TIME

Monday, Mar. 09, 1981

Shaping Life In the Lab

COVER STORIES

And profiting from gene splicing

The whole affair left Wall Street slightly dazed. Within minutes, the new stock leaped from its offering price of $35 a share to $89. As thousands of buyers bid for a piece of the action, brokerage houses had to resort to strict rationing. When a Beverly Hills matron demanded 100 shares, her broker apologetically explained that he could give her only two.

Such was the speculative fever when an obscure company named Genentech came to the over-the-counter market with a $36 million stock offering last fall. Veteran traders had never seen such commotion over an embryonic company, which had only 140 employees, sold no product to the public and showed a profit for just one year, at a rate of 2¢ per share. In fact, Genentech is only one of a growing number of similar companies just coming into existence that offer little more than vague promises of scientific things to come.

But what promises, what dazzling things to come—a new alchemy that may one day turn the basest of creatures into genetic gold. That alchemy is already capable of making new drugs like the antiviral agent interferon, a possible weapon with which to attack cancer. In the future, it may produce vaccines against hepatitis and malaria; miracle products like low-calorie sugar; hardy self-fertilizing food crops that could usher in a new "green revolution"; fuels, plastics and other industrial chemicals, out of civilization's wastes; mining and refining processes to relieve Malthusian anxieties about a future without sufficient raw materials.

Such things now seem within man's reach through the commercial adaptation of gene splicing, or recombinant DNA (for deoxyribonucleic acid). It is a genie capable of transforming the world—a genie that, scientists hope, the world will never want to put back into the bottle.

In recent years, scientists have also developed other techniques in genetic engineering. Most aim at modifying the hereditary mechanisms of microorganisms or cells for purposes of research or commerce. Others include the fusion of cells, DNA synthesis and the creation of hybridomas, long-lived cells that are designed to produce pure antibodies for use against disease. But of all these marvels, it is gene splicing that scientists consider the most exciting. Says the University of Zurich's Charles Weissmann, 50, who last year became the first scientist to make bacteria produce a facsimile of human interferon: "Biology has become as unthinkable without gene-splicing techniques as sending an explorer into the jungle without a compass."

Gene splicing is the most powerful and awesome skill acquired by man since the splitting of the atom. It is an unparalleled exploratory tool for examining, and in the process changing, the complicated machinery of heredity. If a gene of unknown function is inserted into bacteria, it can act as a probe that lets scientists see precisely what it does. By such techniques, researchers will finally speed up the formidable task of identifying, locating and analyzing every one of the more than 100,000 genes found in a human cell.

Already, for the first time, scientists can tailor simple living things. They can do this not just by cleverly mixing different strains, as in the slow and ancient process of crossbreeding roses or dogs, but by directly manipulating the genes—those tiny command posts of heredity that tell living cells whether they will become bacteria, toads or men. Thus a plant or animal might acquire a characteristic from a totally unrelated species and pass this new trait on to future generations.

Often, decades go by before scientific discoveries find their way out of the laboratory and into daily life. Because of its extraordinary potential, gene splicing could prove to be a dramatic exception. Developed in the 1970s at many academic centers, notably Stanford, Harvard and M.I.T., it is fast breaking out of the university research centers into the world of industry. To its boosters, it seems certain to be the technology of the 1980s, just as plastics were in the 1940s, transistors in the 1950s, computers in the 1960s and microcomputers in the 1970s.

The short-term possibilities of the new gene-splicing companies may have been overblown. In the field of medicine, the new chemical creations face lengthy testing by the U.S. Food and Drug Administration before they can be licensed. The application to agriculture will require a great deal of capital, to say nothing of enormous technological advances, before any plants and products can be turned out in sufficient quantities to transform the world. Says James Watson, who with Francis Crick won a Nobel Prize for unraveling the

double-helix structure of DNA and ultimately making recombinant DNA possible: "Let's put it this way: I wouldn't buy gene-splicing stock for my grandmother."

But the prospects for long-term growth can hardly be over estimated. One research firm, International Resource Development Inc., of Norwalk, Conn., forecasts an annual market of no less than $3 billion in recombinant DNA products in the pharmaceutical area alone by 1990. Says Britain's usually reserved Economist: "Biotechnology is one of the biggest industrial opportunities of the late 20th century."

In view of such glowing hopes for doing good and making big dollars, it is not surprising that DNA companies, most of them privately held, are proliferating from coast to coast, particularly in California and the Boston-New York-Washington corridor. Even Watson's Cold Spring Harbor Laboratory on Long Island, N.Y., is planning a research company. Wall Street analysts disagree about which fledgling firms will become the Polaroid, Xerox or Texas Instruments of gene splicing, or indeed survive the infant industry's inevitable shake-outs and growing pains. But a handful seem to be well ahead of the pack, and have attracted wide interest in the fields of both science and industry:

Genentech Inc. was co-founded in 1976, in South San Francisco, by Venture Capitalist Robert Swanson, 32, and University of California Biochemist Herbert Boyer, 44. The company now has a staff of 200. It has signed research agreements with several large pharmaceutical houses, including Hoffmann-La Roche and A.B. Kabi, and leads all gene-splicing firms by offering half a dozen products. Among them: several types of interferon, one of which is now undergoing clinical trials. Genentech is also collaborating with another leading drug company, Eli Lilly, on mass production of human insulin. Last week Genentech announced its latest gene-splicing advance. In collaboration with scientists from the University of Washington, Genentech's teams induced yeast cells to make interferon for the first time. The announcement promptly drove Genentech's stock up $7 a share.

Cetus Corp. was founded a decade ago by a physician, Peter Farley, 40; a biochemist, Ronald Cape, 48; and Donald Glaser, 54, a Nobel prizewinning physicist. It uses not only gene splicing but also other genetic-engineering methods to modify microorganisms and produce such industrial chemicals as ethylene oxide (for making other chemicals and plastics), ethylene glycol (antifreeze) and alcohol. With that many different lines of interest, Cetus has had trouble concentrating its efforts. The company plans a $130-million public stock offering, possibly as soon as this week.

Biogen S.A., of Geneva, is a research-oriented firm founded in 1978 by a consortium of businessmen and

scientists that included Weissmann and Harvard's Walter Gilbert, 48, a co-winner of the 1980 Nobel Prize in Chemistry. Last year it produced the first gene-spliced interferon-like human protein after sifting through 20,000 different genetic fragments. Schering-Plough and Inco (formerly International Nickel) are major investors.

Genex Corp. was started in 1977 by Molecular Biologist J. Leslie Glick, 41, to manufacture enzymes and other industrial chemicals through gene-splicing techniques. Genex, which is based in Bethesda, Md., also does testing and research jobs for other companies and now has a contract with Bristol-Myers to produce gene-spliced interferon. A major investor is Koppers Co., a chemical and engineering corporation.

The future of such firms is complicated further by the fact that few businessmen can really understand the science, and few scientists can comprehend the business mentality. Most of the new firms are tight-mouthed about their products, and the field is full of rumors that smack of the rivalry and intrigue in the early years of the railroad and automobile industries. There are stories of deposed corporate officers furtively arranging private stock sales, of disenchanted employees about to break away and start their own companies. Foreign banks lurk in the background, waving OPEC dollars. Major drug companies are now exploring the possibilities of the gene-splicing game.

Schering-Plough has bought a 16% interest in Biogen. Other drug companies are setting up their own teams. Gene splicing has also piqued the interest of oil companies that not only seek outlets for their cash but are also intrigued by the energy potential. Standard Oil of Indiana and Standard Oil of California together have a 50% stake in Cetus. Twenty percent of Genentech is owned by Lubrizol, an oil supply company. Even academic institutions like Harvard have considered backing gene-splicing firms. So high is investor interest that Molecular Biologist Norton Zinder of Rockefeller University says with a smile, "I could pick up the phone and in 20 minutes raise $25 million to start up a new company." One additional incentive for all potential investors: last June's 5-to-4 decision by the U.S. Supreme Court that man-made organisms may be patented.

Whatever gene splicing ultimately does in business, it has already created rich opportunities for biologists, long the poor cousins of science. Genentech Co-Founder Boyer has be come a millionaire many times over, at least on paper (see box). To create the organisms that may turn those paper profits into real revenue, biologists with the prerequisite gene-manipulating skills are being recruited at a furious pace. Young scientists, the ink barely dry on their Ph.D.s, are being offered $30,000 a year, plus a little stock. Senior researchers are getting large chunks of the new companies. Others are fattening their relatively modest academic salaries by serving as part-time consultants to the new companies at fees of $1,000 or more a day.

Deserving though the biologists may be, their new role raises a real concern. Traditionally, university researchers toil in their labs, usually at the taxpayers' expense, doing basic research—that is, research promising fresh insights into the fundamental truths of nature, regardless of the prospect of immediate payoffs. The bioengineering firms, by contrast, must set their sights on quick returns. Will the new alliance between industry and academia destroy the old objective "purity" of science? Will scientists still freely exchange information or lab specimens, as they have often done in the past, if they know a colleague works for a rival firm? Will they forsake long-term investigations into nagging questions like the origins of cancer in favor of faster and more lucrative projects that might, for example, produce a new tranquilizer?

It was just such questions, asked by faculty members, that prompted Harvard to decide against taking part in a gene-splicing firm founded by Moleculer Biologist Mark Ptashne, even though the venture might have pumped some needed cash into the university's coffers. Stanford's president, Donald Kennedy, a biologist himself, is urging his colleagues to use "caution and deliberation" in responding to the flurry of overtures from gene-engineering firms. Reason: potential conflict of interest between pure science and the demands of their commercial employers.

Bitter legal disputes have already broken out. The University of California has sued Hoffmann-La Roche and Genentech on charges that a line of cells they use to produce a type of interferon was first created in the university's San Francisco labs (Genentech's Boyer was, and still is, a top researcher at U.C.S.F.). That case is still pending in the courts. But another squabble with the university has already cost Genentech $350,000, plus future royalty payments to the school. The money was awarded to the university for work done by one of its researchers on a hormone that induces human growth, which he brought to Genentech when he joined the company. Says John Baxter, the school's chief scientist on the project: "I really felt there should be some compensation."

Naturally, most molecular biologists now enjoying the new prosperity point out that collaboration between universities and industry is neither new nor dangerous. Physicists and chemists, they note, have long worked for private firms—not to mention the Pentagon—with little complaint from their colleagues except, in retrospect, over the atomic bomb. Says Boyer: "Industry is far more efficient than the university in making use of scientific developments for the public good."

The sort of efficient cooperation he has in mind is most evident in medicine. In January doctors at the University of Texas' M.D. Anderson Hospital in Houston began injecting cancer patients with bacterially produced interferon, developed at Genentech. Interferon is part of a natural defense system against such viral diseases as influenza and hepatitis; it also seems to act against certain types of cancer, particularly

cancer of the breast and the lymph nodes. But to date only extremely small quantities of it have been available, all painstakingly collected from blood cells and other human tissue. Relatively few patients, only several hundred out of the hundreds of thousands of cancer victims who might benefit from interferon, have been receiving the drug. Natural interferon is very costly (up to $150 for a daily injection). Most of the people getting it receive extremely small doses—perhaps too small to work. The object of the Texas experiment: to determine whether bacterially manufactured interferon acts any different from the natural stuff. If the synthetic drug lives up to its billing and causes no harmful reactions, bacterial assembly lines could start producing human interferon in wholesale quantities. The price might then come down to $1 a shot.

Another scarce drug now bubbling out of Genentech's stainless-steel fermentation vat is human growth hormone, used to treat dwarfism. Only limited quantities have been available, most of it extracted from the pituitary glands of cadavers. In a test of the hormone, 20 youngsters are currently getting doses of bacterially produced HGH at London's Great Ormond Street Hospital for Sick Children.

Genetically engineered microorganisms are also producing the enzyme urokinase, used to dissolve blood clots; the hormone thymosin alpha1, which shows promise as a treatment for brain and lung cancer; and beta-endorphin, one of the brain's own painkillers.

The drug closest to commercial production by gene-splicing techniques is insulin, the hormone that enables the body to burn sugar for energy. Last December a Derby, Kans., housewife, Sandy Athertone, 37, became the first diabetic to be injected with bacterially made insulin. It came from the pharmaceutical labs of Eli Lilly, which is spending $40 million to build plants in Indianapolis and outside Liverpool, England, to make human insulin by means of recombinant DNA. More recently other diabetics began receiving bacterial insulin in a test program in six U.S. cities. Lilly plans similar trials in Canada and Europe. Says one participating doctor, Fred Whitehouse of Detroit's Henry Ford Hospital: "So far the synthetic insulin appears to be as effective as animal insulin."

Lilly and other drug makers can easily meet current demand for insulin by extracting it from the pancreases of cows and pigs. The trouble is that of all diabetics on insulin—some 1.8 million people in the U.S. alone—5% suffer allergic reactions to the animal hormone because it differs ever so slightly from the human variety. It may also cause some of the circulatory problems associated with diabetes. By contrast, virtually every atom of the bacterial product is identical to insulin made in the body, and so should produce few reactions.

There is, of course, nothing new in harnessing bacteria for human good. Microorganisms have long been used, even if unwittingly, to serve man's needs, from breaking down wastes to making alcohol and

producing antibiotics. Man began interfering with the genes, at least indirectly, long before the 19th century monk Gregor Mendel discovered the laws of heredity, which foretell how such physical characteristics as the color of a person's eyes and hair or the shape of his nose will be passed from one generation to the next. Through cultivation and crossbreeding of plants and livestock—that is, mixing genes—humans were able to make the grand leap from nomadic hunter-gatherers to civilized farmers. They continued such tinkering despite the Bible's stern genetic injunction (Leviticus 19:19): "Thou shalt not let thy cattle gender with a diverse kind; thou shalt not sow thy field with mingled seed."

What is new is that scientists are now able to manipulate directly the very substance that makes up genes: DNA, often called the master molecule of life. Coiled in the chromosomes of all living cells, DNA consists of only a handful of chemical building blocks—a sugar, a phosphate and four bases, adenine (A), thymine (T), guanine (G) and cytosine (C). But its simplicity is deceptive. In DNA's precise architecture—the famed double helix unraveled by Watson and Crick in 1953—lies the secret of how the molecule conveys the message of heredity from one generation to the next.

The twisted, double-stranded DNA, as frequently noted, resembles a spiral staircase, with each step formed by a pair of bases—A always binding with T, G always with C. In fact, it acts more like computer tape. Every three steps serve as a code word for one of the 20 amino acids found in all life on earth. Strings of code words, in turn, provide the sequence for linking these amino acids into proteins, the basic building blocks of living things. DNA thus carries the entire genetic blueprint for assembling any organism, from bacterium to man.

Though the double helix helped unlock many of the mysteries of DNA, even more are still unexplained. How do genes turn on and off—or, in the language of molecular biology, "express" themselves? What about cell differentiation? At a critical moment early in the life of an embryo, identical cells miraculously (no other word will do) begin to take on specialized roles—some forming tissue for the heart, for example, others that of the liver or skin. Each of these different cells still contains all the original instructions for producing the entire organism, but somehow unneeded genes are switched off. How does this differentiation come about? Do certain genes order up particular proteins that serve as "on" and "off" switches?

To answer such questions, scientists in labs around the country began looking for new ways to examine the genetic machine in action. One of them was Biochemist Paul Berg, 54, of Stanford University. Berg wanted to study genes of higher organisms. But their complement of genes tends to be dizzyingly complex, involving thousands of steps along strands of DNA. Instead he and his colleagues plotted an experiment involving viruses, which are nothing more than a short strip of nucleic acid, usually cloaked in a wrapper of

protein. When they invade a living cell, viruses substitute their own genes for their victim's DNA and crank out duplicates of themselves. Berg's clever strategy was to exploit this mischief-making ability by using a virus to invade a bacterium. He hoped that there the new genes from the virus would begin producing proteins unlike any normally ordered up by the bacterium's genes. In so doing, the "foreign" genes from the virus would reveal their nature.

As his source of DNA, Berg turned to a well-known laboratory tool known as SV40, short for simian virus 40 (so called because it was orginally found in monkeys). SV40's genetic structure is relatively simple—it seems to have no more than seven genes (vs. around 5,000 in the cell of a fruit fly and the 100,000 in a human cell). Thus SV40's genes could easily be identified and distinguished from the other DNA of the host cell.

To insert the genetic material into the bacterium, he used as his "vector," or carrier, another variety of virus called a lambda phage, which preys on bacteria. But first he had to cut open SV40's single circular DNA molecule. As his biochemical knife, he used certain enzymes, or helpers in chemical reactions, that cells normally use in such processes of their everyday life chemistry as digestion. Then he employed more enzymes to break into lambda's genes. Still other enzymes were painstakingly used to create the required mortise-like "sticky" ends to attach the two strips of DNA together.

By the time Berg and his team "glued" all this DNA back into a circle, they had achieved a scientific first: genetic material from two different organisms—in this case, two kinds of viruses—had been directly combined by human intervention. Recombinant DNA, or gene-splicing, was born. As its midwife, Berg shared the 1980 Nobel Prize in Chemistry.

The next phase Berg planned for his experiment brought on the hottest controversy that gene splicers have yet confronted. Berg wanted to insert the SV40 genes into the bacterium Escherichia coli, an inhabitant of the human intestine only about one ten-thousandth of an inch long. E. coli has been the regular guinea pig of the molecular biology lab for some 40 years. But a few scientists who learned of Berg's plans were shocked. SV40 seems harmless enough in monkeys. But it causes tumors in mice and hamsters and has turned test-tube cultures of human cells cancerous. What would happen if E. coli containing the monkey virus escaped from Berg's lab, established themselves in the human gut and went on multiplying? Would that plant a slowly ticking cancer time bomb?

Berg voluntarily dropped the planned experiment. Concerned about the possible escape of new and deadly pathogens, he helped persuade his colleagues to observe a self-imposed moratorium on such experiments. Even so, some university towns threatened to ban all recombinant DNA work. The voluble former mayor of

Cambridge, Mass., Alfred Vellucci, spoke darkly, and inaccurately, of breeding "Frankensteins" in the labs at Harvard and M.I.T.

Under federal guidelines drawn up with the help of scientists led by Berg and adopted by the National Institutes of Health in 1976, gene splicing in university labs was strictly controlled. The new rules established levels of biological containment deemed appropriate to possible hazards. If a proposed experiment was low on the risk scale, it could be done on an open bench or perhaps on a special counter protected by a curtain of air. More dangerous experiments required sealed isolation chambers like those used in germ warfare research; only by reaching through a gloved compartment did the scientists have access to their work. The ultimate safeguard: bacteria especially designed to self-destruct if they escaped the nurturing environment of the lab. Yet even without these precautions, subsequent tests showed that probably none of the doomsday scenarios could have occurred. Last year the NIH dropped most of the restrictions on gene-splicing work.

While Berg and his colleagues were agonizing about the possible dangers posed by their experiments, two other scientists were planning an even more dramatic display of gene splicing. One of them was an intense biochemist named Stanley Cohen, 46, whose lab was only two floors below Berg's own quarters at the Stanford Medical Center research building. The other was Boyer, who worked just an hour's drive away at the University of California at San Francisco. Their partnership had emerged accidentally. In November 1972, after a long day of listening to scientific papers at a conference in Hawaii, they met in a Waikiki delicatessen for a midnight snack. Gossiping about their work while munching on corned-beef sandwiches, the two discovered that their research dovetailed in a way that opened up some highly intriguing possibilities.

Almost all of E. coli's 4,000 genes are located in a single circular chromosome. But Cohen had isolated some bits of genetic material that float freely in the bacterium outside this main genetic repository. These bits of genetic "small change" are known as plasmids. A plasmid contains as few as three or four genes linked in a small circle, yet it sometimes is crucial to bacterial survival.

During normal bacterial reproduction, the cell simply divides, passing exactly the same genetic information on to each daughter cell. Thus they are natural clones, genetically identical to their single parent. In this kind of unisex reproduction, there is no chance for bacteria to inherit fresh characteristics that might help improve their chances of survival. But every so often two cells have a sort of sexual dalliance called conjugation. They approach each other, send out thin tubes that bring the cells together, and transfer genes. In the exchange, a bacterium may pick up, say, a gene for making an enzyme that cuts up and destroys certain antibiotics. All the bacterium's offspring will then inherit this life-preserving resistance and, in this way, defy medicine's best efforts to do them in.

Like Berg, Cohen wanted to insert new genes artificially into bacteria. But where Berg resorted to a virus as his transport system, Cohen opted for plasmids, which he had been studying in his lab. As he listened to Boyer's description of his work that night in Waikiki, however, Cohen realized that there might be a short cut. Boyer and his associates had found a so-called restriction enzyme that cuts DNA precisely at predetermined points, and performs this surgery in an especially helpful way: at each end of the severed, twin-stranded molecule, it leaves an extra bit of single strand poking out, automatically creating the "sticky" mortised ends that Berg had labored so hard to achieve.

The twin breakthroughs—Beyer's surgical enzyme and Cohen's plasmids—opened the door to an extraordinary scientific capability. If they were used together, almost any gene—from a virus, a frog or a man—could be spliced into the plasmid. Cohen named this mixed bag of genes a chimera (after the mythological beast that was part lion, part goat, part serpent). Such a plasmid could then be inserted into E. coli. And as the bacteria replicated, the transplanted DNA would be copied down to the last step on the spiral staircase. Any product ordered up by the inserted genes—the antiviral agent interferon, for instance, or perhaps an enzyme to break down oil molecules—would also be made in the offspring. And in abundance: dividing once every 20 minutes, the original bacterium would undergo a population explosion. In 24 hours, a single bug could result in billions of bugs, all of them churning out the desired product.

At first Cohen and Boyer balked at seeking a patent for their work. But Stanford's licensing director, Neils Reimers, changed their minds by citing the case of Alexander Fleming, the British discoverer of penicillin. Fleming had also refused to take out a patent, thinking that this would ensure penicillin's widespread availability. Instead, since no company would take the financial risk of making it without patent protection, the wonder drug did not go into production until World War II, some 14 years after Fleming had identified it.

Cohen and Boyer's own reluctance was overcome just in time: they signed the patent application only a week before the deadline expired. Any royalties were to be turned over to their universities. For a while, it looked as if there might be no royalties for anybody. The U.S. Patent Office refused to grant the application, contending that new life forms were not patentable. But that view was overturned in last June's U.S. Supreme Court decision. Though the test case involved an oil-eating bacterium developed by crossbreeding techniques, the ruling was also held applicable to gene splicing generally. Cohen and Boyer wound up holding the first patent in the recombinant DNA field.

A natural product like synthetic interferon cannot be patented, so what Cohen and Boyer actually did patent was the basic gene-splicing method they had pioneered. Some scientists like James Watson contend, however, that other gene splicers will easily circumvent such legal protection by making just slight changes

in their techniques to avoid patent infringement.

There are certain to be more patent lawsuits, but they are most likely to affect individual scientists and companies, not the future of products created by gene splicing. The multiplication of such products, moreover, does not appear in doubt. A new study scheduled to be released this week by the congressional Office of Technology Assessment lists no fewer than 48 human hormones that may soon be manufactured by minute, gene-spliced organisms. This will vastly increase medicine's arsenal of drugs. Many researchers, for instance, are working on vaccines for stubborn tropical diseases. Concludes the congressional study: "These may profoundly affect the lives of tens of millions of people."

One team of doctors has already tried "gene therapy," the effort to correct hereditary defects like the blood disease thalassemia by replacing abnormal genes with normal ones created by splicing techniques. These initial experiments failed abysmally and were widely criticized as premature. Until much more is learned about how humans might be made to acquire new genes, and how those genes are expressed, future gene therapists are no more likely to succeed.

AIso in the future but perhaps more feasible are gene-splicing applications in the fields of animal husbandry and agriculture. Under a contract with the U.S. Department of Agriculture, Genentech is already working on a vaccine against hoof-and-mouth disease, which kills off millions of food-producing animals a year round the world. Geneticists also hope to endow such basic food plants as wheat, corn and rice with the ability to "fix" or draw their own nitrogen from the air. At present, nitrogen must be provided in expensive fertilizers made from increasingly costly petroleum products. But scientists using plasmids have already cloned some of the nitrogen-fixing genes found in bacteria. And in an experiment at Cornell, a complete set of 17 such genes was transferred from bacteria to yeast, a slightly higher organism. The ultimate goal: to insert these genes in the plants themselves.

Some scientists are already looking ahead to creating bacteria that can help collect scarce metals by leaching (or dissolving) them directly out of the earth, or force out the last drops of petroleum from nearly exhausted wells, or even sift the diffuse quantities of gold in the world's oceans. Like faithful robots, they would work uncomplainingly, without interruption or distraction. All they would require is the appropriate nourishment and the right sort of care.

Not everybody is rooting for the gene splicers to achieve their goals. Were they to do so, they would possess truly Faustian power, not only to make repairs when genetic machinery goes awry, as in such diseases as hemophilia and sickle-cell anemia, but to "improve" the species itself. There may be perils in disturbing a

microbial balance that has been billions of years in the making with strange, new man-made bugs. Asks Biologist Robert Sinsheimer, chancellor of the University of California at Santa Cruz: "Do we really wish to replace the fateful but impartial workings of chance with the purposeful self-interested workings of human will?" Even more dourly. Biochemist Erwin Chargaff notes: "If you can modify a cell, it's only a short step to modifying a mouse, and if you can modify a mouse, it's only a step to modifying a higher animal, even man."

But even Sinsheimer admits there is probably no turning back. The genie is out of the bottle. A great majority of scientists also point out that no gene-spliced monsters, bacterial or otherwise, have yet escaped from the laboratory. What is more, there is a world of difference between splicing a viral gene or two into a humble bacterium and redesigning the complex genes of man, which now seems quite remote.

In any case, as enthusiasm grows for what gene splicing may eventually be able to accomplish, the debate has become moot. Chief Justice Warren Burger himself acknowledged this when he declared, in the 1980 patent decision, that no one will be able to "deter the scientific mind from probing into the unknown any more than Canute could command the tides." What both the public and scientists can do is to ensure that this insatiable inquisitiveness is channeled to serve the common good. So far, the proud record of gene splicers seems to bear out the hope that it will be.

—By Frederic Golden. Reported by Michael Moritz/Los Angeles and Gavin Scott/San Francisco