Molecular Cloning and Gene Regulation in Bacilli

EDITED BY

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Preface

This volume contains articles based on talks given at the Cetus Conference on Genetics held at Stanford University, Stanford, California, June 22–24, 1981. The topic of the conference was *Molecular Cloning and Gene Regulation in Bacilli*. It was sponsored and financially aided by the Cetus Corporation of Berkeley, California and the Stanford University School of Medicine. The chairman of the organizing committee was A. T. Ganesan, and J. A. Hoch and S. Chang were members. More than 200 participants from 12 different countries contributed to the success of the conference. After opening remarks by Dr. R. Cape of the Cetus Corporation and Dr. L. Crowley, Vice President for Medical Affairs, Stanford University Medical Center, the conference was officially opened by Nobel laureate and Stanford Professor of Biochemistry, Dr. A. Kornberg. Dr. S. N. Cohen gave the plenary lecture.

As we better understand the details of bacilli molecular biology, this group of organisms becomes increasingly important to applied research, which in turn could be of considerable benefit to mankind. The contributions to this work reflect both basic and applied aspects of bacilli genetics. During the last four years significant advances have been made in understanding chromosome structure, gene arrangement, molecular cloning, expression of cloned genes, DNA metabolism, transcription, and translation. These conference topics were organized into five program sessions, with Drs. C. Anagnostopoulos, J. A. Hoch, S. Chang, A. T. Ganesan, and R. Doi as conveners. The excellence of the program reflects these efforts.

Opening Remarks
"Bless the Little Beasties"

I am tempted to open this meeting with a talk about DNA replication. But there have been or will be other occasions to tell that story. I suspect, too, that Dr. Ganesan, who organized this conference, hoped that my remarks would be more general and philosophical, and I will therefore speak in that vein.

I once thought that progress in science was orderly and logical. I learned over time that instead it is dictated in large measure by fashion. The events of the last decade illustrate this clearly. In our field of science, the crest of excitement over molecular biology in the 1950s, based largely on microbial systems, drifted in the 1960s toward an interest in more complex eukaryotic systems. In the 1970s this drift turned into a stampede from microbes to mice, flies, worms, and slime molds. Now, the students we interview for graduate school all want to work on eukaryotic gene expression and they pronounce it as one word.

Of course I share in the curiosity and excitement of eukaryotic mechanisms. In fact some of my best friends are eukaryotes. What concerns me is the hysteria and the abandonment of fertile areas of microbiology in which the geese would still be laying golden eggs if only they were fed. So the theme of my talk this morning is a call to support basic studies in microbiology.

To be sure, most of the history of microbiology has been occupied with its practical applications: microbes in medicine, as the causative agents of disease in man as well as in other animals and plants; microbes in industry, as the agents whose fermentations generate cheese, wine, and pharmaceuticals; and microbes in agriculture, the agents responsible for carbon, nitrogen, and other elemental cycles essential to life on Earth.

This *Conference on Molecular Cloning in Bacilli* focuses on these microbes for their most recent practical utility, for exploiting them as factories for producing large quantities of a specific DNA sequence and the useful proteins encoded by these DNAs. The practical motives of this conference do not disturb me, nor does it worry me that the conference has an industry as a major sponsor. What does concern me is that we often forget that the greatest return of our collective research investment comes from a strong emphasis on the basic and broad aspects of microbial chemistry and biology.

People in this audience know, but others need to be reminded that the foundations of genetic engineering were never planned or programmed. They grew out of the basic studies of microbial genetics, DNA chemistry, and DNA enzymology—the nucleases, polymerases, and ligases; all discovered in microbes. These basic

studies in the 1950s and 1960s made possible the recombinant DNAs of the 1970s.

My initial training in microbiology, as a medical student more than 40 years ago, was in the medical tradition that "the only good microbe is a dead microbe." Some of this warped view of microbiology was corrected by a later exposure, in 1951, in Berkeley, to H. A. Barker, who introduced me to the use of enrichment cultures. Two years after that I met C. B. Van Niel. I was a student in van Niel's famous annual summer course at the Hopkins Marine Station. He lectured hours on end about the lives and exploits of the wonderful little "beasties." So extreme was van Niel's hostility to the medical influences on microbiology that he permitted no mention of any virulent microorganism and no consideration of the immunologic responses of animals to them.

He also wanted his beasties intact and in their favorite ecologic niches. I recall giving a research seminar that summer. In it, I described my work on the enzymes of pyrimidine biosynthesis using, as sources, yeast cells and some soil bacteria I had discovered by enrichment culture. Van Neil told me later that he admired the work but confided that he could not have brought himself to grind up the little beasties to obtain their enzymes.

It was in that year (1953) that I took over the chairmanship of the Department of Bacteriology and Immunology at the Washington University School of Medicine in St. Louis. Jacques Bronfenbrenner had been chairman of that department, which some years earlier had also included Alfred Hershey and Sol Spiegelman. The six years I served in reorganizing the staff, teaching, and research of that department, renamed Microbiology, had a profound effect on my subsequent work and career.

My first staff appointment was Osamu Hayaishi, now the doyen of biochemistry in Japan. My second was Melvin Cohn, a founding member of the Salk Institute. Most of the others who came between 1953 and 1956 remain as my colleagues at Stanford: Paul Berg, David Hogness, Dale Kaiser, and Robert Lehman.

In our teaching of microbiology we reduced the traditional emphasis on diagnosis and treatment of infectious diseases. We presented microbial genetics and biochemistry wherever possible. The students were rebellious. They complained of inadequate exposure to syphilis and gonococci. There was no tradition for our course and there were no suitable textbooks. The preparation of students for the National Board examinations was feared to be inadequate. But when we left for Stanford in 1959, Herman Eisen, who succeeded me as chairman, continued the same teaching program. The microbiology textbook by Davis, Dulbecco, Eisen, Ginsberg, and Wood, with its emphasis on genetics and biochemistry, eventually appeared. And we keep getting many letters and verbal comments from doctors whom we taught in St. Louis, expressing their gratitude for a superior preparation for their current practice of medicine.

None of the staff recruited in St. Louis had worked on nucleic acids or had had any interest in them. My own research until 1954 focused on the enzymology of nucleotide biosynthesis. My decision to work on DNA synthesis was not stimulated by the Watson and Crick paper in 1953, as perhaps it should have been, but rather by my teaching responsibilities in microbiology. In preparing course lectures on viruses, I became fascinated by the fact that infections of *E. coli* with T-even phages

caused a 10-fold increase in DNA synthesis within a few minutes. Also, in preparing a student laboratory exercise on Streptodornase, a streptococcal DNase, I had isolated the necessary DNA substrate from calf thymus. I found the alcohol precipitation step, in which the DNA is wound on a rod and lifted out of the beaker like a ball of cotton candy, a thrilling laboratory experience, matching the crystallizations that have seduced people into organic chemistry for generations.

It was in this way that I became aware of the rapid, inducible, synchronous DNA synthesis in a phage-infected cell, and I also became familiar with procedures for handling and isolating DNA. These things prompted me to look for DNA synthesis in an extract of phage-infected *E. coli*.

Of course, such an experiment would have been impossible without a radioactively labeled DNA precursor. Fortunately, Morris Friedkin was in St. Louis in 1954, in the Department of Pharmacology. He was the first to synthesize ^{14}C-labeled thymidine and was using it as a DNA precursor in chick embryos, rabbit bone marrow, and onion root tips. It was with labeled thymidine recovered from these incubations that I made the first attempts at DNA synthesis with *E. coli* extracts.

I had for a long time been interested in cell division and differentiation. I was especially fascinated by liver regeneration. I still am. A few hours after removing part of the liver, there is a dramatic awakening of DNA synthesis, mitosis, and cell division. My work with phages and my lectures on viruses also attracted my interest to the transformation of cell growth in cancer. I had also been concerned in the microbiology course with aerobic spore-forming bacilli and had been intrigued by the biochemistry of sporulation and germination. And so in 1962, after considering many alternatives, I chose bacterial sporulation and germination as an experimental model for cell division and development.

For several years part of my research group worked on the biochemistry of sporulation and germination in bacilli. James Spudich, David Nelson, and Carol Scandella as students and Arturo Falaschi, Peter Bonsen, Pierre Chambon, Murray Deutscher, Henrique Tono, James Vary, and Peter Setlow as postdoctoral fellows were at various times involved in the work. We gained a more realistic view of the biochemical and genetic complexities of sporulation. I realized too that it demanded a full-time commitment. In a choice between sporulation and replication I chose the latter. I am still convinced that work on sporulation will lead to profound and basic insights into cell differentiation. In fact, we may learn more from sporulation and germination about control of replication in animal tissues than from much of the work that deals directly with liver regeneration and cancer.

Microbiology has been a fertile area for basic biology. I am confident it will continue to be. It seems unlikely that the intricate patterns of genetic organization, expression, and replication evolved by microbes, split genes notwithstanding, are not shared throughout Nature.

Some argue that although the universality of biochemical mechanisms might apply to the most fundamental processes, there surely can be no point to studying the special sensory phenomena of eukaryotes in microbes. I have been chided by colleagues who say, "If you want to understand vision you work with retinas, not

bacteria." Well, such remarks may seem trenchant, but they often miss the mark.

Walter Stoeckenius' studies of a halophilic bacterium from San Francisco Bay salt ponds have done more for understanding rhodopsin action than many investigations of animal retinas. The purple membranes of these microbes contain rhodopsin and retinal in arrangements that are virtually indistinguishable from those of the animal retina. However, unlike the animal system, the bacterial purple membrane is obtainable in large quantities, is readily purified, is stable in the light, and has enabled Stoeckenius and Efraim Racker to show in a dramatic way how light energy is transduced through proton pumping to produce ATP. Furthermore, the purple membranes can be crystallized, and their study by Nigel Unwin, Richard Henderson, and Donald Engelman has done the most to advance our understanding of the structure and organization of protein in a natural membrane.

Studies of bacterial motility pioneered by Julius Adler and extended by Daniel Koshland teach us valuable lessons in neurobiology, at least at the level of a membrane-based neural network.

Bruce Ames' studies of the histidine operon in *Salmonella* made it possible for him to provide the best assay for mutagens and carcinogens.

Current studies of eukaryotic DNA replication have been guided by the patterns discovered in microbial systems. This includes the subunit organization of DNA polymerases, the RNA-priming of new chains, the helicases, and the topoisomerases.

We could extend this list all morning, perhaps to the point of mentioning that vertebrate hormone activities resembling those of mammalian insulin, ACTH, B-endorphin, and dynorphin are found in *Tetrahymena, Neurospora,* and *Aspergillus.* Mammalian hormones are even rumored to be in *E. coli.*

It is difficult to convince laymen and even scientists of the importance of basic, apparently irrelevant, research. It is a long-standing problem and I suspect it will always be with us. I have discussed it here at some length because eternal, unremitting vigilance is essential to remind people, scientists included, that technology rests on a foundation of science. We must not allow this scientific base to be obscured and ignored by refinements in technology that make the marketed product seem more important than the knowledge that fathered it.

I want to consider two more social problems. One is easy and gets too much attention; the other is far more serious and gets too little attention. Let's take the easy one first. I want to consider how the explosive developments of genetic engineering have generated confrontations between academia and industry. The situation here is unlike the postwar electronics revolution, which originated mostly in industry. The earliest industrial applications of genetic chemistry have come *exclusively* from academic laboratories. Understandably, the scientists, departments, and universities that provided the ideas and reagents, the techniques and machines, and the very practitioners of genetic chemistry are reluctant to be excluded from its financial rewards by entrepreneurs and venture capitalists.

There have been vacillations and soul-searchings at Harvard and Stanford with wide press coverage in recent months. Obviously, there are dangers if the university as a nonprofit corporation becomes entrepreneurial and employs its faculty for both

academic and commercial performance. There are major dangers, too, if genetic engineering companies appropriate a generation of senior scientists as consultants and junior scientists as employees and seal them off from the free exchange of new knowledge.

There is no putting this genie back in the bottle. For many years we promised applications of genetic chemistry. Now when they are within reach we must not circumscribe or blunt them. Solution of difficult social problems that accompany these applications cannot come from summit conferences, nor should we depend on lawyers and government agents. I am hopeful that scientists, who have been and will remain the major resource of these commercial efforts, will have the character and wisdom to preserve academic standards and combat pressures for secrecy and gimmickry. I believe that a company can be successful working and communicating in a free and open academic manner. I believe that secrecy is as counterproductive in industry as it is in academia. By operating openly and generously a company will attract the best scientists and thereby have the most important ingredient for success.

Despite the irritation or envy one might have about the unfairness of the financial windfalls, the recent commercial success of basic molecular and cellular biology has done these things. (1) It is making, or will soon make, important products for medicine, industry, and agriculture. (2) It has revitalized the American pharmaceutical industry and is spawning related industries. (3) It has created many attractive jobs in biology and genetics, where opportunities had become scarce. (4) It has secured a respectability for basic biologic science among our fellow citizens and their governmental representatives, a stature that dominance of the Nobel Prize awards never could achieve.

Finally, I want to consider a more serious social problem of science. It is our failure to act vigorously in the defense of scientific truths. We have shrugged off rather than rejected forcefully the creationists, cultists, mystics, and fools who erode science and rational behavior.

More than a century after Darwin and Huxley and a half-century after the Scopes trial, creationists are alive and kicking. We had Scopes II in Sacramento three months ago. The Reverend Jerry Fallwell and his Moral Majority are now working on a national scale for legislation requiring that creation as portrayed in the Bible be taught in the public schools. Such a law already operates in Arkansas.

In the Sacramento trial, the Attorney General of California was said to have won his case in defending the State Board of Education against a suit to offer creation as an alternative to evolution in science classes. But it struck me as a defeat, because in his ruling, the judge ordered the Sate Department of Education to make sure the schools avoid the error of making evolution theory an official dogma, taught as if it is beyond dispute.

It troubles me that as scientists we have failed not only to convey to people the true status of evolution, but also the clear understanding we have of heredity and the rapidly emerging knowledge about the chemical basis of behavior. These chemical insights enhance rather than diminish our esthetic appreciation of Nature and human capacities. How sad, then, to observe that our society, by ignorance of evolution, heredity, and behavior, is as captive to creationists, astrologers,

evangelists, food faddists, and gurus as were our ancestors to fears of thunder and lightning.

I apologize for giving a sermon on Monday morning, but I feel these things need to be said. I believe it is our primary responsibility as scientists to do the most creative and dedicated research within our power. But in addition we have individual and collective responsibilities to support basic, so-called irrelevant, research. And we must aggressively reject irrational, antiscientific behavior wherever and whenever it rears its head.

ARTHUR KORNBERG

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