Fall of 1981 by Professors Martin Dworkin and Palmer Rogers, of the University of Minnesota and asked to participate in the orgnization of the 1983 conference in the series, "Interface Between Biology and Medicine". They and the other members of the advisory committee had the vision to realize that this was a time to depart somewhat from the traditional theme, since one of the major areas of interest in the biological and related sciences these days is that of biotechnology in a broader sense than its impact on medicine alone. In designing the format of the Conference, we considered another factor. There has been a plethora of conferences, symposia, and meetings on biotechnology over the past few years, and the faces and topics have become rather familiar. There has been a strong emphasis on the development of the technology and the "biotechnology industry"; less attention has been paid to the science behind it. One might get the impression from some of these meetings and from the popular press that biotechnology has just recently sprung up, apparently full blown; the very fundamental scientific discoveries and the great body of

continuing research that forms that basis for the technology is often obscured.

Thus, those of you who have been attending biotechnology conferences will recognize from this program that the mix of people is quite different. An attempt was made to touch upon points across the entire spectrum, from fundamental biological, biochemical, or genetic research on one end, to bioengineering, perhaps, on the other. We were faced, however, with some constraints and conflicting goals: carrying out the mission of spanning that entire spectrum, but limiting the number of speakers and providing enough time for effective communication and discussion, covering as many areas as possible upon which biotechnology impacts, and doing it all in the space of two and a half days. I hope we have succeeded in our major goal -- to emphasize the great importance of the fact that the new developments in biotechnology have depended upon, and continue to depend upon basic research in a large number of biological and related science disciplines.

At this point, since the theme of this conference is the basic biology of new developments in biotechnology, we should attempt to define what we think biotechnology is. Again, if one reads the popular and semi-popular press, one might get some rather distorted impressions. One, for example, is that biotechnology and recombinant DNA are the same thing; I have seen the two terms used synonymously. I think each of us readily recognizes that biotechnology is not recombinant DNA; neither is it "genetic engineering". Genetic engineering, of course, includes recombinant DNA technologies plus a number of other technologies for manipulating genetic material, but all of that together still represents only one aspect of biotechnology. Another area to be considered is "enzyme engineering". Last Fall, I was invited to a conference in Tokyo, the title of which was, "Biomolecular Technology". The Japanese scientists involved in that conference were putting together a discipline that they propose

to call "biomolecular technology", which is a marriage of genetic engineering and enzyme engineering. That is certainly a valid concept, but it still represents only a part of what I like to think is biotechnology.

Others have wrestled with a definition of biotechnology. A working party of the European Federation of Biotechnology came up with the following in 1980:

> "Biotechnology is the application of biological systems or processes to manufacturing and service industries."

At first glance that seems OK, but after pondering over it, I wondered if that definition also included the horses that pulled the Budweiser beer wagons in the television commericals! The Federation didn't accept that definition, and in 1982 a new definition was promulgated:

> "Biotechnology is the integrated use of biochemistry, microbiology, and engineering sciences in order to achieve the technological application of the capacities of microorganisms, cultured tissue cells, and parts thereof."

Other terms are used in the context of biotechnology: applied microbiology, industrial microbiology, applied biochemistry, biochemical technology, and the previously discussed biomolecular technology. And relatively recently, the scope of the field has been broadened significantly by the inclusion of hybridoma technology. It is clear that a simple, generally acceptable definition of biotechnology is elusive. It is an integrated multidisciplinary field that utilizes many different technologies and impacts on a wide variety of areas. Let me detail some of these.

As a microbiologist, I place microbiology in the center, among the other core disciplines -- biochemistry, enzymology, and molecular genetics. Surrounding this core are the broader areas of molecular and cell biology, immunology (which, especially with the advent of monoclonal antibodies, may well be considered a core discipline), organic chemistry in many of its manifestations, and some more applied disciplines such as agricultural science, food and fermentation science, and special technologies such as animal and plant tissue culture. One can undoubtedly think of others; the point is clear, i.e., that biotechnology involves and is intimately connected with a large number of scientific disciplines and technologies.

And what of the impact areas for biotechnology? A few of the key areas that have received the most attention are pharmaceuticals and human/veterinary health care, chemicals, energy, food, agriculture, and environment. Most of these are touched upon in this conference, but there are other areas, such as microbe/metal interactions and marine science, which have received considerable attention. Indeed, there are few areas of human endeavor which have not received consideration with respect to biotechnology.

Let me return to the theme of the conference, the importance of fundamental science as related to biotechnology. As an example, I've selected what is perhaps the most widely known and popular "breakthrough" that relates to biotechnology -- recombinant DNA. Some think that recombinant DNA is a phenomenon that burst forth suddenly a few years ago. I think most of us recognize that this development represented a series of interdependent breakthroughs, all in turn dependent on a huge body of research in molecular biology, genetics, microbiology, and biochemistry. Examples include the discovery of Class II restriction enzymes by Smith and colleagues; methods of ligating DNA molecules, including the Khorana and Sgaramella work on blunt end ligation with T_4 ligase and the work of two Stanford groups (Lobban and Kaiser; Jackson, Symons, and Berg) on ligating molecules with complimentary cohesive ends; additional

work at Stanford on Eco R1 (Mertz and Davis; Sgaramella); rapid DNA sequencing (Maxam and Gilbert; Sanger); gel methods for analyzing DNA fragments (Sharp). All of these and many more were necessary before Cohen, Chang, Boyer, and Helling produced their well known biologically functional recombinant DNA molecules.

For the Conference, we selected several of the more important impact areas of biotechnology, and have attempted to provide some feeling of the inter-relationship between fundamental research in various disciplines and the development of the related biotechnology. In some areas, there has been a more-or-less orderly progression from fundamental research through technology and on towards commercialization; in others, attempts to develop technology have have proceeded much faster than has been warranted by the science background, and they are languishing, waiting for the science to catch up.

For decades in the drug and antibiotic field, brute screening methods were used for new drug discovery or for the improvement of production. In the past few years, fundamental new understanding in biochemistry and genetics of the antibiotic-producing streptomycetes has opened new pathways for new compounds and for improvements in their production. New approaches to drug design are also based on fundamental new knowledge, e.g., of enzyme mechanisms.

Biotechnology in agriculture has vast and multiple ramifications. In one area, plant genetics is an example where the fundamental work of Barbara McClintock at Cold Spring Harbor Laboratory over several years went practically unnoticed, or more accurately, not understood. Only recently has it been fully appreciated that she was working with the first reported system of movable genetic elements; one of the presentations in this volume addresses this system. Similarly, decades of work on the microbially-caused tumors of plants, known as crown galls, have led to the development of a most promising vector for gene transfer in plants, the Ti plasmid.

The special lecture by Professor Whittenbury deals with organisms, the methane-oxidizing bacteria, that have been known since 1905. In the past decade, basic studies on microbiology, biochemistry, and enzymology carried out in Prof. Whittenbury's lab in Warwick; by a group at the University of Kent; by Prof. Hanson, now director of the Freshwater Institute here in Minnesota; and in our own laboratories at Exxon have led to a very great interest in these methane-oxidizing and related microbes as important biotechnological organisms.

Several papers deal with one of those areas where attempts to develop biotechnology have perhaps been several steps ahead of the required fundamental knowledge in biochemistry and genetics. This relates to the anaerobic bacteria, which carry out many interesting reactions. One of the most famous biotechnological processes is the acetone/butanol fermentation, developed during World War I, and carried on through the Second World War. Work here in Professor Roger's laboratory is now going on in an attempt to better understand these organisms, and another paper in this volume discusses these and other anaerobes. Almost nothing is known about the genetics of anaerobic bacteria, and there is a lot of catching up to do in genetics as well as biochemistry before we can fully exploit their capabilities.

I'll just mention one other area -- that of biodegradation of pesticides, herbicides, and other potential environmental pollutants. While many of these are readily biodegradable, others have proved to be recalcitrant and are persistent in soil and water. In recent years, a great deal of research has been done on the biochemistry and genetics of pesticide-degrading organisms; much important work has been done by Professors Chapman and Dagley, here at Minnesota. Based on this new knowledge, it is now possible to construct new strains that are able to attack substances previously thought to be quite resistant to biodegradation.

Although these proceedings range widely, it can only begin to scratch the surface. What is clear is that there is a great deal to be done in fundamental biology, in biotechnology, and at the interface between the two.