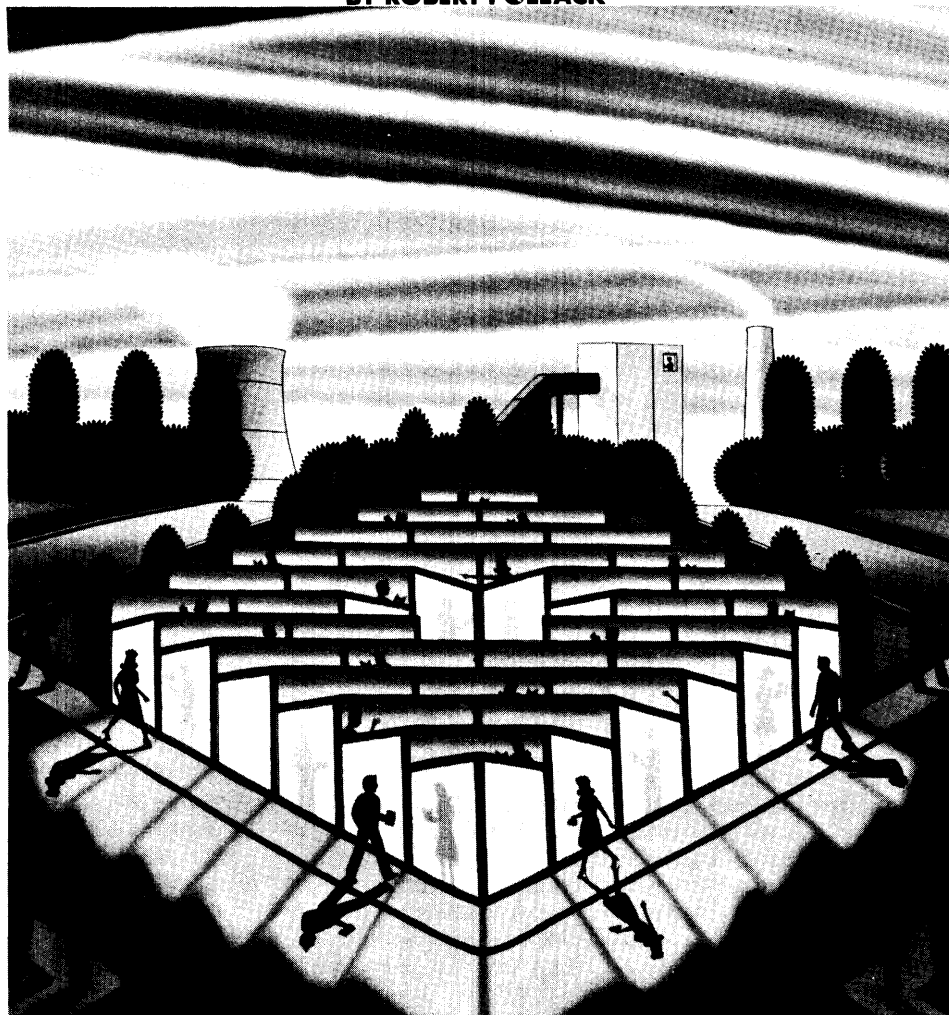


BIOLOGISTS IN PINSTRIPES

Science pauses for a corporate fling

BY ROBERT POLLACK



Courtesy Phyllis Kind Gallery, New York

Roger Brown, Citizens Reading in the Michigan City Modern Library, 1977

A DECADE AGO, molecular biologists began making the products of their dreams—a host of newly synthesized drugs, fertilizers, hormones, and vaccines. Many people worried then that gene-splicing might create test-tube gremlins and loose new diseases upon the world. The worst of those fears have been assuaged. But there is one danger that the critics of genetic engineering ignored: a hazard almost as dam-

Robert Pollack, a professor of biological sciences at Columbia University, recently was named dean of Columbia College. Spectrum is a forum for continuing discussion of issues raised by members of the scientific community.

aging, in its way, as anything the scientists, the press, and the public had foreseen. No one anticipated the effect of the new recombinant DNA technology on the scientists themselves.

Molecular biologists, in surprising numbers, have succumbed to the notion that their science is far enough along to permit a long pause for technological development. The late geneticist Tracy Sonneborn, of the University of Indiana, hinted at the danger of reading science like a definitive recipe book when he first saw James Watson's text, *The Molecular Biology of the Gene*, and remarked, "It is an absolutely brilliant synthesis. But I'm not sure we should allow it to fall into the hands of students . . . it suggests that the story is told,

and not just well begun."

Like the story of molecular biology, the story of any science is forever just begun. The horizons of knowledge recede with each and every discovery, as new questions are posed with the information gained. There is no final knowledge, and those of us who enjoy the process of doing science have learned to appreciate discovery for its own intrinsic elegance.

All of science depends on a constant volley of ideas and techniques. A new discovery will spur technology; a new technique will open doors for basic research. Separate the two, and the volley stops. Ideas without techniques are but dusty, scholastic relics; and though without ideas technology may yield a cornucopia of new

things, eventually a lack of ideas limits the rate of progress in any science and stifles our understanding of how nature works.

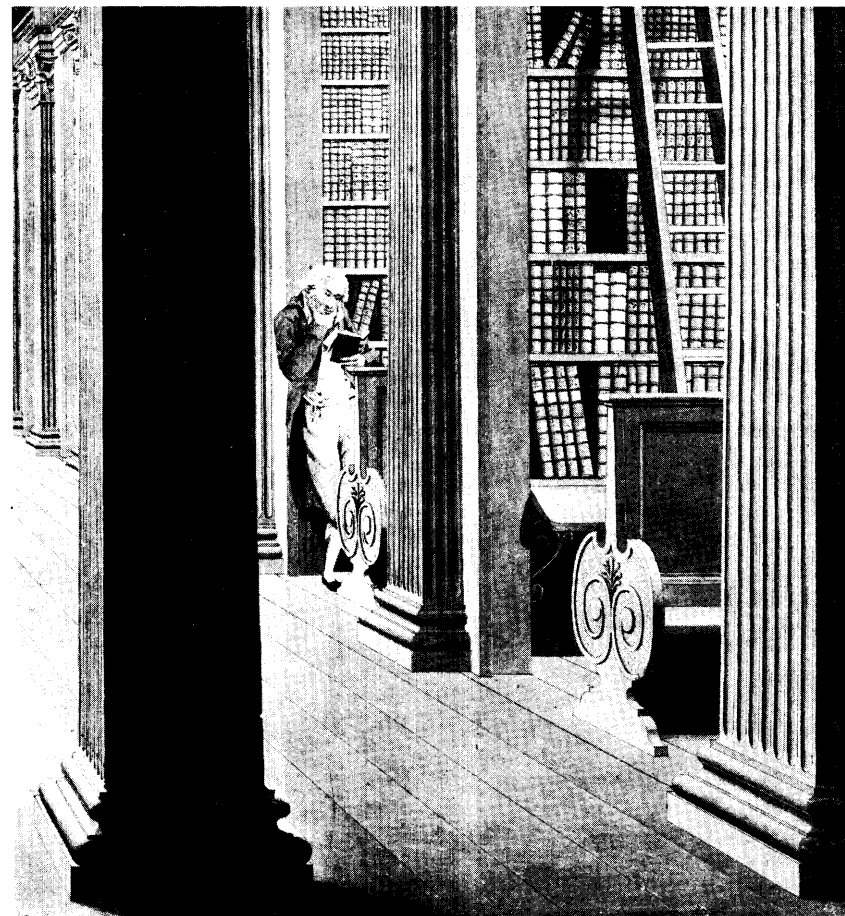
I never thought that any sensible scientist doubted this. Yet many of my colleagues have abandoned the volley to become founders, officers, consultants, and employees of new corporations whose products are the bioengineered fruits of recent insights into gene structure and function.

Do these scientists really suppose that they are finished with asking questions in biology? Perhaps. But that is not the only reason they have divided their attentions between scientific research and industry. As the federal government gets more tight-fisted and universities continue to feel financially pinched, the private corporation remains one of the few options of support for scientists. And that option becomes practically irresistible as companies offer spectacular salaries to excellent new scientists, who might otherwise go to universities and public research laboratories.

AMERE FIFTEEN YEARS AGO, private industry had little to do with gene manipulation. But then, in the late 1960s, molecular biologists, working with DNA from many organisms, started to amass an impressive array of techniques that could be exploited for making such new gene products as the antiviral agent interferon, the antigen for hepatitis-B vaccine, and human insulin.

Scientists learned first how to manipulate the DNA of bacteria, some of whose genes are carried on free circles of DNA called plasmids. Conveniently, plasmids grow to large numbers in a single bacterium and readily yield DNA in large amounts. In addition, bacteria make a set of tools called restriction enzymes that can cut and paste DNA sequences to form new strands, thus creating new combinations of genes. These enzymes find specific sequences up to six base-pairs long and cut the DNA solely at those points. Since any particular six-base-pair sequence (say, part of the gene for insulin) would occur at random only once in a few thousand base-pairs, the restriction enzymes leave sets of DNA fragments of specific lengths, end sequences, and internal sequences. After the restriction enzyme has cut these sequences, the biologist can sort them out for further manipulations by electrophoresis—a procedure that divides the heavier, slower-moving particles from the lighter, faster-moving ones as they are pushed through an agarose gel by an electric charge.

To locate a particular sequence of interest (say, the gene for insulin) after the pieces have been separated by length, they are transferred to a special paper that is then soaked in a solution containing a radioac-



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tive probe, which can be made to match any sequence in the DNA chain, called the genome. Since a given stretch of DNA fifteen base-pairs long, for example, will occur at random only once in about a billion times (four raised to the fifteenth power), a fifteen-base-pair stretch will be unique in a genome as large as ours. A long sequence, such as the gene for insulin, can therefore be located with a short probe. This technique, called molecular hybridization, reveals the size and number of DNA stretches that carry a specific sequence of interest. In fact, DNA sequences can now be synthesized by machine, and stretches of a few dozen base-pairs are available to order from a number of companies.

Once located, the DNA segment can be duplicated and placed in a different DNA molecule, for there is molecular paste to go with the molecular scissors. The paste, like the scissors, consists of enzymes. There are enzymes that link two sequences of DNA that possess the same ends, and other enzymes that give any two pieces of DNA the same ends. So the biologist can splice new sequences together to create a different DNA strand. And the new stretch of DNA, encoding perhaps the instructions for producing the active site of an enzyme or a

small hormone, can be transferred into the bacterium. For example, a sequence coding for a new, modified version of the active site of an enzyme might be inserted in place of the true active site sequence. Then the whole stretch would be placed next to a promoter sequence, and this longer stretch would be inserted into an appropriate plasmid for reintroduction into a bacterium. From there it is just fermentation that stands between the biologist and a big pot of a wholly new gene product.

Each of these gene-splicing techniques generated an explosion of fundamental information about the structure and function of genes in higher organisms. And, sure enough, taken together, these same techniques formed the flow chart of a factory that could produce gene products to order. Not surprisingly, it was the prospect of building such factories, rather than of learning about the structure and function of genes, that perked up the ears of private companies. And so, the first “gene” factories were built.

EVEN BEFORE the first of these new industrial laboratories opened, I began to fear the power of genetic technology and the dangers it posed—not to science but to

human health. Ten years ago, I was working at the Cold Spring Harbor Laboratory, on Long Island, with the tumor virus SV40, whose DNA is comparable in size to a very small plasmid. It just so happens that this virus usually takes up residence in our near relative, the African Green monkey. Naturally, I worried that the genes or gene products of the virus might bypass the immune defenses of the scientists who handled them, and that bacteria carrying these viral sequences would take up residence in the human gut.

Paul Berg, a Nobel Prize-winning professor of biochemistry at Stanford University, agreed that the problem existed in principle, and together with a group of scientists, including Alfred Hellman, of the National Cancer Institute, and Michael Oxman, of the Harvard Medical School, we organized the first Asilomar meeting on biohazards in biological research. But it was not until the second, and famous, Asilomar Conference that the very pioneers of genetic technology volunteered a moratorium on all recombinant DNA experiments that were suspected of being risky until their safety could be verified. The restrictions were matched to the severity of each experiment's risk; certain experiments, such as inserting DNA from cancer cells into bacteria, were forbidden.

In the end, scientists found that a recombinant organism is no more dangerous than the most dangerous sequences it carries. After that worry and hesitation had passed, products, promises, and production lines followed in dizzying profusion. Some scientists looked forward to diagnostic tests and potent new drugs and vaccines against diseases; others dreamed about freeing the world from its expensive dependence on fertilizers by creating "artificial legumes" that would fix nitrogen the way bacteria in the root nodules of naturally occurring legumes do.

At first sight, this all seemed good for research: capital was flowing from private sources into molecular biology just as government money was being cut back, and scientists were finally making money from their discoveries. But when we consider the need to preserve science as an ongoing process separate from product development, the picture looks less rosy.

The problem is not that money is being made from the manufacture of genetic products. On the contrary, there is nothing intrinsically wrong, nothing more natural than to profit from one's own discoveries—but that the manufacturing business is worlds apart from the process of learning, which is an integral part of basic research. Learning is intrinsically nonproductive; while universities turn out both good science and good scientists, the tangible fruits

of universities—the Ph.D.'s and research papers—are neither patentable nor salable.

It is hardly surprising that corporations and their stockholders, who always demand patentable, salable returns for their investments, have little interest in having their money invested in education. Nor is it unusual that in lieu of subsidizing graduate and post-graduate education in molecular biology, private investors pour money into corporations that manufacture biochemical products, fancying that this is equivalent to the support of basic research. But, as a result, most of the new companies are not institutes of research pursuing new knowledge; they are factories concerned with manufacturing products. In a sense, these industrial laboratories are financed at the expense of new scientists, for they draw from the pools of scientist-teachers and of recent graduates and have yet to replenish these pools.

Luckily, not all companies are so narrow as to demand only product development from their employees. A few of the great privately endowed research centers, such as Bell Laboratories, are insulated from corporate bottom lines and attract excellent scientists from universities. There are havens for molecular biologists in a few private corporations as well. I recently visited the Roche Institute, in Nutley, New Jersey, which is funded by the Swiss drug firm Hoffmann-La Roche. Although Hoffmann-La Roche expects some practical results from the research done in its laboratories, the institute is not goal oriented. Its purpose is knowledge, not profit. The Roche Institute demonstrates that molecular biology can be carried out successfully in a corporate setting if there are no strings tying money to a particular line of research.

ONE INTERESTING NEW EXPERIMENT in academic-industrial relations is the Whitehead Institute, directed by David Baltimore, at the Massachusetts Institute of Technology, in Cambridge. There is ample support for graduate students, and the institute's scientific staff is appointed also to M.I.T.'s department of biology. No strings are attached to the research other than the agreement that all patents from the institute go automatically to the donor. This arrangement seems to keep the donor's money from being diluted in the pot of the university, and the university's teaching free from overt violation by Mr. Whitehead's many companies. (We shall see if this delicate balance can last.) Unfortunately, not too many other donors are clamoring to give away 120 million dollars, as Mr. Whitehead did, to set up such a venture.

Since the world has so few ideal philanthropists, we must take steps of our own to

secure the continued viability of research and educational institutes. For a start, scientists in positions of corporate influence should attempt to have private capital tithed back to universities and institutes. And those of us who get federal grants must not watch passively as those grants decline in value each year because of inflation. We must make a much bigger fuss than we have in the past, for the federal government is becoming mean-spirited toward the most vulnerable of new scientists, our graduate students.

Basic research is the motor that pulls us into the technologies of the future. Private money for product development is not a substitute motor. And so when universities pursue private money, as they now must, they should never lose sight of their historic role as places of learning and should never accept private arrangements that do not conserve and enrich their training function. The case of the Harvard Medical School must serve as a reminder of what can happen when the road to product development is paved over the paths of a campus. For an endowment of fifty million dollars, the German chemical company Hoechst bought Harvard's research freedom. Now Hoechst has the right to clear all manuscripts before publication and a say in the recruitment of researchers.

The implications of such restrictions were among the concerns that prompted the heads of five major universities (Stanford, Harvard, M.I.T., the California Institute of Technology, and the University of California) and eleven corporations (including Genentech, Syntex, Gillette, DuPont, Eli Lilly, and Cetus) to meet last March at Pajaro Dunes, California. Stanford University president Donald Kennedy claimed that one of the purposes of the conference was to "set an agenda for further discussion of the issues," though as of now, none of the presidents who attended this conference has announced any plans for holding another.

Yet there must be more meetings. Somehow we must decide how to protect the research that will bring us the technologies of the future. We are so far from answering all the questions in biology that we might well think of ourselves as having just begun. Acting as if all questions are answerable, and most have been answered, generates a self-fulfilling prophesy. Unless private money is funded directly to university programs and to individuals who want to teach, the time will quickly come when the best scientists cannot afford to teach and the next generation of scientists arrives stillborn, unable to ask the next set of questions. We are making a great feast in molecular biology by cooking up our seed corn. It isn't smart. ■