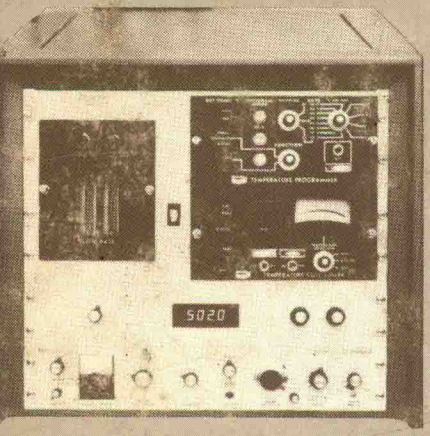
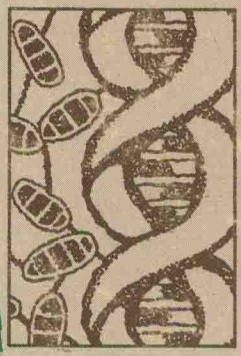
The Impact of Chemistry on Biotechnology

Multidisciplinary Discussions





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The Impact of Chemistry on Biotechnology

Multidisciplinary Discussions

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Foreword

The ACS SYMPOSIUM SERIES was founded in 1974 to provide a medium for publishing symposia quickly in book form. The format of the Series parallels that of the continuing ADVANCES IN CHEMISTRY SERIES except that, in order to save time, the papers are not typeset but are reproduced as they are submitted by the authors in camera-ready form. Papers are reviewed under the supervision of the Editors with the assistance of the Series Advisory Board and are selected to maintain the integrity of the symposia; however, verbatim reproductions of previously published papers are not accepted. Both reviews and reports of research are acceptable, because symposia may embrace both types of presentation.

Preface

BIOTECHNOLOGY, BROADLY DEFINED, includes any technique that uses living organisms or parts of organisms to make or modify products, to improve plants or animals, or to develop microorganisms for specific uses. Historically, techniques applying biotechnology have followed time-consuming methods of locating mutations with the desired characteristics, which may be naturally occurring or enhanced. These have involved relatively slow processes that have allowed the scientific community and the regulators of new products to keep pace with the progress. Progress changed abruptly in the 1970s when the first gene was cloned, and the first expression of a gene cloned from a different species in bacteria was accomplished. A precise alteration of the DNA nucleotide process bypasses the slow process of seeking improvements through mutation.

Chemists and chemical engineers since then have played an important role in realizing the potential of biotechnology through advancement in the molecular-level understanding of biomolecular structure, function, and mechanism, and their application to chemical problems. Increasing numbers of chemists and chemical engineers from a broad range of disciplines have identified with this mission.

History of the Biotechnology Secretariat

The American Chemical Society is also playing a major role in the use of chemistry in biotechnology by providing a forum for the exchange of research results, application information, analytical uses, and other benefits of biotechnology. The role of biotechnology is spread across many disciplines within the Society. Consequently, a full discussion of the subject required cooperation by many of the constituent divisions of the ACS. After two years of discussion and meetings, the Biotechnology Secretariat was formed. It evolved from the attractive feature of coordinated programming of biotechnology presentations. Through this organization, the programming would be presented to minimize conflicts in schedules, to permit members of the Society to attend many presentations on the topic, and to allow for a planned progression of the overall programming on a regular basis over the next several years. Through the Secretariat, divisions would develop symposia on common topics to ensure that all relevant issues are covered.

A large number of divisions are participating in the activities of the Biotechnology Secretariat: Agricultural and Food Chemistry; Agrochemicals; Analytical Chemistry; Biological Chemistry; Carbohydrate Chemistry; Cellulose, Paper, and Textile; Chemical Education, Inc.; Chemical Health and Safety; Chemical Information; Chemical Marketing and Economics; Chemistry and the Law; Environmental Chemistry; the History of Chemistry; Industrial and Engineering Chemistry; Medicinal Chemistry; Microbial and Biochemical Technology; Petroleum Chemistry, Inc.; Physical Chemistry; Polymer Chemistry, Inc.; and Polymeric Materials: Science and Engineering.

The initial coordinated activity of the Secretariat occurred during the ACS national meeting in Anaheim, California, in September 1986. The Secretariat invited participation from the divisions for the symposium cluster titled "The Impact of Chemistry on Biotechnology." From the symposia that were presented, an outline was developed for this book.

The book is divided into several sections, each of which has a focus related to the interests of the contributing division. The contribution of the book is to illustrate by means of examples, which are not all-inclusive, the impact of chemistry on biotechnology. Our purpose was to demonstrate that biotechnology encompasses a broad spectrum of chemistry with tangible quantitative examples. We hope that the overview and the divisional sections collectively address the multidisciplinary topic of biotechnology.

Acknowledgments

The program chairs of the participating divisions deserve a special note of recognition. Their consideration and cooperation were vital parts in enabling the Program Chair of the Secretariat to organize and present the symposium cluster. John Crum, Executive Director of the ACS, and Randall Wedin, Special Assistant to the Executive Director, provided important assistance in the organization of the Biotechnology Secretariat.

The Committee on Science chaired by Paul Gassman provided a financial grant to the Biotechnology Secretariat to initiate our organization and to launch our first symposium. Numerous people in the divisions, in the staff of the Society, and in the Society in general provided time, counsel, ideas, and patience. The editors acknowledge the following:

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These six divisional organizers of the subsymposia for the cluster symposium in Anaheim provided the introductory chapters for this book. Their efforts and time made the symposium and this book possible. To those many individuals we say thanks.

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OVERVIEW

Chapter 1

The Role of Chemistry

Leroy Hood

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There has been a revolution in the techniques of biology over the past ten years that has dramatically changed the face of modern biology. Three biotechnologies, recombinant DNA techniques, monoclonal antibody techniques and microchemical instrumentation, have made especially important contributions to this revolution that has come to be called the new biology. These biotechnologies are synergistic and together they have greatly shortened the time between many fundamental biological observations and their clinical applications in the world of medicine. Most have some perception of the recombinant DNA and monoclonal antibody techniques. I will focus on the third, microchemical instrumentation, machines that synthesize and sequence genes and proteins, because it demonstrates the power of chemical techniques in biology.

DNA and proteins

The double-stranded DNA molecule makes up the central core of the 23 pairs of human chromosomes and is the blueprint repository for information on how to construct human organisms. DNA has four subunits, the G, C, A, and T nucleotides, and one strand of a DNA molecule always exhibits molecular complementarity for its partner because an A subunit always pairs with a T and the G subunit always pairs with a C. The fundamental units of information in the DNA molecules, the genes, are translated into intermediate messenger RNA molecules, essentially working computer tapes capable of enormous amplification, and these in turn are fed into specialized organelles that synthesize proteins. The four-letter language of DNA is read three units at a time into the 20-letter language (amino acids) of proteins. The primary sequence of amino acids in a protein dictates how the individual protein folds into a particular three-dimensional configuration. Thus, the linear information of the genes is changed into the three-dimensional information of proteins. Proteins are the molecular genes that give the body size, shape, and form, and catalyze the chemical reactions of life.

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The genetic code dictionary relates the DNA and protein languages so that knowledge of the DNA sequence (order of nucleotides in a gene) allows one to predict precisely the amino acid sequence of its corresponding protein, and conversely, knowledge of the amino acid sequence of a protein permits one, with some ambiguity, to predict the gene sequence. The ability to employ the genetic code dictionary to determine protein sequences from gene sequences and conversely gene sequences from proteins is important in later methodologies we will discuss.

Each human cell has sufficient DNA in its 23 pairs of chromosomes, its genome, to encode 3 million average-sized genes 1,000 nucleotides in length. This calculation is somewhat misleading in that most genes are divided into two or more coding regions (exons) and intervening sequences (introns). Moreover, it has been estimated that only 3% of the genome is actually involved in coding regions for the estimated 100,000 genes necessary to construct a human organism. Nevertheless, recombinant DNA techniques permit individual genes to be isolated and characterized.

Recombinant DNA techniques

The discovery of DNA cutting enzymes, the restriction endonucleases which cut precisely at particular double-stranded DNA sequences, and the DNA joining enzymes, the ligases which join together DNA fragments, paved the way for the new recombinant DNA techniques. These enzymes enable one to take a particular human gene, γ-interferon, and splice it into the DNA sequence of an appropriate DNA vector, such as a circular bacterial plasmid, which is approximately 5,000 nucleotides in length. Then this hybrid DNA molecule may be placed in bacteria where it replicates and thus amplifies the number of interferon genes which can accordingly be removed from the vector sequences by restriction endonucleases. The challenge in this procedure is to isolate from among the potential 3 million genes worth of DNA in the human genome a particular gene of interest. This goal is relatively straightforward for genes that transcribe ample quantities of messenger RNA. It is far more difficult for the so-called rare-message genes that make little messenger RNA. It was a consideration of this problem that led in part to the development at Caltech of the collection of instruments that have come to be known as the microchemical facility.

Microchemical Facility

Over the past ten years my laboratory has developed a series of instruments (Table I) that permit us to sequence and analyze genes more effectively than had been possible heretofore. Let me discuss several of these instruments and consider the impact they have had and will continue to have on problems of central importance to modern biology.

Table I. Michrochemical Facility at Caltech

FINISHED	
GAS PHASE PROTEIN SEQUENATOR	- SEQUENCES PROTEINS
PEPTIDE SYNTHESIZER	- SYNTHESIZES PROTEINS
DNA SEQUENATOR	- SEQUENCES GENES (DNA)
DNA SYNTHESIZER	- SYNTHESIZES GENES
COMPUTER	- UNIQUE PROGRAMS FOR THE ANALYSIS OF PROTEINS AND GENES
HEXAGONAL ARRAY PULSE FIELD GEL ELECTROPHORESIS	- SEPARATES LARGE FRAGMENTS OF DNA
UNDER DEVELOPMENT	
GENE ANALYZER	- INSTRUMENT FOR FINGER-PRINTING HUMAN GENES
SECOND GENERATION PROTEIN SEQUENTATOR	- 10^3 TIMES MORE SENSITIVE THAN CURRENT MACHINES
COMPUTER SUPERCHIP	- APPLICATION OF TRW SUPERCHIP TO NEW APPROACHES FOR DNA AND PROTEIN ANALYSIS

Automated Protein Sequence Analysis. Automated protein sequence analysis employs Edman chemistry to sequentially cleave individual amino acid residues from the N-terminus of the polypeptide chain. Since the introduction of the automated spinning cup sequenator by Per Edman in 1967 (1) revolutionary improvements have led to striking increases in the sensitivity of protein sequence analysis (Table II). Our objective at Caltech is to further increase the level of protein sequencing sensitivity by 2-3 orders of magnitude. This level of sensitivity will permit us to routinely use two-dimensional polyacrylamide gel electrophoresis (2), currently the most sensitive and highly resolving analytic technique for the separation of complex mixtures of proteins, as a preparative device for isolating polypeptides for sequence analysis.

Table II. Improvements in Protein Sequenator Sensitivity

nmol	µg*		Instrument
100	5,000	1967	Edman Spinning Cup
10	500	1971	Commercial Spinning Cup
0.1	5	1978	CIT-modified Commercial Spinning Cup
0.02	1	1979	CIT Microsequencing Spinning Cup
0.005	0.25	1980	CIT Gas Phase Sequenator

*Weight of 50,000 dalton protein, assuming 100% sequenceable material.

To improve the overall sensitivity level of protein sequencing, simultaneous improvements in all aspects of the complex protein sequencing process are required. Improvements must be made

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