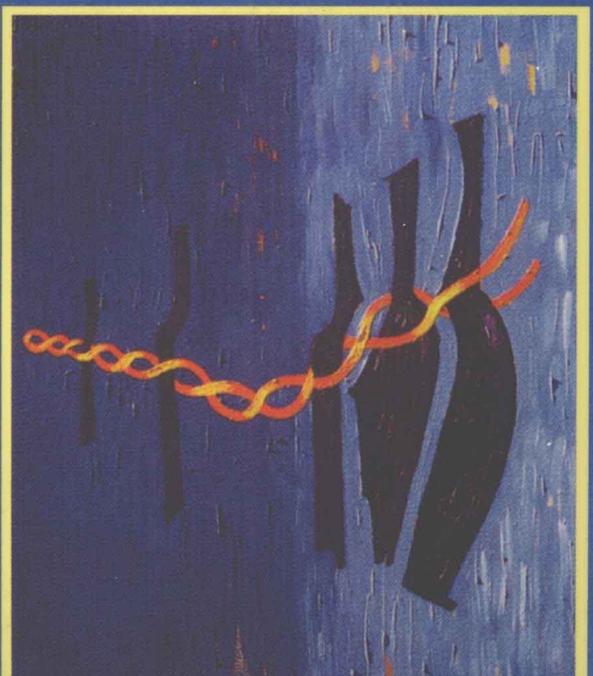
THE GOLDEN HELIX

ARTHUR KORNBERG



Inside Biotech Ventures

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INSIDE BIOTECH VENTURES

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Necessity is seldom the mother of invention.
Rather, true inventions beget necessities.

Preface

Genetic engineering and associated technologies have brought about the most revolutionary advances in the history of biological and medical science. Applications of this genetic and chemical knowledge created a biotechnology industry with vast economic and social potential. The biologists and biochemists who invented these new technologies in their academic laboratories came to the forefront of entrepreneurial ventures to use this knowledge to develop drugs and devices for the diagnosis, prevention, and treatment of disease.

Along with other biologists and biochemists engaged in basic research who previously had shunned all commercial connections, I found myself attracted by the resources that industry could provide to apply the novel techniques we all helped to discover. The twenty-five years I spent finding the enzymes that make DNA in our cells supplied the reagents for others to create recombinant DNAs and to trigger an avalanche of ingenious ways to use these techniques to advance basic knowledge in biology, as well as to devise highly useful industrial products and procedures.

Of the thousand or more biotech ventures in the United States, virtually all were financed by venture capitalists and investors whose interest in research was to create a profitable business rather than to acquire knowledge for its own sake. There was little sympathy for the usually long and always unpredictable time scale required for innovative discoveries. With Alejandro Zaffaroni, a scientist and intimate friend, who for three decades had successfully applied his entrepreneurial skills in the pharmaceutical industry, I could share the faith that creative scientists at a frontier of medical science would, in due course, make novel discoveries worthy of industrial development. We were joined by Paul Berg and Charles Yanofsky—Stanford colleagues, friends, and innovators in biotechnology—who had the same dedication to basic science. Together we founded the DNAX Institute of Molecular and Cellular Biology, Inc., in 1980.

The Schering-Plough Corporation, a medium-size pharmaceutical company based in New Jersey, acquired DNAX a little more than a year later, a move directed by Robert Luciano, its CEO. The acquisition of DNAX was based on his conviction that the industry would become biotechnology-driven and that a venture both strong on science and located outside the company's establishment in New Jersey was needed to provide the means for Schering-Plough to achieve that transformation. DNAX, in turn, found in Schering-Plough an ideal patron with an understanding of the style and time scale required for basic research.

In this narrative, which features the DNAX–Schering-Plough partnership, I describe how it made DNAX a world leader in basic immunology and at the same time generated for Schering-Plough multiple candidates for drug development far earlier than expected. Because the success of this venture depended so much on the people on both sides—academic and industrial—emphasis will be placed on their personalities and how they bridged the cultures and missions of their different worlds.

Beyond DNAX and other biotech ventures (Genentech, Amgen, Chiron, and Regeneron) to be described more briefly, I reflect on some general issues that affect the conduct of science—in particular, liaisons and conflicts between academia and industry. I consider the pros and cons of biotech ventures, secrecy, patents, and the current oxymoron: targeted (or strategic) basic research. From my varied experiences, I find a renewed confidence in the power of science to allow us to understand ourselves and our world in rational, molecular terms and in the capacity of motivated people to apply this knowledge in practical ways to improve the quality of our lives.

In 1994, the outlook for biotech ventures turned bleak. Obituaries were being written for an industry overexpanded by greed for profit and unmindful of the slow and tortuous course from discovery to a marketable product. Turning the DNA helix into gold seemed another alchemist dream. We can expect that, after an inevitable shakedown, mature biotech ventures will exploit the new science and will evolve technologies to shape the chemistry that defines our state of body and mind well into the next millennium.

To those who gave their time for interviews and to those who read drafts of various sections of the book, I am most grateful. I am especially indebted to the many who expended great effort in reading the entire manuscript and then made highly useful suggestions. These include Jane Ellis, Hugh D'Andrade, Spyros Andreopoulos, Carol Dempster, Horace Judson, Charlene Kornberg, Ken Kornberg, Roger Kornberg, Tom Kornberg, Robert Lehman, Paul Lubetkin, Paul Schimmel, W. Denman Van Ness, and Charles Yanofsky. I offer special thanks to Paula Hagen at Schering-Plough and Constance Mitchell at ALZA for fact-checking and helpful suggestions. To Beverly Forsyth, who typed the manuscript from handwritten copy; to Bruce Armbruster, friend and publisher; to Gunder Hefta, editor; and to Robert Ishi, book designer, I give my heartfelt thanks.

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INSIDE BIOTECH VENTURES

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CHAPTER 1

Currents and Eddies in Biotechnology

At the end of 1993, there were 1272 biotechnology companies in the United States. These companies employed 80,000 people directly, and they employed at least again as many in the construction of laboratories, the publication of news reports, the manufacturing and distribution of reagents, and in a variety of other activities, including Wall Street banking and analysis. Biotechnology, with annual sales in 1993 of $6 billion (a 35 percent increase over the previous year) is expected to reach five to ten times that volume by the year 2000. The phenomenal growth of the industry is fueled by investors, academic institutions, politicians, and the hopes of many millions who suffer from incurable diseases, for which, they trust, the industry will soon find a cure.

The truly revolutionary developments in medicine and biology in recent decades are based on genetic engineering and its associated biotechnologies and (although this is less widely appreciated) on the coalescence of the medical and biologic sciences into a unified discipline whose messages are expressed through the language of chemistry.

Revolutionary, an overused word, is justifiably applied to these extraordinary movements in science. Another development that is surely astonishing, if not revolutionary, is the extensive involvement of biologists and biochemists in entrepreneurial activities, something that was utterly unimaginable only a decade or so back.

Biotech Ventures

Because the techniques of the biotechnology explosion were created entirely by academic scientists, virtually all biotech ventures in the United States include biologists and biochemists as founders, managers, or advisors. In most vigorous university departments of the medical and biologic sciences, prominent faculty members have one or several industrial connections. I never thought that, in 1968, after more than 25 years of full-time academic research in biochemistry, having avoided all commercial associations, I would become an advisor to a new biotech venture. Nor did I believe that, in the next 25 years, I would be a founder, advisor, or director of a half dozen more. Such affiliations entail advantages and threats to the progress of science and the betterment of human welfare that must be analyzed in order to be understood, and be understood in order to guide our actions.

With the prospects of novel drugs and procedures for medicine and agriculture, major pharmaceutical companies were spurred to join in some of these ventures, as well as to initiate similar programs of their own. In many cases, the relations between the corporate giants and the fledgling enterprises were awkward and stormy. In at least one instance, however, the match worked to create a symbiosis of world-class basic research that generated a pipeline of products for drug development.

Viewed from ten years after the fact, the acquisition of the DNAX Research Institute by the Schering-Plough Corporation is a story of how personalities, philosophies, and sustained policies combined to make this union a unique success. In this chronicle, I will reflect upon these people, their backgrounds, their attitudes, and their actions, all of which were essential to blending the alien cultures of academia and big business. These people—scientists, advisors, and managers, both academic and industrial—gave DNAX the constant devotion that was needed to keep it nourished and on course.

On the DNAX side, the entrepreneurial drive came from Alex Zaffaroni. Trained in biochemistry and endocrinology, and with extensive pharmaceutical experience in the applications of scientific discoveries to medical uses, he saw an industrial potential for developments in molecular biology in the 1960s and 1970s. Paul Berg, Charles Yanofsky, and I, who had contributed significantly to these developments, had been turned off by overtures from venture capitalists, but we felt that, with Zaffaroni, we could create an enterprise in which pursuit of basic research with a communal focus could be linked to the development of drugs for treating disease.

On the Schering-Plough side, Robert Luciano, the chief executive officer, was captivated by the notion of biotechnology as the frontier of the pharmaceutical industry. He regarded the acquisition of DNAX as a means to drive Schering-Plough to that frontier. He set no timetable, and he had no illusions about short-term returns on the investment. To Hugh D'Andrade, the director of strategic planning, he entrusted the arrangements for this novel academic enterprise, which was culturally and geographically remote from the company's New Jersey operations.

On both sides, friendships were cultivated and lessons were learned. DNAX founders and scientists came to respect the skills needed for drug development, manufacture, regulatory approval, and marketing. Schering-Plough managers and scientists became aware of the haphazard nature of discovery, the erratic pace of research progress, and the futility of establishing milestones. Mutual respect and affection at the top level resolved misunderstandings, maintained adherence to academic standards, and kept the long-range goals in sight.

The focus in this narrative will be on DNAX and its Schering-Plough sponsor not only because I know them best but also because, in this joint biotech venture, I found principles and practices that merit attention and emulation. Inasmuch as other successful ventures in biotechnology have differed widely from DNAX in their conception, development, and personality, I have included brief accounts of some of them—Genentech, Amgen, Chiron, and Regeneron. In every case, biotech ventures must confront profound problems in the general conduct of science, the waves of fashion that move research, conflicts between academia and industry, and the need to bridge the age-old gap between the cultures of chemistry and biology.

Currents and Eddies in Science

River metaphors offer a framework for describing the progress of history and science: Brooks grow to streams that merge to form mighty rivers. The once discrete medical disciplines of anatomy, physiology, biochemistry, bacteriology, pharmacology, and pathology have coalesced into a single, powerful flow of knowledge that can be expressed in the universal language of chemistry. So too have the emerging biological disciplines of genetics, cell biology, developmental biology, and molecular biology. At times, forces obstruct the flow, creating eddies and diverting it from its main course, which is approaching ever closer to the secrets of nature. So it has been with the flow of the medical and biological sciences in this century.

Ryszard Kapuscinski, a Polish journalist, said of the French historian Fernand Braudel: "He wrote that history is like a river. On the surface it flows rapidly and disappears. But down below, there is a deep stream which moves more slowly, doesn't change quickly, but is the more important because it drives the whole river." What interests us all is finding that deep current—in my case, the most rational understanding of life: its reduction to the molecular details of chemistry.

Anatomy, once the most descriptive of the life sciences, is now understandable in terms of the assembly of macromolecules to form the organelles, cells, and tissues of the organism. Genetics, only a few decades ago the most abstract, has been reduced to simple genetic chemistry. These two disciplines, previously at the extremes, have intersected. Embryology and genetics have become indistinguishable in their mission to identify the temporal and spatial expression of genes that encode the traits of each individual of a species. All these disciplines offer a variety of approaches with the same end in view: an understanding of the molecular basis of growth and senescence and of health and disease—and, therefore, an understanding of how best to intervene in order to forestall and correct the aberrations caused by genetic deficiencies and environmental stresses.

Like the geographical features that arrest or alter the currents of rivers, human and societal factors may divert or completely dam the progress of biological and medical science. A gulf separates the cultures of chemistry and biology; fashions in research lead to the abandonment of fertile subjects; scientific curiosity is discouraged when it may seem irrelevant to urgent, practical needs; confusions between biology and technology—confusions in the minds of academics, industrialists, and the public—pit academia against industry; pressures are exerted to meet milestones set for industrial targets irrespective of the deeper pursuit of knowledge for its own sake; secrecy and espionage stifle scientific pursuits; unfounded and debilitating patent litigation beclouds an era of the most profound scientific and social change and progress. All this turbulence leads people to question the concept of progress, and it invites politicians, ideologues, and journalists to arouse fear and to spread misinformation about science and biotechnology.

Fashions in Research

Fashions prevail in research as in all other departments of human behavior; tides erode one beach as they create another. The hunting metaphor introduced by Paul de Kruif in his *Microbe Hunters* aptly describes the succession of movements in medical science in this century. Those hunters, who in the first two decades found the microbes responsible for many of the scourges of mankind, were replaced in the next two decades by the *vitamin hunters*, who discovered that deficiencies of vitamins could cause other epidemic diseases—pellagra, rickets, and scurvy. The vitamin hunters were superseded by the *enzyme hunters*, who showed how enzymes were assisted by vitamins in the metabolic operations responsible for cell growth and energy metabolism.

In recent decades, the *gene hunters* have dominated. With an inexhaustible supply of genes and the capacity to manipulate them in the minutest detail, the gene hunters have shown that species can be modified at their will. Bacterial, plant, and animal factories are created to produce massive quantities of the rarest hormones, cytokines, and antibodies for medicine, agriculture, and industry. A cadre of gene hunters is busy looking for the genes for human traits and the defects in these genes that cause inborn errors of metabolism. But the searches by these disease hunters are not basically different from those established for bacteria, fungi, plants, flies, and other animals. The greatest mystery now resides in brain processes—mood, memory, mental illness—which, when probed successfully with novel technologies, will turn the spotlight on a new breed of hunters (to whom we might refer as *head hunters*).

As observed by the Swiss physicist–philosopher Marcus Fierz, the scientific insights of an age can shed such glaring light on an area as to leave the rest in even greater darkness. The incandescence of enzymology was so dazzling that attention to nutrition as a science faded nearly to the vanishing point, leaving the major questions of human nutrition unattended. Why do deficiencies in vitamins, which are needed by every cell in the body, cause diarrhea, dermatitis, and dementia in the case of niacin and neuritis in the case of thiamine? The refined knowledge of biochemical mechanisms has obscured our gaping ignorance about the physiology of cells and the organism. For lack of such basic information, the science of nutrition is in a sorry state and controversies rage over what and how much to eat. With widespread concerns about the value or avoidance of cholesterol, sugar, salt, fiber, fat, and megadose vitamins, the only clear winners are the zealots and quacks.

Just as enzymology eclipsed nutrition, so has genetic engineering, with its mastery over DNA, cast a shadow over enzymology. To the current generation of molecular biologists, enzymes come in kits and are as faceless as buffers and salts. Yet, for lack of attention to enzymes, the truly molecular basis of biology will remain obscure; profound questions of how cells and organisms function and develop will not be answered. How is the chromosome rearranged by enzymes to produce the genes for antibodies? What enzymes direct embryonic tissues to become specialized adult organs? How do the enzymatic processes of growth and senescence proceed in response to different programs and circumstances?

Fashions prevail within, as well as among, disciplines. The enormous research effort to prevent and treat AIDS (acquired immune deficiency syndrome) has increased interest in the structure and life cycle of HIV (human immunodeficiency virus, the causative agent of AIDS). Yet with all this clearly important activity, the ways in which this and other viruses enter cells and are uncoated to expose their genomes for replication are largely ignored. Studies of bacterial viruses, as well as those of animal viruses, long ago identified a particular surface protein on each virus, the "adsorption protein," and the structure on the host-cell surface to which each attaches, the "receptor." Once they were named, little more was done to learn their molecular details and how they operate. Further, it remains a mystery how the viral chromosome (RNA or DNA), upon entering the cell, instantly appropriates key elements of the cellular replication machinery in competition with a host genome a thousand or more times its size. Knowing more about these operations is bound to be of wide significance and of invaluable help in coping with the many viral infections that will continue to plague us.

As scientific explorations overlap one another, they widen our knowledge base, but they also inevitably increase the perimeter of our ignorance. In the pursuit of the unknown, the deployment of resources is influenced more by social, economic, and political forces than by curiosity and inspiration. Fertile fields are left fallow as scientists cluster in fashionable areas for the security of being a part of a popular movement.

Few scientists have the courage, confidence, or independence to pursue a problem that appears irrelevant to their colleagues or that lacks a practical objective. It may seem, even to many scientists, unreasonable and impractical (call it *counterintuitive*) to address an urgent problem, such as a life-threatening disease, by pursuing apparently unrelated questions in basic biology or chemistry. Yet, the pursuit of curiosity about the basic facts of nature has proven, throughout the history of medical science, to be the most practical and the most *cost-effective* route to successful drugs and devices.

In an often retold parable, a surgeon, while jogging around a lake, spotted a man drowning. He dove in, dragged the victim ashore, and resuscitated him. His duty done, he wearily resumed his jogging, only to see two more people drowning. He also saw a colleague, a professor of biochemistry, standing nearby, apparently absorbed in thought. He called to him to go after one while he went after the other. When the biochemist was slow to respond, the surgeon shouted, "Why don't you do something?" The biochemist said, "I *am* doing something. I'm trying to figure out who's throwing all these people in the lake."

This parable is not intended to convey a lack of regard for fundamental issues among physicians nor a callousness among scientists. Rather, it is meant to portray the reality that a serious problem, such as a war on disease, is often best fought on several fronts. Some contribute their special skills to the distressed individual, while others try to gain the breadth of knowledge necessary to outwit both present and future enemies.

Investigations that seemed totally irrelevant to any practical objective have yielded most of the major discoveries of medicine: x rays, from a physicist observing electrical discharges in a vacuum tube; penicillin, from enzyme studies of bacterial lysis; the polio vaccine, from learning how to grow cells in culture; nylon and neoprene, from showing that polymers are linked by the same forces as small molecules; and the discovery of genetic engineering and