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CRITICAL ISSUES IN GLOBAL HEALTH

FOREWORD BY
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CHAPTER THIRTY-THREE

Biomedical Research in the Next Century

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Bruce Alberts, PhD, *President of the National Academy of Sciences in Washington, D.C., is known for his work in both biochemistry and molecular biology. He chaired the Department of Biochemistry and Biophysics at the University of California, San Francisco, before moving to Washington in 1993 to head the National Academy and its operating arm, the National Research Council.*

One needs to be very bold to try to predict the future of science and technology in the twenty-first century, considering our striking inability to predict the major advances of the past hundred years. Even after a revolutionary new technology emerges, the experts often fail to appreciate its impact. Witness the often quoted 1978 statement by the CEO of Digital Equipment Corporation that he could not imagine why anyone would want a computer in his home or the claim by one of the early critics of the Human Genome Project in 1987 that it is "a ploy to raise money . . . justified for its public relations value, not its scientific value" (Burris, Cook-Deegan, and Alberts, 1998). Both of these remarks were made by unusually wise and accomplished people, pioneers in the relevant technologies. Our past difficulty in predicting the future should give us pause.

Nevertheless, because new knowledge in science is built through combinations of old knowledge, it does seem safe to anticipate that the pace of scientific discovery will continue to accelerate throughout the twenty-first century, with unpredictable new technologies arising periodically to greatly facilitate the research process. I also believe that we will see a dramatic acceleration in the speed of translating progress at the laboratory bench into progress at the bedside, due to an enormously increased number of transient, rapidly established collaborations between small groups of researchers and clinicians who have complementary expertise.

In this chapter, I begin by expanding on the two predictions I just made, using some examples from my own experience. In the process, I suggest a few changes in our traditional mode of operation that would seem to be warranted if we are to exploit to the fullest the vast opportunities before us in biomedical research. Last but not least, I shall try in a small way to fulfill what I suspect was meant to be my main task: to forecast one promising new area of biomedical research with profound implications for human health.

AN ACCELERATING PACE OF DISCOVERY

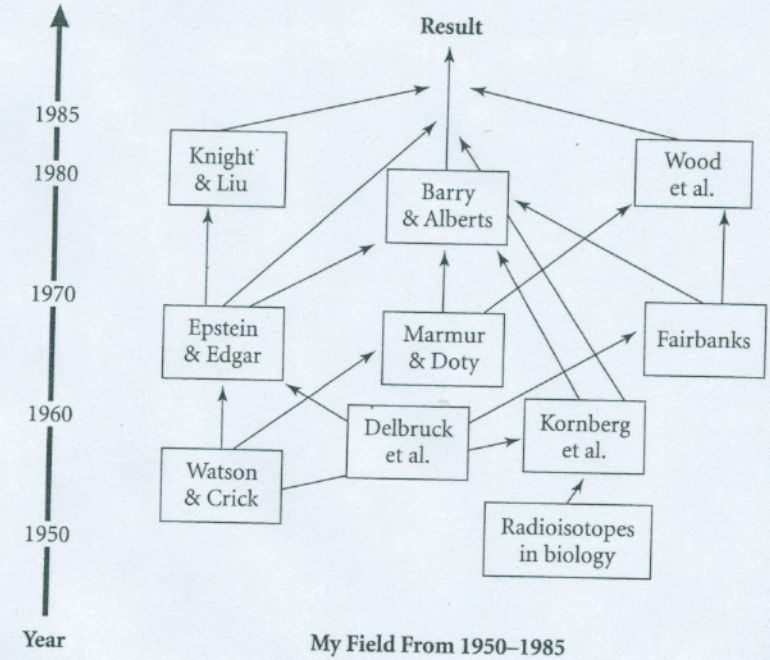
I began my career as a research scientist in the summer of 1959, just before my senior year at Harvard College. This was only six years after the discovery by James Watson and Frances Crick of the DNA double helix and six years after the demonstration by Fred Sanger that a protein is formed from a unique sequence of amino acids. I have therefore been active as a researcher throughout a period when incredible advances have been made in our understanding of how cells and organisms work at the molecular level. In 1983, when the first edition of *The Molecular Biology of the Cell* was published, my coauthors and I felt that we could include nearly all of the critical information then known about cells in the twelve hundred pages of this advanced undergraduate textbook. In fact, so little was known then about how things actually worked that we often felt forced to guess at possible mechanisms. As I write this article, we are in the midst of preparing the fourth edition of the same textbook. So much is now known that the most difficult decisions concern which large sets of well-studied mechanisms are to be left out so as to avoid producing an encyclopedic volume that is undigestible for most students.

My own research focused on the molecular mechanisms that cells use to replicate their chromosomes. In 1961, when the critical point of action was discovered to be a DNA replication fork, this Y-shaped structure was drawn with a fig leaf over the Y, in recognition of our ignorance of what was going on beneath it. Today, we know that an incredibly efficient, tiny protein machine makes the DNA at a replication fork, and scientists have even worked out where the atoms are in the three-dimensional structures of nearly all of its many protein parts. This striking progress is the result of studies carried out by thousands of scientists, each building on the knowledge accumulated by their predecessors and published in scientific journals. The knowledge needed came from many different fields of investigation, and it was often combined in unexpected ways to produce a significant advance. Some of this progress involved the development of new methods, which in turn greatly increased the speed and power of the science that followed.

Figure 33.1 presents a highly schematic comparison of the early progress of my field (left side) with the much more rapid progress that is being made today (right side). The pace is accelerating primarily because of a large increase in the total pool of relevant scientific knowledge that can be combined in new ways to create new knowledge. Mathematically, there is an explosive increase in the possibilities: for example, 100 units of knowledge can be combined in 1,000 times more ways than 10 units of knowledge can. Even scientists seem surprised by the modern explosion of scientific progress. Could the root of this surprise be our failure to appreciate fully the counterintuitive power of combinatorics?

THE COMBINATORIAL PRINCIPLE APPLIED TO RESEARCH LABORATORIES

So far I have expanded on the first of my two general predictions about the future of biomedical research. My second main point is a corollary of the first: our biomedical knowledge is now so extensive, with so many specialized new methods and scientific approaches, that no single laboratory can hope to master all of the techniques that can usefully be brought into play in a particular scientific investigation. Nor can laboratories with a specific expertise or technology hope to be able to apply that expertise to the most important biomedical problems without outside collaborations.



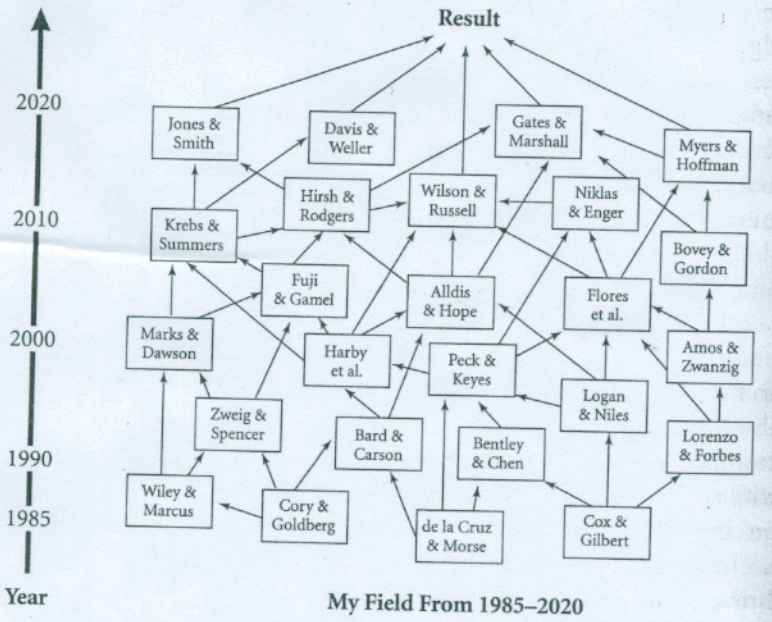


Figure 33.1. The Accelerating Pace of Biomedical Research.

In 1985, I pointed out the benefits of a laboratory group in biology that is limited to ten or so researchers, led by a scientist who is fully involved in the research process (Alberts, 1985). That article was based both on my personal experience in trying to run a larger laboratory and on a sense that there had been a decrease in the innovation and creativity of most of my colleagues once the laboratories they led became too large. As an extension of the arguments made there, I emphasize the great advantage to be gained from a research tradition in which two such laboratory groups form transient, opportunistic collaborations that exploit the unique skills of each—if you wish, the power of the combinatorial principle when applied to biomedical research laboratories.

Today, such collaborations are perhaps most common when one laboratory is expert in a highly specialized technique, such as X-ray crystallography, and the other laboratory provides the biological material to be analyzed by that methodology. But in the future, some type of interlaboratory collaboration is likely to become the standard practice for nearly all biomedical investigations. As an especially important example, if we are to bring modern biomedical science to bear much more effectively at the bedside, we will need to find better ways of promoting highly productive collaborations between MDs carrying out clinical studies and laboratories headed by PhDs skilled in fundamental biomedical research. Today, this must be viewed as an "unnatural act," but one that has tremendous future potential. The reason for the potential is clear: we have finally reached a stage in our understanding of cell biology and immunology (and in the development of powerful, highly sensitive analytical technologies) where an effective, intelligent attack can be made in understanding, and then ameliorating, almost any human disease. But this will happen only if the special expertise of clinicians and basic scientists can be brought together in much more vigorous ways than are generally feasible today.

NEW EXPERIMENTS IN SCIENCE POLICY

My former colleagues in the basic science departments of research universities seem to be busier than ever; they work nights and weekends and still seem to be always behind. How can they hope to keep up with the exploding amount of biomedical knowledge, much less to explore new collaborations with clinical scientists in those areas of

human biology where their expertise could be especially valuable? The natural path for an individual scientist to take as the amount of knowledge explodes is to drill deeper in one ever-narrowing area of biomedicine. Will we eventually be giving PhD degrees in departments of ribosome function or departments of membrane transport, rather than in departments of cell and molecular biology? I certainly hope not; but it will take a concerted effort from our scientific leadership to counteract the strong tendency to overspecialize.

What kind of leadership makes sense? We are fortunate that the explosion of scientific knowledge has been accompanied by a computer and telecommunications revolution. This revolution now provides biomedical scientists with powerful, no-cost ways of finding relevant knowledge through electronic searches (for example, see PubMed at http://www.ncbi.nlm.nih.gov). It also enables free access to valuable databases of genes, gene sequences, chromosome maps, protein structures, mutations, and many other research resources on the World Wide Web, along with relevant computing tools. The next step in this revolution would be to make the full electronic text of all biomedical publications freely available to researchers around the world at their desktop, as recently proposed by Harold Varmus, the director of the National Institutes of Health (Marshall, 1999).

An ability to immediately access all of the relevant literature in this way—going instantaneously from one journal abstract in PubMed to a list of related articles (available today) or from a journal article to the full text of any of its citations (available tomorrow)—should greatly facilitate the broadest possible cross-fertilization of ideas between biomedical scientists, as needed to optimize scientific progress. It should also speed progress at the bedside by improving the connections between clinical and basic researchers.

What can we do to make this valuable knowledge resource fully effective? Experience shows that researchers in different fields are unlikely to start a collaboration, unless they have first met each other face to face. I propose that this be done in special workshops, organized as a series of "mixers," each carefully designed to bring together scientists whose differing expertise might be profitably combined at some future time.

Some of us first became aware of the power of such settings when we were brought together in a 1994 workshop in Seattle focused on the brain tumor known as glioma. We were there because of a common friend, the scientist Harold Weintraub, who was dying of this dis-

ease. We spanned the gamut from molecular biologists working on gene regulation in bacteria to cell biologists to clinicians treating the disease. During two days of intensive discussions, it became clear to all of us that this important subfield of cancer research would benefit from a much more intensive, ongoing interaction between clinical and basic researchers.

The same could be said for many other areas of biomedical research. Scientists often attend seminars and scientific meetings, but these are generally so specialized that we often fail to benefit from the broader types of cross-fertilization that can produce real innovation. As an experiment, small meetings focused on catalyzing specific types of collaborations in areas with important medical implications could be regularly sponsored by the National Institutes of Health, each cochaired by a distinguished clinician and a distinguished basic scientist. The attendees at the meeting might be invited to compete in pairs for a modest catalytic research grant that would give equal status to a clinician and a basic scientist, both of whom serve as principal investigators (PIs). (Currently, there can only be a single PI on a grant, with a collaborator serving as a co-PI.) If skillfully arranged, I am convinced that some powerful new types of biomedical research would emerge.

When promoting these new connections between scientists, we must admit to a cultural problem. Medical schools are organized into departments of two different kinds: the so-called basic science departments like physiology, microbiology, and biochemistry and the clinical departments like medicine, pediatrics, and surgery. The two types of departments have very different traditions, the basic science departments containing mostly PhDs and the clinical departments almost all MDs. The faculty and students in each type of department naturally seek to emulate the most prestigious individuals in their professions, who are PhDs or MDs, respectively. Young scientists are constantly being evaluated as individuals so that the best can be selected for leadership positions, and for this reason cooperative work is discouraged. And yet it is precisely these scientists—the postdoctoral fellows and assistant professors—who one hopes would start new research laboratories at the interface between clinical and basic research in biomedicine.

In my opinion, our present system strongly discourages innovation and risk taking among young scientists. Far too many of the most successful young scientists go on to establish a research program that

simply extends the work that they did in their mentor's laboratory. As a result, large numbers of scientists are competing with each other by working on an unnecessarily narrow range of research problems, while many important, newly accessible opportunities at the interface between conventional disciplines remain largely unexplored and unexploited. Finding a solution is a critical task for the twenty-first century—and a challenge to our universities, our charitable foundations, and our government funding agencies.

A MAJOR ROLE FOR GROWTH FACTORS IN THE TREATMENT OF DISEASE

I now come to part of the chapter where I stick my neck out and risk future embarrassment. Here I shall extrapolate from my eight years of experience as a volunteer scientific adviser to the Scleroderma Research Foundation, run and inspired by a woman with the disease, Sharon Monsky. I have learned that there are many debilitating human diseases, of mysterious origin, that lead to the degeneration of a specific tissue, or set of tissues, and often result in death. These diseases eventually cause an abnormal immune response, and for this reason they are often classified as "autoimmune diseases."

However, treatments that suppress the immune response have no effect on the fundamental course of many of these diseases, suggesting that a production of specific self-antibodies is an effect, rather than a cause, of a disease like scleroderma. What, then, is the cause of the progressive tissue degeneration?

At this point, I enter the realm of speculation, based on what we know about the mechanisms that individual cells use to decide how to behave in the functional cell cooperative that we call a tissue (muscle, bone, or skin, for example). The cells in tissues are constantly sending sets of signals to each other by producing special proteins that are loosely called "growth factors." These are either displayed on the cell surface of the sending cell or secreted into its surroundings. When they contact a receiving cell, the growth factors bind to specific receptors embedded in the cell's plasma membrane that transmit a message to the cell interior, generally by regulating enzymes called protein kinases that change the state of phosphorylation of selected proteins in the receiving cell. The cells in a tissue are both senders and receivers of multiple signals, and each cell has been programmed during its

development in the embryo to interpret each of the many combinations of signals it will receive so as to either remain quiescent, multiply, differentiate further, or commit suicide (the last cell function is called apoptosis, and its importance in tissue maintenance has only recently been recognized).

It is this complex signaling system that makes multicellular life possible by ensuring that the cells in our body cooperate rather than compete, and there is much that remains to be learned about it. The first complete genome sequence obtained for any multicellular organism is that of the tiny nematode (worm), *Caenorhabditis elegans* (*C. elegans* Sequencing Consortium, 1998). Among the nineteen thousand proteins encoded in this worm's genome are a large number specific to cell signaling, including more than four hundred protein kinases and many growth factors, as I have broadly defined them. And for humans, DNA sequencing studies have already revealed many hundreds of growth factors, a number that is certain to rise considerably when most of the human genome sequence is completed in the next few years.

We already know that these signaling pathways contain many feedback loops, and in such a complex system, pathologies can develop in which the network becomes altered in a way that causes abnormal amounts of signaling molecules to be produced. This could in turn profoundly perturb the structure of a tissue. One such pathology is well known—cancer, in which inappropriate signals cause a clone of cells to multiply without the usual restraints and produce tumors. But many other types of pathologies are to be expected, in which signals go awry so as to cause inappropriate cell differentiation, a deficit of cell proliferation, or excess cell death. This type of problem, one suspects, is the underlying cause of scleroderma and numerous other degenerative diseases whose cause is presently mysterious (see, for example, Liu and Connolly, 1998).

Because each growth factor has an effect on cells that depends both on the cell type and on the other growth factors present, the combinatorial use of these powerful reagents and their agonists and antagonists should provide medicine in the new century with a precise and powerful new tool for controlling cell behaviors in a wide variety of different human diseases. The analyses of a particular pathological tissue for growth factor anomalies may eventually require that the levels of perhaps a thousand different proteins be measured routinely and cheaply—including all of the growth factors, their receptors, and

perhaps selected other signaling molecules. Thus the mass production of the appropriate low-cost probe arrays, containing a thousand nucleic acid probes to test for levels of gene expression or a thousand antibodies to test for protein levels, for example, would seem to be warranted (Brown and Botstein, 1999). And I predict that the pharmaceutical industry will be investing heavily in the production of growth factors and their antagonists in the years ahead as a major market develops for them in the treatment of human disease.

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