GENETIC ENGINEERING – THEN & NOW

Scientific & Societal Origins of Genetic Engineering
Magazine Articles of the Time!

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The Miracles of Spliced Genes – Newsweek Magazine, March 17, 1980

Shaping Life in the Lab – Time Magazine, March 9, 1981

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Gene Therapy for Hemophilia B – Reuters, December 10, 2011

Gene Therapy for Bubble Babies" – UCLA Newsroom, September 14, 2012

Gene Therapy Cures Leukemia – WebMD, December 10, 2012

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TIME
Monday, Apr. 18, 1977

DOOMSDAY: TINKERING WITH LIFE

It is one of the lowliest of nature's creatures, a rod-shaped beastie less than a ten-thousandth of an inch long. Its normal habitat is the intestine. Its functions there are still basically unknown. Yet this tiny parcel of protoplasm has now become the center of a stormy controversy that has divided the scientific community, stirred fears—often farfetched—about tampering with nature, and raised the prospect of unprecedented federal and local controls on basic scientific research. Last week the bacterium known to scientists as Escherichia coli* (E. coli, for short) even became a preoccupation at the highest levels of government.

Appearing before a Senate subcommittee on behalf of the Carter Administration, HEW Secretary Joseph Califano asked Congress to impose federal restrictions on recombinant DNA research, a new form of genetic inquiry involving E. coli. The urgency of Califano's request underlined the remarkable fact that a longtime dream of science, genetic engineering, is at hand —and, some fear, already out of hand. In laboratories across the nation, scientists are combining segments of E. coli's DNA with the DNA of plants, animals and other bacteria. By this process, they may well be creating forms of life different from any that exist on earth.

That this exciting new research holds great promise but could also pose some peril was stressed in the day-long testimony before Senator Edward Kennedy's health subcommittee. Califano called recombinant DNA "a scientific tool of enormous potential." He also warned about possible—though unknown—hazards and concluded: "There is no reasonable alternative to regulation under law." Massachusetts Governor Michael Dukakis, involved in the controversy over genetic-engineering projects at Harvard and M.I.T., argued for the public right to regulate the research. Said he: "Genetic manipulation to create new forms of life places biologists at a threshold similar to that which physicists reached when they first split the atom. I think it is fair to say that the genie is out of the bottle."

The issue, stated simply, is whether that genie is good or evil. Proponents of this research in DNA—the master molecule of life—are convinced that it can help point the way toward a new promised land—of understanding and perhaps curing cancer and such inherited diseases as diabetes and hemophilia; of inexpensive new vaccines; of plants that draw their nitrogen directly from the air rather than from costly fertilizers; of a vastly improved knowledge of the genetics of all plants and animals, including eventually even humans (TIME special section, April 19, 1971).

Opponents of the new research acknowledge its likely bounty, but fear that those benefits might be outweighed by unforeseeable risks. What would happen, they ask, if by accident or design, one variety of re-engineered E. coli proved dangerous? By escaping from the lab and multiplying, their scenario goes, it could find its way into human intestines and cause baffling diseases. Beyond any immediate danger, others say, there are vast unknowns and moral implications. Do not intervene in evolution, they warn in effect, because "it's not nice to fool Mother Nature." Caltech's biology chairman, Robert Sinsheimer, concludes: "Biologists have become, without wanting it, the custodians of great and terrible power. It is idle to pretend otherwise."

The scientific community is bitterly divided about the unknown risks of genetic engineering. The wrangling has been public, and traditional scientific courtesy has all but vanished. Infuriated by unreasoning opposition to the new discoveries, James Watson—who, with Francis Crick, won a Nobel Prize for determining the double-helix structure of the DNA (for deoxyribonucleic acid) molecule—has labeled the critics "kooks,"

"shits" and "incompetents." One of his targets is fellow Nobel Laureate George Wald, who has supported efforts to ban recombinant DNA research at Harvard and M.I.T. Wald contends that instead of trying to find the roots of cancer, for example, through genetic research, society can fight the disease more effectively by taking carcinogens out of the environment.

The concern of Caltech's Sinsheimer is partly philosophical —some might even say mystical. He fears the unpredictable consequences of breaching what he calls nature's "evolutionary barrier" between different kinds of creatures—the genetic incompatibility that in most cases prevents one species from breeding with another. In the same vein, retired Columbia Biochemist Erwin Chargaff asks: "Have we the right to counteract, irreversibly, the evolutionary wisdom of millions of years in order to satisfy the ambition and the curiosity of a few scientists?"

For every salvo from the critics, though, a return round comes from defenders of recombinant DNA research. Bernard Davis, a Harvard Medical School microbiologist, is so sure the new technique is safe that he has publicly offered to drink recombinant DNA. He insists that those who worry about infections are totally ignorant of medicine's long history of safely handling highly contagious bacteria and viruses. Nor, he says, do they understand how difficult it is for a microbe to become pathogenic. He adds: "Those who claim we are letting loose an Andromeda strain are either hysterics or are trying to wreck a whole new field of research." Less acerbically, Chemist John Abelson pointed out in last week's Science that in five years of work with recombinant DNA there has not been a single reported case of infection. The evidence so far suggests that virulent combinations of genes are highly unlikely; the host bacteria simply reject the unwanted genes or die. "Thus," he concludes, "it is probably not possible to create a strain that would overgrow the laboratory and head for the town, as depicted in movies of the 1950s."

Brushing off Chargaffs fears of violating "evolutionary wisdom," Molecular Biologist Stanley Cohen, at the Stanford University School of Medicine, notes that man has been intervening in the natural order for centuries—by breeding animals and cultivating hybrid plants and, more recently, by the use of vaccines and antibiotics. With undisguised sarcasm, Cohen adds that it was Chargaffs "evolutionary wisdom that gave us the gene combinations for bubonic plague, smallpox, yellow fever, typhoid, polio and cancer."

The DNA furor has already intruded on the free exchange of information so vital to scientists. Longtime associates are no longer talking to each other. Fearful of losing out on tenure or research grants by taking the "wrong" stand on the issue, some junior researchers are lapsing into monklike silence. At Harvard, at least one graduate student has been disowned by her thesis adviser for getting into the fray. Says Microbiologist Richard Goldstein of the Harvard Medical School: "The level of animosity is unbelievable. There have been character assassinations left and right." Sometimes the argument has sounded like a replay of old Vietnik protests. At a forum of the National Academy of Sciences in Washington last month, unruly opponents of genetic research, chanting "We shall not be cloned," took over the stage and unfurled a banner reading: WE WILL CREATE THE PERFECT RACE—ADOLF HITLER.

Scientists clearly do not have any diabolical intent, but their emotional and unusually public debate over DNA has made ordinary citizens sit up and take notice. Newspaper and magazine articles have carried such chilling headlines as: NEW STRAINS OF LIFE—OR DEATH, SCIENCE THAT FRIGHTENS SCIENTISTS and MAN-MADE BACTERIA COULD RAVAGE EARTH. The Public Broadcasting Service (PBS) produced a special hour-long show, "The Gene Engineers," for its Nova series. Taking the genetics fuss as his cue, Columnist Russell Baker recently wrote of a plan by depilatory makers to combine the genes of man and ape. Their goal: to produce more hirsute customers.

Art Buchwald also got into the act. He described a visit to a futuristic "people" lab, where he asks the white-coated salesman if there have been any accidents. Yes, the salesman replies. "Someone once accidentally mixed the genes of Jack the Ripper with a donkey ..." "What was the result?" "We reproduced Idi Amin." Hollywood, too, is aware of the box office value of converting re-engineered cells into celluloid. In the new film, Demon Seed, a scientist's wife (Julie Christie) is "ravished" by his supersmart computer, which somehow manages to combine its "genes" with hers. The fruit of that union: an offspring that appears at first to be—well, a miniature knight in armor.

Science is not interested in pursuing such bizarre fantasies; the real advances are exciting enough. About five years ago, California scientists learned how to combine genes from different organisms, regardless of how low or high they are on the evolutionary scale. Though the researchers added only one or two new genes to a bacterium's collection of thousands of genes, the creation of such hybrid molecules was a

stunning feat. The accomplishment seemed to breach one of nature's more inviolable barriers. Even primates as closely related as gorilla and man are so different genetically that they cannot produce offspring. Thus it was not size alone that made King Kong and his ladylove a mismatch. The real species barrier is in the genes.

Molecular biology's wizards have managed to cross that obstacle in their work with bacteria. Unlike higher organisms, bacteria are single-celled creatures that usually reproduce not by sexual mating but by simply dividing. Thus their ability to acquire new and possibly advantageous genes would seem to be highly limited. But the tiny creatures have devised a cunning alternative. Besides their single, large, ringed chromosome (which is the repository of most of their genes), they possess much smaller closed loops of DNA, called plasmids—which consist of only a few genes. This extra bit of DNA—genetic small change, as it has been dubbed—serves a highly useful purpose. When two bacteria brush against each other, they sometimes form a connecting bridge. During such a "conjugation," a plasmid from one bacterium may be passed into the other.

These natural transfers can be crucial to the survival of the bacterium. It is through new plasmids, for example, that bacteria like Staphylococcus aureus have become resistant to penicillin. The plasmid acquired by the staph bug contained a gene that directs the production of a penicillinase, an enzyme that cracks apart invading penicillin molecules, making them ineffective. Different plasmids, sometimes passed from one bacterium to another, can order up still another kind of chemical weapon, a so-called restriction enzyme, which can sever the DNA of an invading virus, say, at a predetermined point.

Observing these bacterial tricks, molecular biologists began isolating various restriction enzymes. They had already discovered another type of bacterial enzyme, called a ligase (from the Latin word meaning to bind), which acted as a form of genetic glue that could reattach severed snatches of DNA. Using their new biochemical tools, the scientists embarked upon some remarkable experiments. As usual, they turned to their favorite guinea pig, a lab strain of E. coli, and soon they had learned to insert with exquisite precision new genetic material from other, widely differing organisms into the bacteria (see diagram).

E. coli did not merely accept the hybrid plasmids. When the bacteria reproduced—by dividing and thus doubling—at a rate of about once every 30 minutes, they created carbon copies of themselves, new plasmids and all. In only a day, one bacterium could make billions of duplicates of a transplanted gene.

The tremendous potential of these recombination techniques was not lost on the scientists. They reasoned that if the appropriate genes could be successfully inserted into E. coli, they could turn the bacteria into miniature pharmaceutical factories. The tiny creatures could churn out great quantities of insulin for diabetics (now obtained from the pancreases of pigs and other animals), clotting factor for hemophiliacs (currently both scarce and expensive), vitamins and antibiotics.

Re-engineered bacteria could have many other tasks. Scientists are already considering creation of special nitrogen-fixing bacteria, which would live in roots of crops that now do not have them, thus making it unnecessary to fertilize fields. A General Electric researcher has already added plasmids to create an experimental bug that produces enzymes capable of degrading a wide range of hydrocarbons; an organism engineered by recombinant DNA might some day be used to clean up oil spills. (Even this scheme alarms some opponents of the new research. They fear that a bug designed to gobble up oil spills might get into a pipeline or the fuel tanks of a jet in flight. Jokes one observer: "Some day you may have to worry about your car being infected.")

Most important, recombinant techniques are of enormous help to scientists in mapping the positions of genes and learning their fundamental nature. Stanley Falkow, a University of Washington microbiologist, recently used the method to isolate two toxin-producing bacterial genes that cause diarrhea in humans and livestock. This discovery may lead, in time, to a vaccine against the disorder. But far greater biological bonanzas are in the offing. After three decades of intense study, only one-third of E. coli's 3,000 to 4,000 separate genes have been identified. Higher organisms are much more complex. Humans, for example, have hundreds of thousands of genes. Trying to find out what each of them does has stymied scientists. But if human genes could be transplanted, one at a time, into E. coli and replicated in wholesale amounts, researchers would for the first time have great enough quantities of genes and their products to analyze them fully. Eventually, the genes on all 46 human chromosomes could be precisely located and studied. Not the least of the benefits might be a vastly increased understanding of the

molecular basis of disease —especially cancer, which seems to occur when the cell's genetic machinery goes awry.

No one has given more thought to Andromeda-strain scenarios than the scientists who most strongly support the new research. Indeed, it was their own caution that first brought these possibilities before the public. In the summer of 1971, while lecturing on the safe handling of cancer viruses at James Watson's Cold Spring Harbor Laboratory on Long Island, a young cancer researcher named Robert Pollack learned from a visiting scientist that her boss at Stanford Medical Center planned a novel experiment. He hoped to insert a monkey virus, SV40, into E. coli. Although the virus seems harmless enough in its original hosts, it can cause tumors when injected into lab animals; it also turns laboratory cultures of human cells cancerous, although there is no evidence that it can cause cancer in people.

Highly concerned about the uncertainties of infecting laboratory bacteria similar to those in man with known cancer genes. Pollack immediately called Stanford and raised his doubts. The experimenter, Biochemist Paul Berg, listened politely but saw no reason for alarm. He knew that SV40 had been handled without ill effects by countless laboratory workers and had even been inadvertently included in some of the first batches of oral polio vaccine without doing any apparent harm. Indeed, Berg felt that the experiment was not only safe but extremely important. SV40's appeal lies in the fact that it has only a few genes, one of which apparently has the ability to turn normal cells into cancerous ones. If anyone could unlock the mysteries of this lethal gene—a goal of laboratories around the world (and the kind of discovery that might well win a Nobel Prize) —he would have taken a major step toward understanding the elusive mechanism of cancer.

When Berg asked his colleagues about the experiment, some of them also expressed misgivings. What if an altered E. coli, carrying SV40 genes, planted a slow-ticking cancer time bomb in the human gut? Nagged by such questions, Berg canceled his experiment. But even while Berg was agonizing over the decision, scientists made two dramatic discoveries that would vastly simplify recombinant work.

At the University of California at San Francisco, Herbert Boyer and his colleagues found an exceptional new cutting enzyme. Unlike available restriction enzymes, it did not break apart the twin-stranded DNA with a simple slice. Instead, it caused an overlapping, mortise-type break that automatically left a bit of '"sticky" single-stranded DNA at each end, to which new mate rial could be readily attached. Previously, Berg and others who worked in the field had to create such sticky tails synthetically.

The other breakthrough came when Stanley Cohen and his team, working in a Stanford lab two floors below Berg's, found a remarkable plasmid, which was promptly dubbed pSC (Cohen's initials) 101. It had the uncanny ability to take on a new gene and to slip into E. coli. Word of Cohen's miraculous little gene conveyor spread rapidly, and experimenters from all over the world besieged him for samples. Usually, scientists are more than willing to oblige such requests. But because pSC 101. in conjunction with Boyer's new enzymatic scalpel, made the creation of novel gene combinations so easy, Cohen was hesitant about distributing the material.

Up to this point, little news of these developments had passed outside the tightly knit community of molecular biologists. Any reports that did appear were in scientific journals, in a language virtually incomprehensible to laymen. But as molecular biologists scrambled to isolate other useful plasmids and enzymes for recombinant work, it became increasingly clear to Berg, Cohen and others that the emerging science needed some controls—at least until the risks, if any, were explored. Nowhere was this more apparent than at a private meeting of some 140 leading molecular biologists in New Hampshire during the summer of 1973. When Cohen described his latest work, the scientists were electrified. As the meeting's cochairman, Maxine Singer, a DNA specialist at the National Institutes of Health (NIH) recalls: "Here was someone talking about putting any two kinds of DNA together." Before the meeting broke up, the scientists voted to ask the National Academy of Sciences to examine the new technique for risks. They also agreed to voice their concern in a public letter to Science, the foremost U.S. science journal.

The academy bounced the problem right back to the molecular biologists by forming an investigatory committee and choosing Berg as its head. As far as Berg and Cohen were concerned, the action came none too soon. Some of the requests for plasmids had been sent by scientists planning precisely the same type of tumor virus implant that Berg had voluntarily forsworn two years earlier. "I was really shocked," Berg recalls. At a meeting of his special committee at M.I.T. in April 1974, the other members promptly agreed to a highly unusual move. They asked all researchers to honor a temporary ban on certain types of recombinant DNA experiments deemed potentially the most dangerous: those involving animal tumor viruses, and those increasing drug resistance or toxicity in bacteria. This time they published their appeal in both Science and the British journal Nature. Not since 1939—when a handful of physicists asked their colleagues to stop publishing atomic data to

prevent the information from falling into German hands—had scientists tried such self-policing.

The moratorium, however, was only a stopgap. In February 1975, at Berg's invitation, 134 scientists, including many leading molecular biologists, plus a handful of lawyers and 18 interested reporters, assembled at the picturesque Asilomar retreat among the pines and redwoods of California's Monterey Peninsula. The serenity of the setting was shattered by four lawyers, led by Daniel Singer, Maxine's husband, who lectured the scientists on their legal responsibilities. If an accident did occur during recombinant work, they pointed out, a technician might sue the lab chief. And if a dangerous bug escaped and infected people outside, the lawyers warned, the situation could turn into a legal—to say nothing of a medical—disaster.

The calculated shock treatment worked. Toiling through the night, Berg and his committee drafted recommendations that the conferees readily accepted before their departure the next day. They voted not only to continue the ban on the worrisome experiments, but also to press NIH to establish levels of safety that should be required for different experiments. In addition, they decided that precautions to keep research organisms from escaping from laboratories had to include "biological containment." This required the creation of mutated strains of E. coli so disabled that they could live nowhere but in a test tube. If they did escape their special broth and enter the atmosphere—or human gut—they would die almost instantly (see box).

Although the scientists left Asilomar thinking that they had allayed public fear about their work, they had only managed to fan it. Newspapers, which had until then paid scant attention to the story of recombinant DNA, erupted with scare headlines, alarming the nation with exaggerated doomsday prophecies. Two months later, Ted Kennedy held his first hearings on the new genetics. Some scientists, joined by politicians, began questioning whether the molecular biologists should do their own policing. Said one: "This is probably the first time in history that the incendiaries formed their own fire brigade."

The gibe seemed aimed particularly at another Stanford scientist, David Hogness, who was leading the way in a new form of genetic roulette, appropriately called "shotgun" experiments. Hogness was using enzymes to fragment the DNA of fruit flies and then was inserting the gene material piecemeal into bacteria. That way he could reproduce the inserted genes in vast quantities and discover their functions. The technique seems to be working. To date, he has managed to isolate and identify 36 of the thousands of the fruit fly's genes. But critics fear that because the nature of many of the genes is totally unknown beforehand, the host bacteria might be endowed with some dangerous new characteristic. What irritated the opponents of recombinant DNA even more was the fact that Hogness was in charge of a subcommittee appointed by the National Institutes of Health to draft the guidelines. That, said M.I.T.'s Jonathan King, leading member of the radical Science for the People organization, was like "having the chairman of General Motors write the specifications for safety belts."

Despite the sniping, the NIH group by last summer managed to turn Asilomar's directive into concrete rules. The guidelines continue the ban against the potentially most dangerous experiments. They also provide two principal lines of defense against lesser hypothetical risks. They establish four levels of physical containment; these range from standard laboratory precautions (dubbed "P-l") for experiments in the lowest-risk category—say, injecting harmless bacterial genes into E. coli—to ultrasecure laboratories ("P-4") for work with animal tumor viruses or primate cells. At present, two new P-4 facilities are almost ready. One is a gleaming white trailer parked behind a bar bed-wire fence on the grounds of the National Institutes of Health in Bethesda, Md. It has a totally sealed environment, airlocks, decontamination systems, showers for workers after experiments, and sealed cabinets accessible only through attached gloves. Some "worst case" experiments, involving animal tumor viruses, will begin in the trailer this summer. NIH is also converting some of the abandoned germ-warfare labs at Maryland's Fort Detrick into similar super-containment facilities. In addition to the labs, the guidelines require the use of the self-destructing, escape-proof microbes for certain higher-risk experiments.

Most researchers, eager to continue their work in cracking various genetic riddles, welcomed the guidelines. Numerous universities across the country had already begun work on new P-3 labs, which have a lower and less costly level of containment (air locks, limited access, safety cabinets with curtains of flowing air) than P-4 facilities. Not everyone, though, was pleased.

Egged on by Wald and his biologist wife, Ruth Hubbard, Cambridge's Mayor Alfred Velluci used the escalating DNA furor to badger his old foe, Harvard. He convened the city council in an effort to halt DNA research at the school. Said Velluci: "Something could crawl out of the

laboratory, such as a Frankenstein." At the council's request, Harvard and M.I.T. agreed to a moratorium on P-3 research while an eight-member citizens' review board studied the issue. In February, the council overrode Velluci and passed an ordinance permitting recombinant DNA work to be resumed in Cambridge—under standards only slightly more strict than the NIH guidelines.

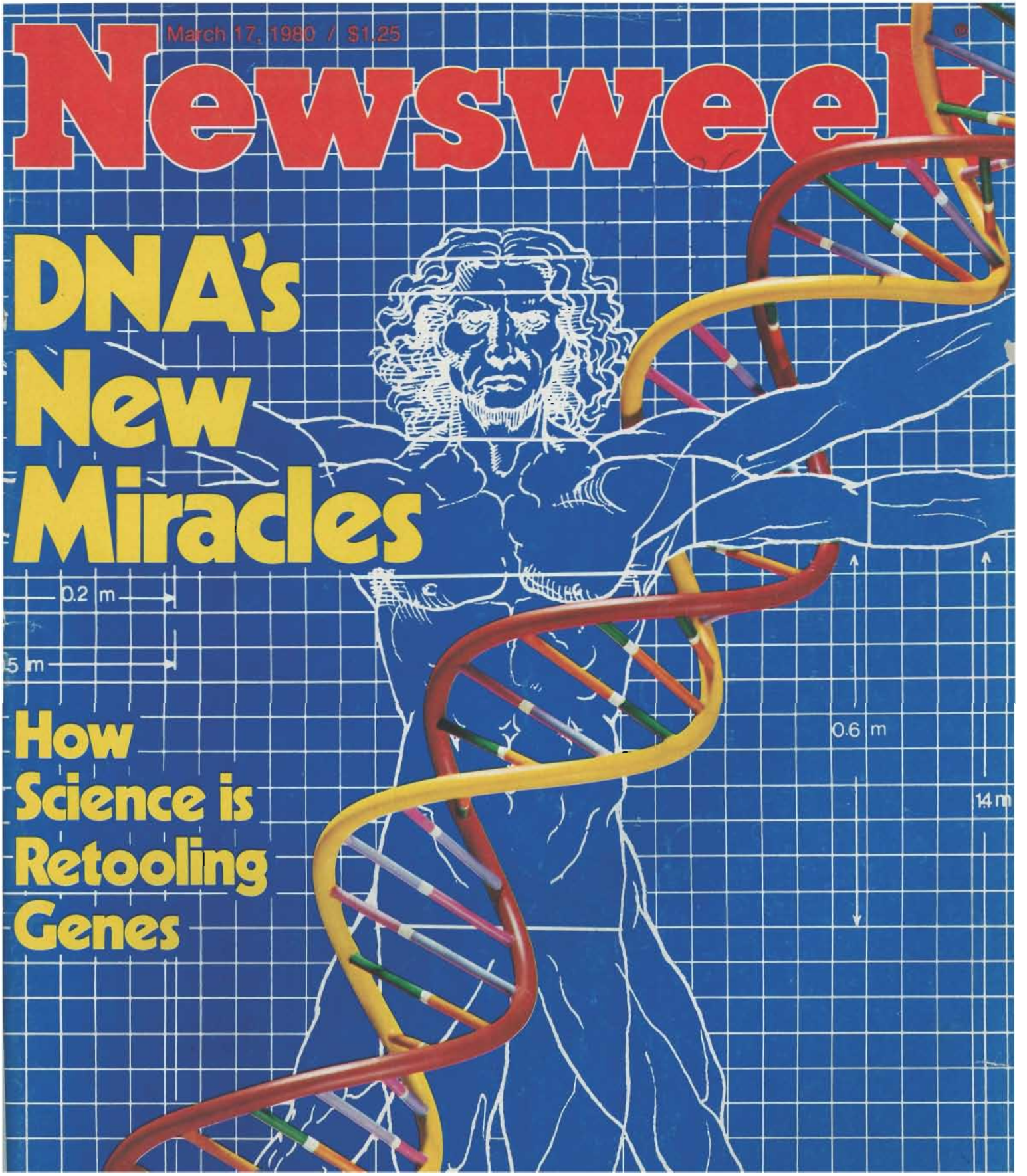
Most scientists breathed a sigh of relief; the specter of local governments proclaiming a hodgepodge of crippling restrictions on the freedom of inquiry had faded—at least temporarily. Local politicians now may go along with the impending federal legislation, which is expected to impose restraints on all researchers—including those at previously unregulated industry labs. Still, scientists remain concerned over any political controls on their work. At last week's Senate hearing, these fears were voiced by Norton Zinder, a molecular geneticist at Rockefeller University. Said he: "We are moving into a precedent-making area —the regulation of an area of scientific research—and I must plead that this be done with extreme care and without haste. The record of past attempts of authoritative bodies, either church or state, to control intellectual thought and work have led to some of the sorriest chapters in human history."

Zinder has reason for worry. But he and other scientists should find reassurance in the experience of Cambridge. There, citizens patiently ignored political demagoguery, perceived the false notes in the voices of doom, mastered the complex issues and then cast their votes for the continuation—with reasonable restraints—of free scientific inquiry. Congress should do no less.

* Named for its discoverer, the German pediatrician Theodor Escherich, who isolated it from feces in 1885, and for its habitat, the colon.

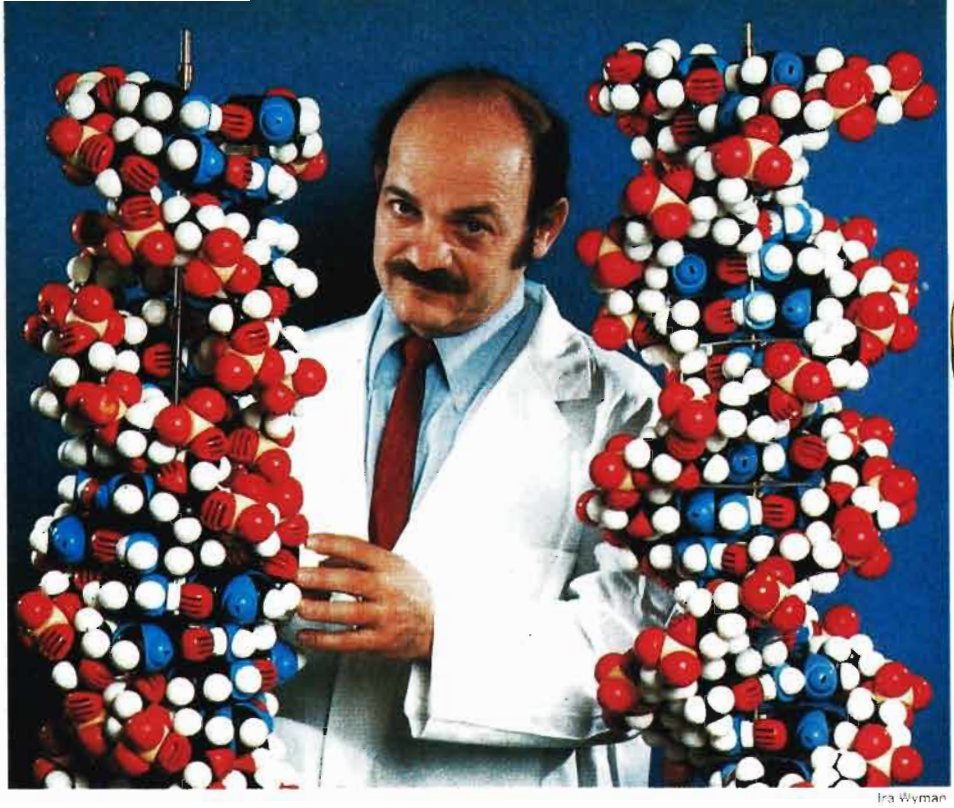
March 17, 1980 / $1.25

Newsweek



DNA's New Miracles

How Science is Retooling Genes



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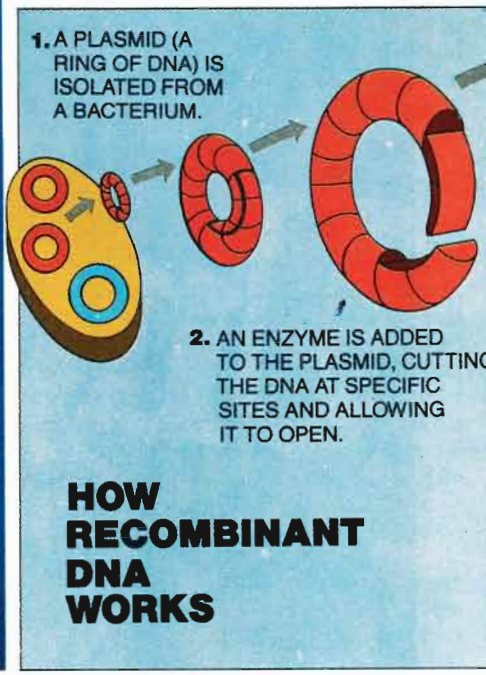


MIT's Alexander Rich with left- and right-handed DNA models (left), diagram of recombinant DNA: 'It's still like a new baby'

The Miracles of Spliced Genes

Scientists call it "the construction of biologically functional bacterial plasmids *in vitro*." To laymen, what it means is the creation of new forms of life.

The technology, popularly known as recombinant DNA, is only about seven years old, but it has already become almost routine. In laboratories all over the world, biologists are taking genes from one organism and planting them into another. So far, the gene splicers have succeeded in inducing bacteria to make human insulin and several other hormones. And that's only the beginning. Someday, bacteria will be turned into living factories: they will churn out vast quantities of vital medical substances, including serums and vaccines, to fight diseases ranging from hepatitis to cancer and the common cold. "Anything that is basically a protein will be makable in unlimited quantities in the next fifteen years," says David Baltimore of the Massachusetts Institute of Technology.

Revolution: The impact of genetic engineering on the world's economy could almost equal the recent revolution in microelectronics (page 70). Single-celled organisms might yield the proteins that now come from cattle, which would help alleviate world food shortages. Implanted genes could increase the yield of alcohol from corn. Genetically engineered bacteria are being designed to eat their way through oil spills and to extract scarce minerals from the soil. "There has been a golden age of chemistry and a golden age of physics," says Peter Farley, president of Cetus Corp., one of the young companies organized to capitalize on recombinant DNA's potential. "Now it's biology's turn."

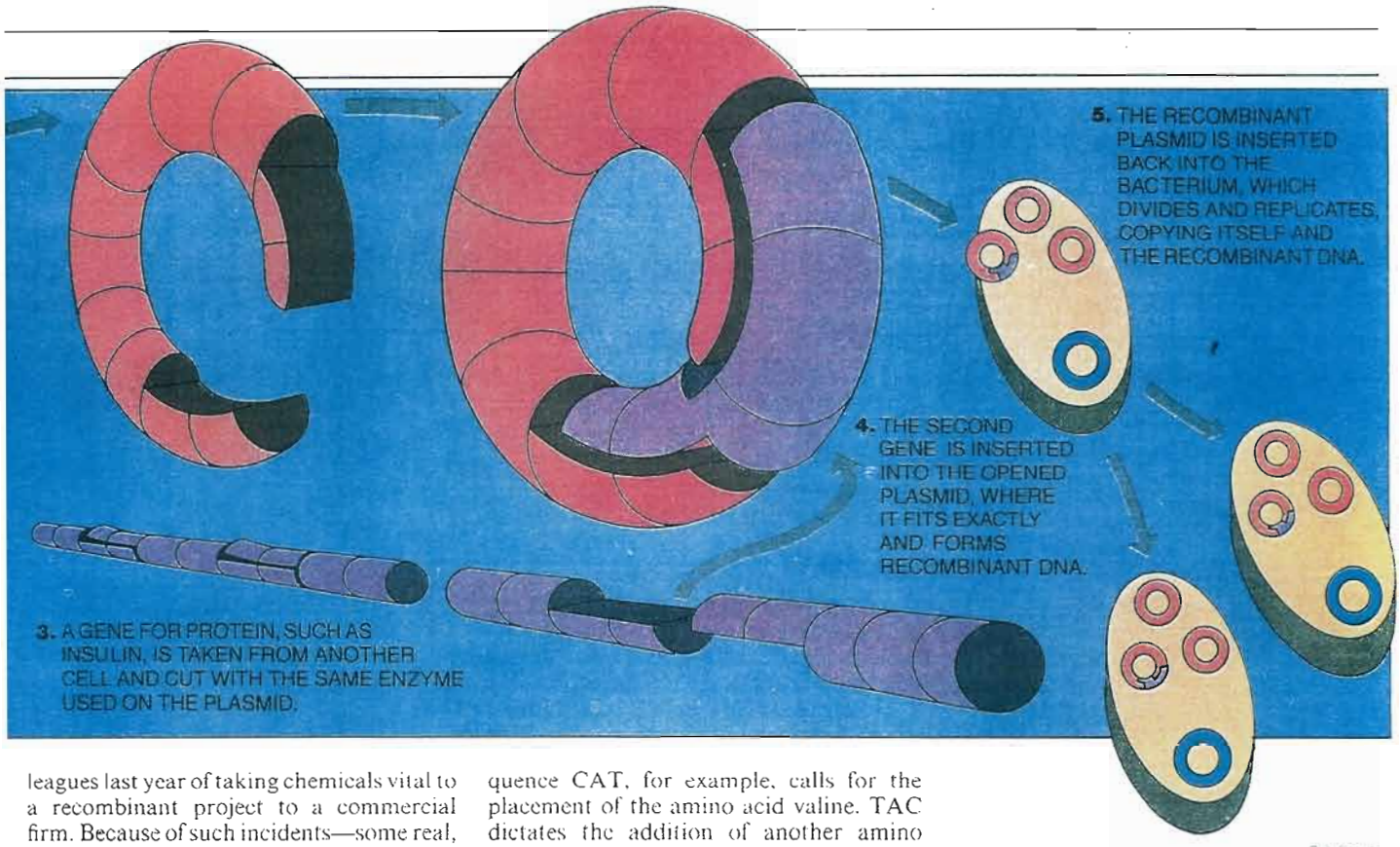
As pure science, recombinant DNA represents the most significant step in genetics since James Watson and Francis Crick discovered the double helix in 1953. It will enable scientists to identify each and every one of the 100,000 genes in the human cell. This knowledge might be used to replace defective genes with healthy ones and overcome such genetic diseases as hemophilia and sickle-cell anemia. Some technologists even suggest that the breakthrough will enable science to fashion "better" human beings. By harvesting genes at will, researchers also hope to find the answers to baffling biological questions. How do cells with the same genes differentiate into skin, muscle and nerve? What makes a normal cell turn malignant? "Recombinant DNA will not only let us understand diseases such as birth defects and cancer, but will also help us understand ourselves," says molecular biologist Phillip Sharp of MIT.

By turning bacteria into living factories, scientists can cure disease and create new forms of life.

All scientific revolutions—from Galileo's observations of the planets to the splitting of the atom—evoke the cry of heresy. Recombinant DNA is no exception. From the dawn of the recombinant era, many laymen have wondered whether scientists have gone too far by mixing genes that nature ordained to live apart. Among the first to challenge the new technology were scientists themselves. They feared that bacteria containing noxious genes could burst out of the lab and spread the earth with a man-made plague of untold horror.

While they pondered such scenarios, scientists imposed upon themselves a moratorium on most recombinant studies. Expanded research programs began in 1976 only after the National Institutes of Health issued guidelines imposing strict safeguards in the laboratory. Fortunately, no real-life Andromeda Strain has emerged, and most scientists agree that their worst anxieties were unfounded. "There was an overreaction from the beginning," says Howard Goodman of the University of California, San Francisco. "The concern exceeded the hazards, which were all theoretical." In January, the NIH relaxed its guidelines to facilitate research.

Locked Drawers: Now the scientists have other concerns. They worry that the pristine realm of pure science may become contaminated by the tantalizing economic promise of the new DNA research. They fear that exclusive patents may become as coveted as Nobel prizes. A California researcher was accused by university col-



Bob Conrad

leagues last year of taking chemicals vital to a recombinant project to a commercial firm. Because of such incidents—some real, some rumored—scientists worry that the free exchange of information traditional to science will give way to closed notebooks and locked drawers. "With millions of dollars coming into labs, suddenly scientists aren't scientists anymore," complains one prominent biologist.

Faustian bargains between the scientist and the entrepreneur have been struck before. But in this deal, the item for sale is nothing less than the fundamental chemical blueprint of life—the gene. The form and function of every living plant and animal are determined by molecules of deoxyribonucleic acid (DNA), formed into the famous double helix described by Watson and Crick. Whenever cells divide, the DNA duplicates itself, passing on its genetic inheritance to the next generation of cells. DNA also guides the cell in the manufacture of proteins essential for life, including hormones like insulin, antibodies to fight disease, hemoglobin to carry oxygen and enzymes that carry out chemical reactions.

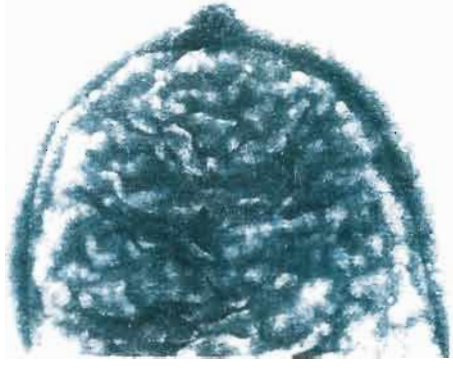
DNA resembles a spiral ladder. The sides are formed of sugars and phosphates. The rungs are formed of pairs of the four chemical bases, adenine (A), guanine (G), cytosine (C) and thymine (T). To form a rung, A always joins with T and C with G. The sequence of bases running along a strand of DNA forms a code that tells the cell what protein to make. Proteins consist of amino acids hooked together like the cars of a train. A specific three-letter sequence of DNA bases orders up a particular amino acid that, after a series of intermediate steps, takes its place on the protein the cell is assembling. The sequence CAT, for example, calls for the placement of the amino acid valine. TAC dictates the addition of another amino acid, methionine. Three-letter codes of bases exist for each of the twenty amino acids that living cells use to make proteins.

Fragment: In recombinant technology, DNA is spliced from one type of cell to another (diagram). Researchers take bacteria, viruses, animal cells or plant cells, break them apart and extract the DNA. They use enzymes to cut the DNA chemically at specific points along its length. They can then pull out a DNA fragment with the particular array of bases they want to study. This gene is linked to the DNA of one type of *Escherichia coli*, a bacterium that normally flourishes harmlessly in the intestinal tract.

E. coli contain rings of DNA called plasmids. The researchers remove a plasmid, open the ring with a cutting enzyme and insert the new fragment of DNA. They close the ring with an annealing enzyme and put the plasmid back into the bacterium. Each time the bacterial cell divides, it will pass the new gene along to the next generation and, in a matter of hours, the researchers have thousands of bacteria containing the hybrid DNA. The new colony, a genetic clone, will produce the specific protein determined by the inserted gene. In the pioneering experiment described in 1973, Stanley Cohen and Annie Chang of Stanford and Herbert Boyer and Robert Helling of UCSF inserted a gene into E. coli that makes the salmonella germ resistant to the antibiotic streptomycin. The E. coli then became resistant themselves.

Virus enters E. coli: A staggering potential

Maria Schnoss



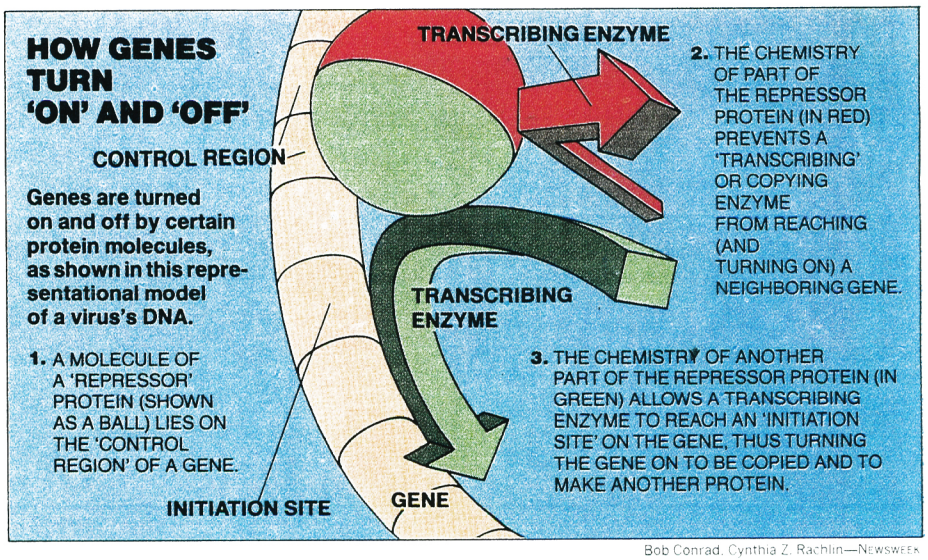
Potent Poisons: The possibility of accidentally spreading genes that make bacteria resistant to antibiotics was one of the concerns that triggered the debate over the safety of recombinant research. And under the new NIH guidelines, research on resistance genes remains largely restricted. Also under tight controls are experiments involving the DNA of disease-causing bacteria or viruses, and genes for the synthesis of potent poisons. Such research must be carried out in top-security "P4" labs, in which workers must change clothes and shower before leaving, and handle their bacteria under sealed hoods to ensure containment. No such research is going on now. Under the revised guidelines, nearly 80 per cent of recombinant research can be done with the sterile procedures that normally prevail in any hospital lab. These include decontaminating items before disposal and a ban on food at the workbench.

Scientists revised their thinking about the hazards of recombinant work after achieving a better understanding of the bugs

they were working with. The K-12 strain of E. coli used in most experiments has lost its capacity to survive for long outside the laboratory and spread dangerous genes. Human genes, moreover, differ so much from the genes of their bacterial hosts that they function only under conditions controlled by the researcher. "People worried about inadvertently creating something dangerous," says Walter Gilbert of Harvard. "But scientists now know they could not even deliberately create something dangerous."

Still, some researchers believe that the safety issue is being swept under the rug. "For the first time, biologists have a chance to get rich so there is very strong peer pressure to go along," says Richard Goldstein of Harvard. Allegedly, some researchers have lost their jobs for voicing their concerns too publicly. One safety question that remains is the potential hazard to workers in plants where protein-producing E. coli are grown in vat-size quantities. "At such levels, you might have a direct toxic effect," says Baltimore.

Chains: Among the first recombinant products to be manufactured in enormous quantities will be human insulin. Insulin is a protein consisting of two chains of amino acids. In 1978, researchers at City of Hope National Medical Center, Duarte, Calif., took the first step by making chemically some fragments of the gene for insulin. Scientists at Genentech, Inc., of South San Francisco, another of the new firms set up to exploit recombinant research, assembled the fragments and inserted the synthetic genes for each of the two insulin chains into E. coli plasmids. Alongside, they implanted a regulatory mechanism called the lac operon, which serves as an "on-off" switch to activate the insulin genes. Once the plasmids were put back into E. coli, the insulin genes responded and the bacteria began turning out insulin chains. The insulin now used by diabetics comes from cattle or pigs and contains impurities that can cause allergic reactions. Once full-scale production begins, human insulin made by bacteria promises to provide a cheaper and safer alternative.



Bob Conrad, Cynthia Z. Rachlin—NEWSWEEK

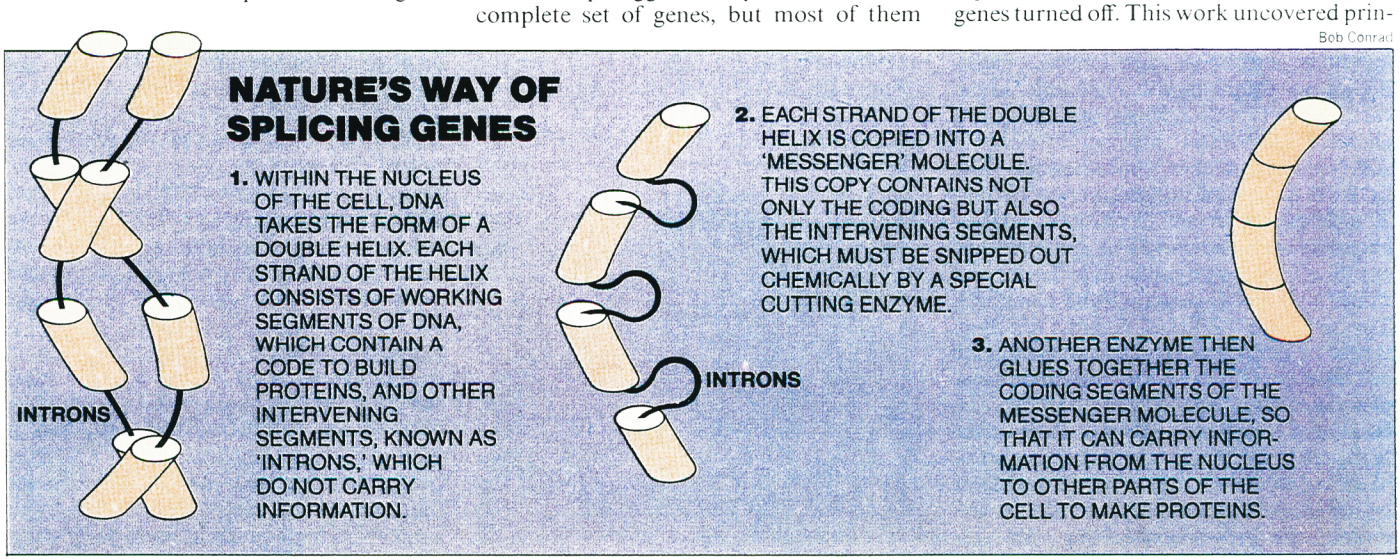
Recombinant techniques have started to produce other important human proteins. Two months ago, researchers at the University of Zurich and Biogen, S.A., of Geneva reported inducing E. coli to make interferon, a natural virus fighter. Interferon may help prevent flu, hepatitis and other viral infections and is now being tested against cancer. The quantity of interferon that could be made available through bacteria is significant; interferon research has been hampered by the fact that the substance can now only be extracted in small amounts from such sources as white blood cells. Costs of a single course of treatment run as high as $50,000. Pituitary growth hormone necessary for the treatment of certain types of dwarfism is also scarce and costly, but researchers have begun producing it through recombinant methods. Some day, they may use the same techniques to make Factor VIII, the blood protein that victims of hemophilia need to prevent bleeding.

Scientists are also using recombinant methods to unravel basic mysteries about genes. One is how genes are regulated. All cells, except eggs and sperm, contain a complete set of genes, but most of them don't do anything until they are somehow "turned on." At least one type of gene regulation has now been explained by Mark Ptashne and his colleagues at Harvard, using a standard lab virus called "lambda."

Lambda readily invades E. coli, where it adopts either of two radically different lifestyles. In one, lambda DNA takes over the machinery of the bacterium and forces it to make more lambda viruses. The E. coli bursts, releasing the new lambdas, then dies. In its other mode, the lambda DNA remains harmlessly quiescent as the bacteria reproduce generation after generation.

Message: How the lambda genes behave, the researchers showed, depends in large part on "repressor" molecules (top diagram). Normally, DNA sends messages for protein syntheses with the aid of a "transcribing" enzyme. But if a repressor molecule lies on a gene, the enzyme can't pick up DNA's instructions, and the gene remains inactive. Ptashne discovered that the same repressor molecule can also turn genes on. Depending on how the repressor is positioned within the "control region" of the DNA, it can either attract the transcribing enzyme, thus turning on the genes for viral reproduction, or deflect it, thus keeping the genes turned off. This work uncovered prin-

Bob Conrad



ciples of gene regulation that may let scientists insert genes of higher organisms into bacteria, and also switch them on.

Scientists now can also determine both the exact sequence of bases in a piece of DNA and the precise locations of genes within chromosomes. There are hundreds of thousands of possible combinations of sequences within genes; because researchers have the ability to produce genes in enormous quantities, they can finally study enough genes to map the bases.

Similarly, biologists can tell how the total of more than 100,000 human genes fit into the 46 chromosomes. To accomplish this, scientists clone a gene and mix it with chromosomes whose DNA spirals have been split down the middle. The DNA bases of the "test" gene automatically find their natural partners in the appropriate split chromosome, A to T and C to G. Thus, researchers will learn both which chromosome the gene naturally fits into and where on that chromosome the gene normally rests. This "gene mapping" might make possible the cure of inherited diseases like sickle-cell anemia and hemophilia, which result from defects in a single gene. If scientists locate the proper chromosome, they could repair the defective gene or insert a properly functioning new gene into the cell.

Clue: The new DNA research could even help cope with the riddle of cancer. J. Michael Bishop and his colleagues at UCSF have cloned genes of viruses that cause tumors in chickens and isolated those that turn cells malignant. One of the tumor-causing genes instructs the cell to make an enzyme that transfers phosphate molecules to proteins. "Our hypothesis is that this transfer of molecules causes cancerous growth," Bishop says. So far the hypothesis has not led to the development of a therapeutic strategy.

Scientists have also found that the tumor genes that invade the cell are virtually the same as genes that already inhabit it. Bishop suggests this may indicate how cells grow and differentiate: if the invading gene causes cancer by making cells proliferate uncontrollably, its harmless counterpart might normally control growth and differentiation. Thus, the study of cancer, a medical problem, may lead to a better understanding of the science of cell differentiation.

Now that gene splicing is so relatively easy, scientists find they can re-examine old genetic dogmas. Until recently, for instance, microbiologists assumed that the genes of bacteria were just like those in higher organisms. But scientists led by Sharp at MIT and Philip Leder of NIH independently discovered a startling difference. All the bases in bacterial DNA are read by enzymes three by three and translated directly into amino acids. But in viral and mammalian DNA, they found, the elements of DNA that code for amino acids that are used to make protein are separated by sequences that don't seem to get translated into any protein at all.

The discovery of these intervening sequences, or "introns," alters the conventional picture of how human genes work (bottom diagram, page 64). DNA bases are copied into a molecule of ribonucleic acid (RNA). But before the appropriate information is carried to the region of the cell where amino acids are assembled to make proteins, enzymes must first process the RNA. They must cut the introns out of the RNA and splice the remaining coding segments together. "This discovery is the biggest thing yet to come out of cloning DNA," wrote John Rogers of UCLA.

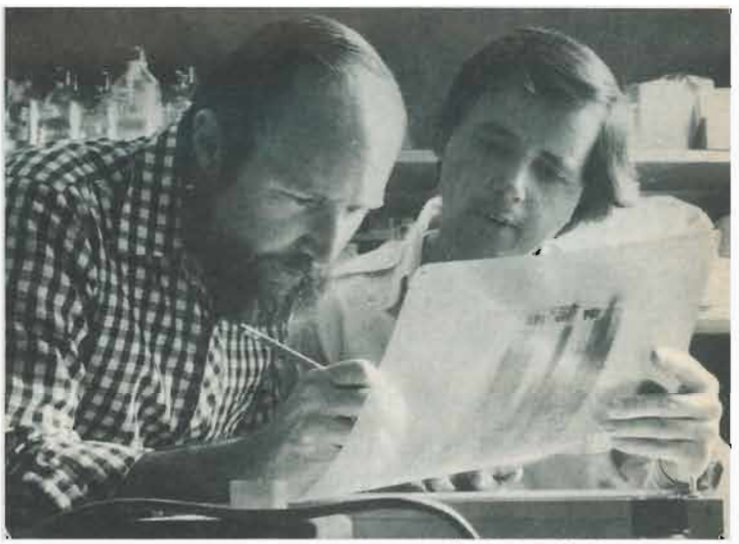
If genes are divided into pieces, nature must have a reason. Harvard's Gilbert thinks that piecemeal genes may have helped man evolve. Words separated by spaces can be moved around to form meaningful new sentences with less confusion than if words were strung out in an uninterrupted line. Similarly, Gilbert suggests, the messages of DNA can be shuffled more easily into new combinations that make new genes if they are separated by introns. These fresh combinations of DNA might change the character of a cell and give the organism a selective advantage.

Another surprise came from the lab of Alexander Rich at MIT. Rich and his colleagues made crystals of DNA and found that they didn't look anything like Watson and Crick's graceful spiral. The pioneers of the double helix propounded their model from studying vague X-ray scattering patterns. Rich's crystals yielded sharp pictures that showed individual atoms in DNA for the first time. The crystallized DNA formed a zigzag shape that twisted left instead of a smooth curve twisting right. It is still uncertain why or when it takes that configuration at times.

Ideal Human: Rich thinks that the "Z-DNA," as he calls it, may possibly be involved in cancer. Cancer-causing chemicals could more easily reach the exposed bases. The smooth spiral of DNA can change into the Z form at special sequences of bases, so a small number of such transformations could attract carcinogens and trigger the start of cancer. Rich also believes that genes may change from smooth to Z-DNA to turn themselves off in certain circumstances. "It's still like a new baby," he says. "We don't really know yet what it will grow up to be."

At the extreme of the new genetic research is the question of whether gene splicing could be used to create the ideal human being. Reputable scientists regard that prospect as fantasy. It is one thing to understand the basic blueprint written in the genes; it is quite another to translate the blueprint into an individual. In the formation of any organism, many gene products interact, and the circuitry is staggeringly complex. Besides, the final product of the genes—be it an Einstein or an idiot—is also shaped by environment. "Because of these complexities," says Jonathan King of MIT,

Paul Fusco



Rick Friedman—Black Star

Harvard's Ptashne, UCSF's Goodman with aide: Promises of vast quantities of serums and vaccines

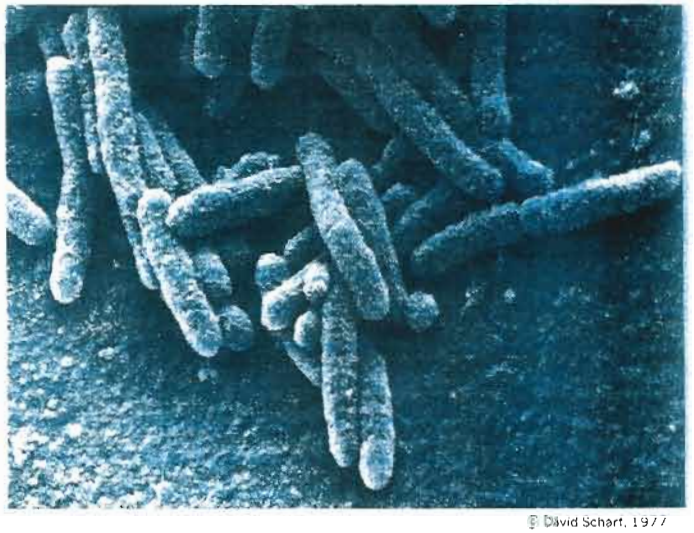
"attempts to modify human beings through genetic manipulation is a policy of false eugenics. It will do more damage than it will anything else."

There is much that scientists don't know about DNA, and one tangential element of their rapidly advancing research troubles many of them. They fear that the commercial potential of their findings may hamper the flow of information that helps make research succeed. Traditionally, many important scientific ideas have arisen from free and informal contacts among researchers. The Cohen-Boyer collaboration that led to the first recombinant-DNA breakthrough began over sandwiches during a lunch break at a biology symposium. "Scientists go off in the evenings and kick ideas around," says MIT's Sharp. "People who are being secretive won't participate and they'll suffer for it."

Ethics: The tantalizing lure of profits from recombinant DNA has already intruded on the sanctity of the academic lab. Scientists were shocked last year when Peter Seeburg, an assistant of John Baxter's at UCSF, left for Genentech and took with him some material to be used in producing growth hormone. Some researchers questioned the ethics of Seeburg's action, but he maintains that he had started the project and was entitled to the material and a share in any patent rights that might come from it.

The role of commercialism in DNA research may be decided soon by the U.S. Supreme Court. Last year, the Court agreed to decide whether new forms of life can be patented. If they can, a scientist and a company would be entitled to sell the resulting product exclusively for seventeen years. Should the Court rule against patents, some scientists fear that their colleagues will resort even further to secrecy. "I hope we will be able to go the patent route and publish freely," says a university biologist who is also associated with a

Bridgid Hanggi—Hoffman-La Roche



© David Schart, 1977

Turning germs into assembly lines: Hoffman-La Roche researcher studies culture dish; colony of E. coli awaiting new genes

How Molecular Biology Is Spawning an Industry

How big is the market for a process that makes plants manufacture their own fertilizer? For microorganisms that mine silver, gold and copper ore? For chemicals that could be used for everything from floor wax to salad dressing? The answers are impossible to calculate with any precision, but by every estimate, the possibilities for the infant industry spawned by molecular biology are staggering. "This work is broader in importance than anything since the discovery of atomic particles," says Irving S. Johnson, vice president for research at Eli Lilly and Co. "The commercial applications for recombinant DNA are limited only to the imaginations of the people using it."

The visionaries of the business world are already hard at work. Over the past few years, a handful of small companies have sprung up for the purpose of harnessing the commercial potential of gene splicing. Big corporations are funding their work and starting in-house projects of their own. So far, not a single new product has come to market as a result of the research. And some formidable problems stand in the way of full-scale development—from questions of public safety to disputes over patents and marketing ethics. But from Wall Street to the boardrooms of the West, investor interest in DNA is steadily quickening. "We don't know whether its great impact is going to be in medicine or industrial processes or in the agricultural area," says Gordon C. McKeague, manager of corporate development for Standard Oil of Indiana. "But three years ago we saw the need and the possibilities, and felt the best thing was to get in on it then."

What businessmen find so intriguing about recombinant-DNA technology is the promise that it may someday do many jobs more efficiently—and at less cost—than the techniques they now use. "You can take the DNA from a conventional antibiotic-producing strain of microorganism, which normally grows very slowly," explains molecular biologist J. Leslie Glick, "and stick it into a fast-growing microorganism to produce a good deal of that antibiotic in a much shorter time." The same process could be used to enhance the natural ability of certain fungi and bacteria to produce small amounts of petrochemical derivates, from plastics to organic pigments, thus eliminating the need for conventional chemical synthesis. "The cost is lower because the amount of energy consumed in the process is much lower," says Glick. "Pollution is no problem because only natural products are excreted."

Stock: To explore and exploit the new market, Glick and other like-minded scientists have formed companies of their own. Glick heads Genex Corp., in Rockville, Md., which has grown from a full-time staff of three last May to 30 today and, claims Glick, is worth $75 million. Genentech, Inc., a South San Francisco company, relies heavily for funds on venture-capital firms—one of which recently paid $10 million for 15 per cent of Genentech's stock. Cetus Corp., of Berkeley, Calif., says it is worth $300 million, with 65 per cent of its stock held by Standard Oil of California, Standard Oil of Indiana and National Distillers and Chemical Corp. The latest comer is Switzerland's Biogen, S.A.,

private firm. But others find no benefit in this manner of exclusivity. "There is enough potential in the field that it doesn't need patent protection to stimulate activity," says MIT's Baltimore.

Research Standards: DNA research has attracted so much attention from the public, and from investors, that it has generated still another anxiety—what researchers call "science by press conference." Instead of presenting their work in traditional fashion to a scientific journal, where it can be "refereed" or evaluated by authorities before it is published, some scientists now rush their findings directly to the media. The City of Hope-Genentech team, for example, announced the production of insulin at a press conference before it had done the additional—and necessary—work to show that the hormone actually functioned. (Only about nine months later did Eli Lilly and Co. show that the bacteria-created insulin really worked.) Such premature announcement of results could reduce scientists' credibility and lower the standards of research. But many scientists remain confident that pure science and industry can work together. "Biologists have been unworldly," says Rich. "Chemists have been living in the commercial world for 50 years and still do exciting research."

To good scientists, research is exciting for its own sake. That's why they split atomic nuclei, listen to electronic impulses from the galaxies and fiddle with strands of DNA in the first place. Whether their discoveries simply add arcane footnotes to the scientific literature or launch whole new fields of industrial endeavor remains of secondary concern. The burgeoning gene research promises to do a great deal of both. It will lift the curtain further on the ultimate secrets of life on Earth. And it will also enrich the lives of the planet's restless inhabitants.

MATT CLARK with SHARON BEGLEY
in Cambridge, Mass., and San Francisco
and MARY HAGER in Washington

which boasts heavy investments by Schering-Plough Corp., a big U.S. pharmaceutical firm, and International Nickel Co., Inc.

According to Nelson M. Schneider, drug-industry analyst for E.F. Hutton, it was Biogen's January announcement that it had successfully produced human interferon through gene splicing "that showed recombinant-DNA research had reached beyond the Model T stage," and spurred investor interest in the field. All the projects at the new gene companies are at least one to five years from commercial exploitation. But many seem to have breath-taking potential. Genex, for example, is experimenting with DNA technology to correct sickle-cell anemia, a genetic defect that affects about 50,000 black Americans. Cetus is working on one strain of microbes that could substantially boost the efficiency of distillers' alcohol production. Genentech has arranged a joint venture with the U.S. Department of Agriculture to produce a vaccine that combats foot-and-mouth disease, a global plague that forces the slaughter of 100 million animals a year.

Meanwhile, at least a dozen major drug and chemical companies have launched their own DNA projects. Merck and Co. of Rahway, N.J., for instance, is equipping a $23 million addition to its laboratory complex for work on recombinant DNA—especially its application to antibiotics. Upjohn Co. of Kalamazoo, Mich., and Eli Lilly and Co. of Indianapolis both have scientists at work on manufacturing human insulin. Most experts believe, however, that the biggest markets will develop not in medicine, but in the nation's $150 billion-a-year chemical industry and its $130 billion-a-year agricultural sector. Glick of Genex estimates that recombinant-DNA techniques could be applied to 25 per cent of all chemical production. Du Pont scientists have turned to plant breeding. Today, says Ralph F. W. Hardy, director of life sciences in the company's central research department, technicians trying to improve plant species by increasing their food yield or their capacity for survival must rely on time-consuming methods of crossbreeding used by Gregor Mendel in the mid-nineteenth century. But by splicing one plant's desirable genes into another species, researchers might short-cut the process, with incalculable benefits to the world's food supply.

Before the marvels of gene splicing hit the market full force, serious issues will have to be resolved. Patent law, for one, has yet to deal with the emerging technology. The U.S. Supreme Court will hear arguments next week in a case brought by General Electric Co., which wants to patent a microorganism it developed through genetic engineering: GE was turned down by a Patent and Trademark Office that opposes licensing life forms. Then there is the problem of public concern about safety. Several firms, such as Hoffman-La Roche, Inc., of Nutley, N.J., which is working on interferon, have supported community study committees to soothe fears about the research.

Ballyhoo: Finally, there is growing concern within the recombinant-DNA industry over marketing ethics. Even though most of the payoffs are a long way off, each announcement of a breakthrough is accompanied by great public ballyhoo that is often not backed up by scientific papers. The aim, dissidents charge, is to hype company stock and stampede investors into putting more money into research projects that may be considerably further from the market than the hoopla suggests. "They are telling you where they will be ten months from now," says one industry insider angrily, "as if they were there today."

Some skeptics doubt that recombinant DNA will ever fulfill the commercial promise held out by its most avid promoters. At General Electric, for instance, scientists insist that conventional genetic engineering can do many of the same jobs without the long lead times and costly investments. A single pilot plant for demonstrating the feasibility of the new technology can cost $50 million and take three years to build. Many big companies—among them, Bristol-Myers Co., American Home Products Corp. and Warner Lambert Co.—are holding off, hoping to cash in later if their competitors prove successful.

Safe look: Genex scientist in protective gear

Susan T. McElhinney—Newsweek

The delay could turn out to be costly. Already, the new technology is outpacing all forecasts. Just last September, for example, experts at an investor-sponsored recombinant-DNA conference predicted that the bacterial production of human interferon was at least three years away; Biogen's announcement followed just four months later. "Eventually, those who have held out will have to scramble to get into the game," says analyst Schneider. "They're going to have to buy into it, and the price will be high." Still, the market for DNA's wonders will almost certainly be so huge that even a late investment may well be worthwhile.

MERRILL SHEILS with SUSAN DENTZER
in New York, PAMELA ABRAMSON
in San Francisco and bureau reports

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

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Immune systems of 'bubble babies' restored by gene therapy, UCLA researchers find

By Kim Irwin | September 11, 2012

UCLA stem cell researchers have found that a gene therapy regimen can safely restore immune systems to children with so-called "bubble boy" disease, a life-threatening condition that if left untreated can be fatal within one to two years.

In the 11-year study, researchers were able to test two therapy regimens for 10 children with ADA-deficient severe combined immunodeficiency (SCID), which has come to be known as "bubble boy" disease because some of its victims have been forced to live in sterile environments.

During that time, the researchers refined their approach to include a light dose of chemotherapy to help remove many of the blood stem cells in the bone marrow that were not creating the enzyme adenosine deaminase (ADA), which is critical for the production and survival of healthy white blood cells, said study senior Dr. Donald Kohn, a member of the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA.

The refined gene therapy and chemotherapy regimen proved superior to the other method tested in the study, restoring immune function to three of the six children who received it, said Kohn, who is also a professor of pediatrics and of microbiology, immunology and molecular genetics in UCLA Life Sciences Division. An even further-refined regimen using a different type of virus delivery system will be studied in the next phase of the study, which already has enrolled eight of the 10 patients needed.

The study appears Sept. 11 in the advance online issue of the peer-reviewed journal Blood.

"We were very happy that in the human trials we were able to see a benefit in the patients after we modified the protocol," Kohn said. "Doctors treating ADA-deficient SCID have had too few options for too long, and we hope this will provide them with an efficient and effective treatment for this devastating disease."

Children born with SCID, an inherited immunodeficiency, are generally diagnosed at about 6 months old. They are extremely vulnerable to infectious diseases and don't grow well. Chronic diarrhea, ear infections, recurrent pneumonia and profuse oral candidiasis commonly occur in these children. SCID occurs in about one of every 100,000 births.

Currently, the only treatment for ADA-deficient SCID calls for injecting patients twice a week with the necessary enzyme, Kohn said, a lifelong process that is very expensive and often doesn't return the immune system to optimal levels. These patients also can undergo bone marrow transplants from matched siblings, but matches can be very rare.

About 15 percent of all SCID patients are ADA-deficient. Kohn and his team used a virus delivery system that he had developed in his lab in the 1990s to restore the gene that produces the missing enzyme necessary for a healthy immune system. To date, about 40 children with SCID have received gene therapy in clinical trials around the world, Kohn said.

Two slightly different viral vectors were tested in the study, each modified to deliver healthy ADA genes into the bone marrow cells of the patients so the needed enzyme could be produced and make up for the cells that don't have the gene. Four of the 10 patients in the study remained on their enzyme replacement therapy during the gene therapy study. There were no side effects, but their immune systems were not sufficiently restored, Kohn said.

In the next six patients, the enzyme therapy was stopped, and a small dose of chemotherapy was given before starting the gene therapy to deplete the ADA-deficient stem cells in their bone marrow. Of those patients, half had their immune systems restored. The human findings confirmed another study, also published recently in Blood by Kohn and UCLA colleague Dr. Denise Carbonaro-Sarracino, which tested the techniques in parallel, using a mouse model of ADA-deficient SCID.

One of Kohn's clinical trial patients enrolled in the first study was a baby boy diagnosed with ADA-deficient SCID at age 10 months. The boy had multiple infections, pneumonia and persistent diarrhea and was not able to gain weight. He received the enzyme replacement treatment for three to four months but did not improve and joined the gene therapy study in 2008. Today, that boy, who lives with his family in Arizona, is a thriving 5-year-old.

"You would never know he had been so sick," Kohn said. "It's a very promising response."

The boy's younger sister, also born with ADA-deficient SCID, was diagnosed at 4 months of age and is enrolled in the second phase of the study. She's also doing well, Kohn said. In fact, it appears that children who are diagnosed and treated younger seem to do better.

The study was funded by the Doris Duke Charitable Foundation, the National Heart, Lung and Blood Institute at the National Institutes of Health and the U.S. Food and Drug Administration's Orphan Product Development award (1P50 HL54850 and RO1 FD003005).

The Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research: UCLA's stem cell center was launched in 2005 with a UCLA commitment of $20 million over five years. A $20 million gift from the Eli and Edythe Broad Foundation in 2007 resulted in the renaming of the center. With more than 200 members, the Broad Stem Cell Research Center is committed to a multidisciplinary, integrated collaboration among scientific, academic and medical disciplines for the purpose of understanding adult and human embryonic stem cells. The center supports innovation, excellence and the highest ethical standards focused on stem cell research with the intent of facilitating basic scientific inquiry directed toward future clinical applications to treat disease. The center is a collaboration of the David Geffen School of Medicine at UCLA, UCLA's Jonsson Cancer Center, the UCLA Henry Samueli School of Engineering and Applied Science and the UCLA College of Letters and Science.

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Cancer Health Center

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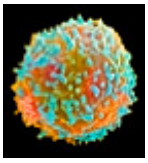
Gene Therapy Cures Adult Leukemia

CLL Tumors 'Blown Away' in 2 of 3 Patients Given Experimental Treatment

By Daniel J. DeNoon Reviewed by Laura J. Martin, MD
WebMD Health News



Aug. 10, 2011 -- Two of three patients dying of chronic lymphocytic leukemia (CLL) appear cured and a third is in partial remission after infusions of genetically engineered T cells.

The treatment success came in a pilot study that was only meant to find out whether the treatment was safe, and to determine the right dose to use in later studies. But the therapy worked vastly better than University of Pennsylvania researchers David L. Porter, MD, Carl H. June, MD, and colleagues had dared to hope.

"Our results were absolutely dramatic. It is tremendously exciting," Porter tells WebMD. "These kinds of outcomes don't come around very often. We are really hopeful that we can now translate this into treatment for much larger numbers of patients and apply this technique to other diseases and to many more patients."

Excitement is spreading as oncologists learn about the findings. "I think it is a big deal," says Jacque Galipeau, MD, professor of hematology and medical oncology at Emory University Winship Cancer Center. Galipeau was not involved in the Porter study.

"Here's this guy, the handwriting is on the wall, any hematologist will tell you he is a goner -- this guy was essentially cured," Galipeau tells WebMD. "These genetically engineered cells did what everyone in the field has tried to do for 20 years. The man probably had kilograms of disease in his body, and the cells mopped it up completely."

The treatment uses a form of white blood cells called T cells harvested from each patient. A manmade virus-like vector is used to transfer special molecules to the T cells. One of the molecules, CD19, makes the T cells attack B lymphocytes -- the cells that become cancerous in CLL.

All this has been done before. These genetically engineered cells are called chimeric antigen receptor (CAR) T cells. They kill cancer in the test tube. But in humans, they die away before they do much damage to tumors.

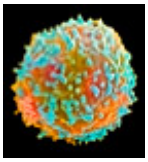
What's new about the current treatment is the addition of a special signaling molecule called 4-1BB. This signal does several things: it gives CAR T cells more potent anti-tumor activity, and it somehow allows

the cells to persist and multiply in patients' bodies. Moreover, the signal does not call down the deadly all-out immune attack -- the feared "cytokine storm" -- that can do more harm than good.

This may be why relatively small infusions of the CAR T cells had such a profound effect. Each of the cells killed thousands of cancer cells and destroyed more than 2 pounds of tumor in each patient.

"Within three weeks, the tumors had been blown away, in a way that was much more violent than we ever expected," June says in a news release. 'It worked much better than we thought it would."

CLL Patient Describes CAR T-Cell Treatment



The treatment was not a walk in the park for patients. One of the three patients became so ill from the treatment that steroids were needed to relieve his symptoms. The steroid rescue may be why this patient had only a partial remission.

"Those engineered T cells don't hug the cells to death. They release an array of substances, nasty things that have evolved to clear virus- infected cells from your body," Galipeau says. "But now they are using this to melt down a couple of pounds worth of tumor burden, you will get some side effects."

One of the patients, whose case is reported in the *New England Journal of Medicine*, described his experience in a University of Pennsylvania news release. The patient chose not to identify himself by name, although he discloses that he has a scientific background. He was diagnosed with CLL at age 50; 13 years later his treatment was failing. Facing a bone-marrow transplant, he jumped at the chance to enter Porter's clinical trial of CAR T cells.

"It took less than two minutes to infuse the cells and I felt fine afterward. However, that fine feeling changed dramatically less than two weeks later when I woke up one morning with chills and a fever," he says. "I was sure the war was on. I was sure the CLL cells were dying."

A week later the patient was still in the hospital when Porter brought him the news that the CLL cells had disappeared from his blood.

"It was working and I was winning," the patient says. "It was another week later that I got the news that my bone marrow was completely free of detectable disease. It has been almost a year since I entered the clinical trial. I'm healthy and still in remission."

Is he cured? Doctors hate to declare a cure until patients have been cancer-free for at least five years. But there are signs the CAR-T cells persist in patients' immune memory, ready to mop up any CLL cells that reappear.

And there's a big downside. The CAR T cells that fight CLL also kill off normal B lymphocytes. These are the cells that the body needs to make infection-fighting antibodies.

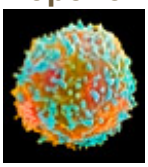
As long as the CAR T cells persist -- which may be for the rest of patients' lives -- patients will require regular infusions of immune globulin.

Hope for Cancer Patients, but Treatment Years Away

CLL is the second most common form of adult leukemia. In the U.S. there are about 15,000 new cases and about 4,400 deaths each year.

Cure is possible, but it requires a risky bone marrow transplant. About 20% of patients don't survive this treatment -- and even when they do, there's only a 50-50 chance of a cure.

Hope for Cancer Patients, but Treatment Years Away continued...



CAR T cells appear to be a much better option. But the amazing success now reported came very early in the development of this new treatment. Only a few of the thousands of CLL patients facing death will be able to enter the still-small clinical trials testing CAR T cells.

"The distressing thing is the need will far, far, far outweigh any slots in clinical trials," Galipeau says.

But Porter says his team is energized by the early success and is pushing forward as quickly as possible. Even so, a lot of work remains to be done.

"We've treated only a very small numbers of patients," Porter says. "So part of the goal is to see these results in more people, see that the results are sustained, and that it is safe over time. We need to find the appropriate dose and to make incremental modifications. And now we have shown activity, we can try and apply it earlier in the course of the disease. We have reason to think treating patients sooner may be even safer and more effective.

Although the CAR T cells in the study were designed to fight CLL, there's good reason to hope they can be effective in other forms of cancer. The catch is that it can work only on tumor cells that carry markers flagging them for destruction. Normal cells that carry the same markers will also be destroyed.

Many cancers are known to carry such markers, and there's hope of finding more.

"We have a clinical trial at the University of Pennsylvania with an anti-mesothelin molecule [which marks mesothelioma, ovarian, and pancreatic tumors]," Porter says. "There are other trials around the country trying to target renal cell carcinoma [kidney cancer] and myeloma [skin cancer]. We are hoping to identify other tumor targets, particularly in other leukemias, to adapt this technology."

Porter, June, and colleagues report their findings in the Aug. 10 early online versions of two major journals: *The New England Journal of Medicine* and in *Science Translational Medicine*.

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SOURCES:
News releases, University of Pennsylvania.
Kalos, M. *Science Translational Medicine*, published online, Aug. 10, 2011.
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REUTERS

TOP NEWS

Gene therapy proves effective for hemophilia B

Sat, Dec 10 22:11 PM EST

By Deena Beasley

SAN DIEGO (Reuters) - A single treatment with gene therapy, an experimental technique for fixing faulty genes, has been shown to boost output of a vital blood clotting factor, possibly offering a long-term solution for people with hemophilia B.

Researchers said the same technology was also being studied as a treatment for hemophilia A, the far more common type of the inherited bleeding disorder.

"It is a technique for potentially permanently curing patients," said Dr. Charles Abrams, American Society of Hematology secretary and associate chief of hematology/oncology at the University of Pennsylvania in Philadelphia.

Both safety and efficacy have held back the field of gene therapy. One experiment cured two French boys with a rare immune disorder but gave them leukemia in 2002, and an Arizona teenager died in a 1999 gene therapy experiment.

The approach used by researchers at the University College London Cancer Institute and St. Jude Children's Research Hospital in Memphis, Tennessee, involved the use of a novel viral "vector," designed to target the liver specifically.

The strategy involves replacing the defective gene that causes the bleeding disorder with a correct version delivered via the virus to the patient's liver cells - the only cells in the body capable of producing certain clotting factors missing or deficient in people with hemophilia.

The factors are numbered using Roman numerals. The two main forms of the disease are hemophilia A, caused by a lack of clotting factor VIII, and hemophilia B, caused by a lack of clotting factor IX.

Researchers have so far treated six men with severe hemophilia B who were producing clotting factor IX at less than 1 percent of normal levels. The general goal of current treatment with recombinant factor IX is to achieve factor levels greater than 1 percent of normal.

Four of the six trial participants have stopped routine treatment and remain free of spontaneous bleeding. The other two have increased the interval between factor infusions to once every 10 days to two weeks from two to three times a week, said Dr. Andrew Davidoff, chairman of the department of surgery at St. Jude's and co-author of the study.

HIGH COST FOR CURRENT TREATMENT

Frequent treatments with manufactured factor IX, known as recombinant factor concentrates, can cost hundreds of thousands of dollars a year, making hemophilia a tempting target for gene therapy.

The trial "is truly a landmark study," Dr. Katherine Ponder, hematology and oncology professor at Washington University in St. Louis, said in a New England Journal of Medicine editorial.

"If further studies determine that this approach is safe, it may replace the cumbersome and expensive protein therapy currently used for patients with hemophilia B," she wrote.

The trial results were published in the NEJM and reported on Saturday at a meeting of the American Society of Hematology in San Diego.

The six trial subjects were broken into three groups with each group receiving a different concentration of new genes.

Factor IX levels in the first subject have remained at 2 percent for nearly two years, while the two patients treated with the highest dose have seen FIX levels rise to between 3 and 12 percent, researchers said.

One high-dose subject developed elevated levels of transaminases, an indicator of possible liver damage, and another had a slight increase in liver enzymes. Both cases were resolved with steroids, the researchers said.

Plans are to treat more patients with the highest dose used so far, and if research continues to succeed, the treatment could be widely available "in the next five years or so," said Dr. Amit Nathwani, co-lead study author of the Department of Hematology at UCL Cancer Institute in London.

He also said the team was working to use the technique for treating hemophilia A.

ISI Group analyst Mark Schoenebaum said the gene therapy could pose big competition for companies such as Biogen Idec that are producing recombinant factor concentrates.

"This clearly presents a curveball to our (and much of Wall Street's) assumptions around the future of the hemophilia market," he said in an email to investors.

The analyst said estimated sales of the hemophilia factors accounted for between $10 and $17 of his $125 price target for shares of Biogen, which closed at $112.95 on Friday.

People with hemophilia bleed more following trauma than people without the disease, and those with severe disease may bleed spontaneously. Since the gene is carried on the X chromosome, hemophilia is almost exclusively a disease of men.

But women can pass the gene to their offspring.

Hemophilia has often been called the "Royal Disease" since it was carried by Britain's Queen Victoria and affected many of the royal families of Europe.

Hemophilia B is much less common than hemophilia A. About one in five hemophilia patients has hemophilia B, according to the National Institutes of Health.

The global market for Factor VIII products is about $5 billion, while the market for Factor IX is worth about $1 billion.

Worldwide, about one in 5,000 men is born with hemophilia A and 1 in 25,000 men is born with hemophilia B each year.

(Reporting by Deena Beasley; Editing by Peter Cooney)

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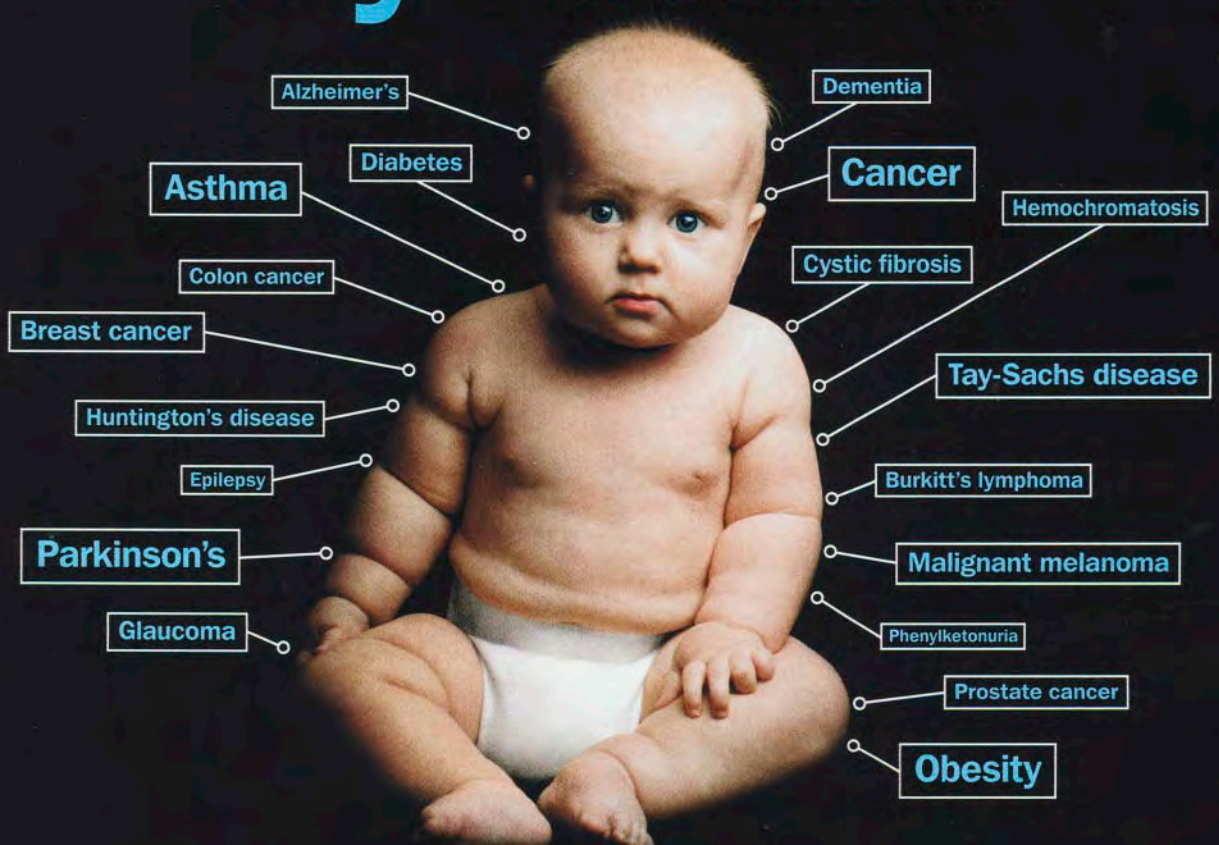


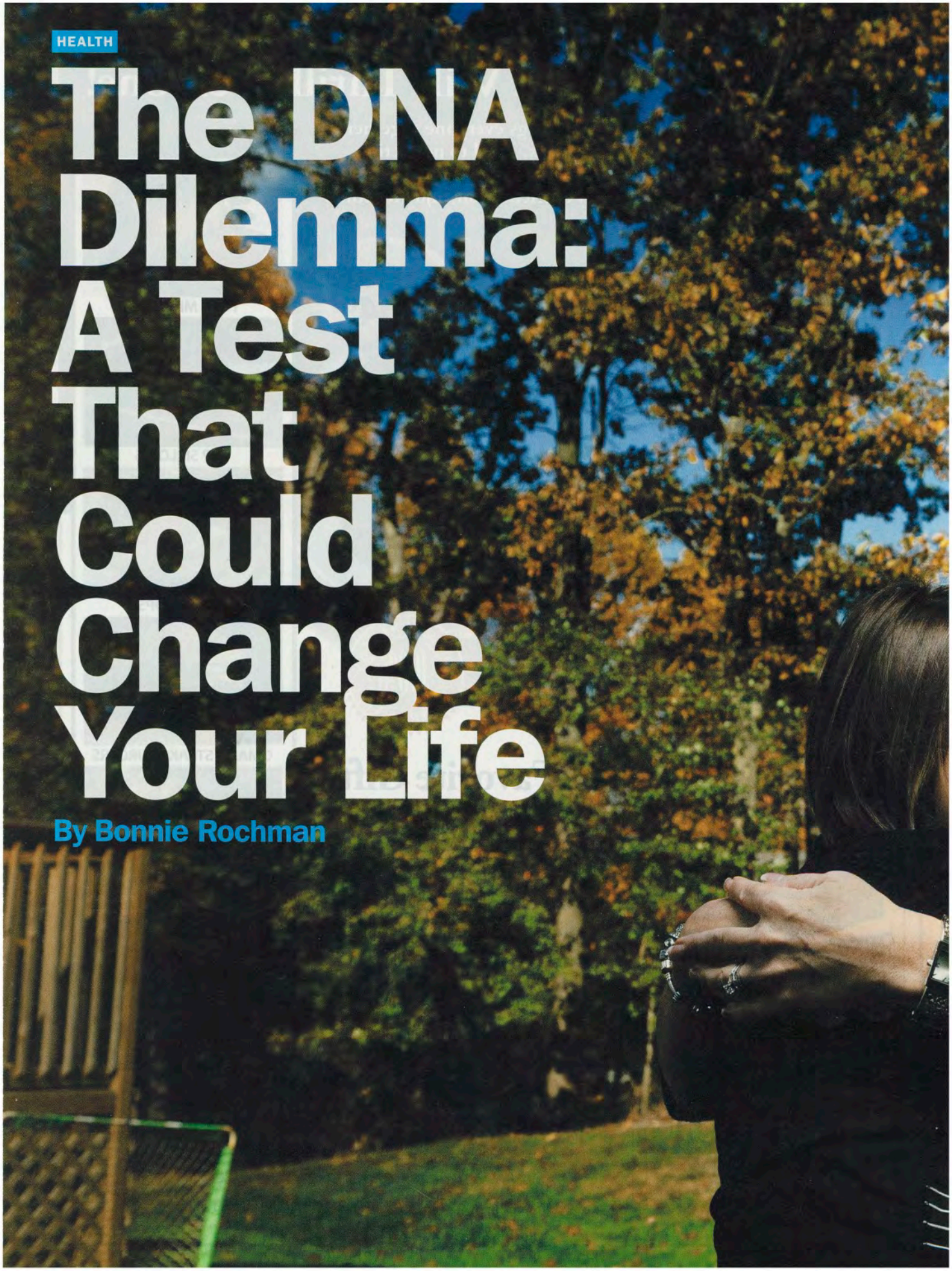
New genetic tests can point to risks—but not always a cure

BY BONNIE ROCHMAN

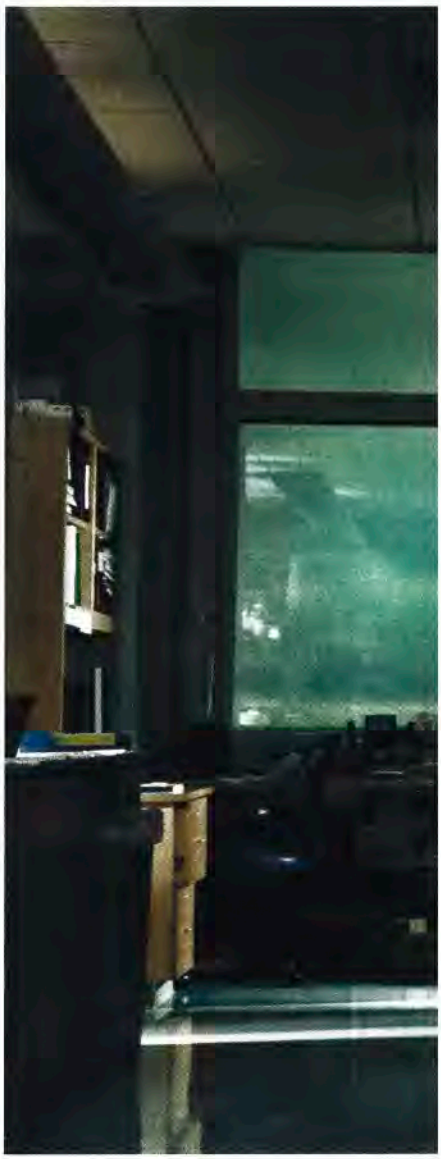
HEALTH

The DNA Dilemma: A Test That Could Change Your Life

By Bonnie Rochman



Know your enemy, we tell ourselves;



knowledge is power. Laurie Hunter wanted to know what disease was attacking her daughter Amanda, who by the age of 2 months was not developing normally. Her muscle tone was low. She wasn't lifting her head. She was slow to talk, and she didn't walk until she was 2.

"As a mother, you know that everything that happens to your child is not your fault, yet you still feel responsible," says Hunter, 42, a high school English teacher who lives in Jackson, N.J. "We turned to genetic testing because I wanted answers." The first tests, done at the Children's Hospital of Philadelphia (CHOP) when Amanda was 4, came back normal. So did another round when she was 9. Doctors could not figure out what was making Amanda weak—even as she got weaker and slower and stopped being able even to blow her nose. "It's like her muscles are getting tighter and not moving in the way they should," Hunter said. But the doctors held out hope. Genetic testing grows more sophisticated every day, they said, allowing researchers to explore a child's health down to every last typo on a chromosome.

In March, a third round of tests found seven genes missing from Amanda's first chromosome. At last, Hunter thought, when the genetic counselor called and asked to see her. "It felt like finally I might have an answer." But it was not the answer she was looking for. The small deletion, the counselor said, did not explain Amanda's condition. That was still a mystery. And now a whole new threat appeared.

One of the seven deletions has been linked to very rare tumors. The geneticists wanted Amanda, who is 14, to be screened by an oncologist. "It was like, Oh, my God, now we are adding cancer to the mix," Hunter says. "Never in a million years did I think this would be an issue."

She was even more surprised when a counselor called after her own tests came back. "I know you're going to be upset," the counselor said, "but we found that you have the same deletion." And so might her other two children.

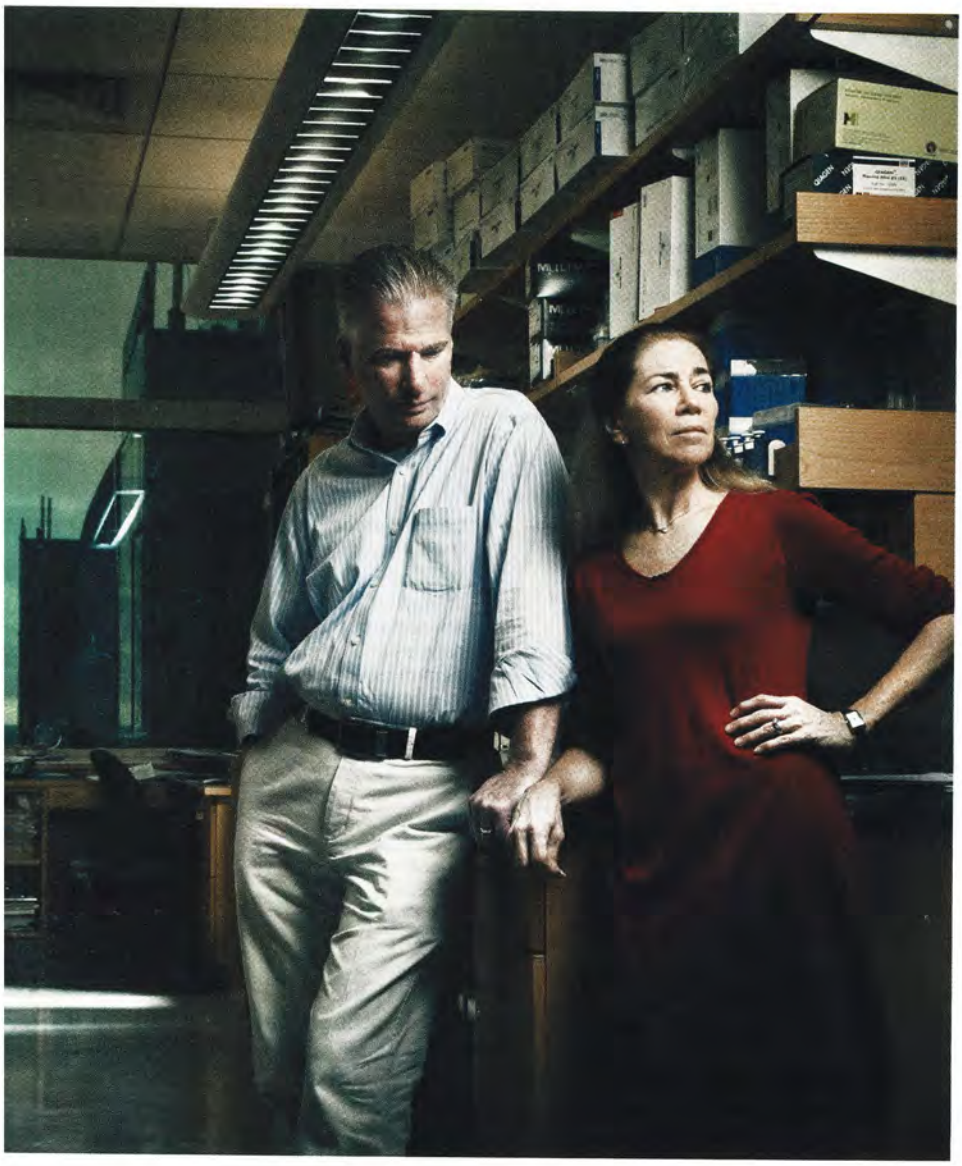
This is the world we are heading into: one with powerful new weapons against age-old diseases and a host of questions about how to use them wisely and not turn them on ourselves. Imperfect knowledge can make us crazy—or bankrupt—chasing down threats that may never materialize. The human genome is an exquisitely complex blueprint. Geneticists hunting for answers to mysterious symptoms invariably trip over incidental findings, genetic twists they were not even looking for that might signal a risk of cancer or Alzheimer's or Parkinson's in the near or distant future. But do doctors have to tell patients everything they learn, even about the risk of diseases for which there are not yet cures? Do parents have to tell their children what might await them as adults? And who will pay for all this? "Everyone at this point is flying by the seat of their pants," says Dr. James Evans, a medical geneticist at the University of North Carolina School of Medicine. "The technology is outpacing us."

From Labs to Living Rooms

THE MAPPING OF THE HUMAN GENOME, completed in 2003, cost $2.7 billion. Now the cost for an individual's whole-genome sequencing (WGS) is $7,500 and falling fast. One day WGS could be as easy to get as a pregnancy test at the drugstore. To do the testing, lab technicians need less than a teaspoon of blood, which is chemically treated to burst open the cells so the DNA inside them can be collected. Those microscopic strands are then fed into sophisticated machines that read each of the 3 billion bits of information, called base pairs, that make up a person's genetic alphabet. Computers scan the data for the equivalent of spelling mistakes. Some mistakes cause disease; others don't. And in between is a vast gray area where scientists just don't know what the changes mean.

In an ideal world, genetic analysis could save money by catching diseases early, offering targeted treatments and identifying the most effective preventive measures. Dr. Katrina Armstrong, a professor at the University of Pennsylvania School of Medicine, notes that testing 21 genes could reveal which breast-cancer patients are unlikely to benefit from a particular chemotherapy—knowledge that could

MILLER MOBLEY—REDUX FOR TIME



Tough call *Dr. Ian Krantz and Nancy Spinner at the Children's Hospital of Philadelphia decided not to tell parents their baby will likely develop early-onset dementia*

spare women the treatment and save $400 million each year. "If genomics can help us understand who will get the most benefit and who will get little or no benefit from an intervention," Armstrong says, "it will take us a long way toward improving patient outcomes and saving money."

But a majority of doctors in a recent survey predicted that more testing will trigger higher costs, as patients with ambiguous results begin to seek frequent screenings—and potentially unnecessary procedures—for diseases they might never develop. "If we open the door to a test that has no clear, well-defined purpose, that is a recipe for unnecessary medical care," says Dr. Wylie Burke, a geneticist who chairs the department of bioethics and humanities at the University of Washington. "Instead, we could say, Here are the 1,000 mutations we should check in everyone." The American College of Medical Genetics and Genomics is already working on that, painstakingly assembling a list of a few dozen conditions that it says should be routinely looked for during genome sequencing. The hope is that focusing on certain hot spots—contenders include several syndromes that increase the risk of various cancers—will lead to improved analysis and, with it, better patient outcomes.

Nearly all the parents said they would want to know about every disease risk, even if there's no treatment available

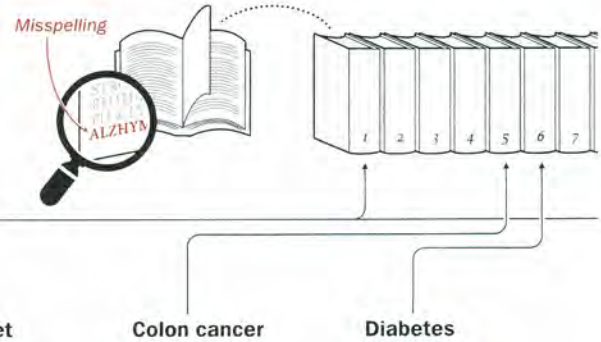
Some genetic testing has already moved out of the lab and into the living room. Companies like 23andMe offer DNA analysis directly to consumers—no doctor required. Since 23andMe's founding in 2006, more than 180,000 people have been tested as the price has fallen from $999 for information on 14 specific traits and health risks to $99 for more than 200. The promise boils down to "forewarned is forearmed." If parents learn that their child carries a gene called ApoE4, indicating a higher risk of Alzheimer's, they might discourage the child from playing youth hockey or football, since research has linked traumatic brain injuries with a greater likelihood of brain disease in people who test positive for ApoE4.

"I do believe at some point in time everyone will be genotyped at birth," says 23andMe co-founder and CEO Anne Wojcicki. Her husband, Google co-founder Sergey Brin, has a genetic mutation that increases the risk of Parkinson's disease up to 80%; she has already tested their two children. Wojcicki's grandmother had macular degeneration; when testing revealed that some of Wojcicki's nieces and nephews are at increased risk for it, she bought them high-quality sunglasses. If her kids were predisposed to developing diabetes, she says, she'd encourage healthier eating. "I want to do everything I can to potentially enable my children to be disease-free."

But having more-detailed genetic information does not always point to a clear path. Dr. Ian Krantz and Nancy Spinner, a husband-and-wife team at CHOP, are working with an $8.8 million federal grant to understand what genomic

Decoding Disease

INDIVIDUAL GENES
Think of human DNA as an encyclopedia. Testing a **specific gene** involves pulling out the right volume (chromosome) and looking for spelling errors on a particular page



CONNECTING THE DOTS
Some diseases are caused by a single mutation, while others involve a complex interplay among many genes and environmental factors

Early-onset Alzheimer's disease
Chromosomes 1, 14 and 21
Someone who inherits one of several mutations on chromosomes 1, 14 or 21 is almost certain to develop a rare form of Alzheimer's (accounting for less than 5% of cases) between the ages of 30 and 60

Colon cancer
Chromosome 5
Most cases of familial adenomatous polyposis, a rare form of colon cancer in which polyps have been detected in kids as young as 7, are caused by mutations in a tumor-suppressor gene on chromosome 5

Diabetes
Chromosome 6
Mutations on chromosome 6 play a role in Type 1 diabetes, but so do other factors, including early diet. If an identical twin has the condition, formerly called juvenile diabetes, the other twin has at most a 50% chance of developing it

information patients and parents want to know. Most parents go in looking for the cause of a mystery illness. "If you tell parents their child also has an increased risk for colon cancer or breast cancer," says Krantz, a pediatrician who oversees medical-genetics training at CHOP, "that's a whole different level of stress."

If you want to start an argument, ask doctors and patients what they think doctors should do when they discover genetic results they weren't looking for. It can be an emotional blow—and a lifelong burden—if a mom learns that her baby girl carries a mutation that increases her risk of ovarian cancer or a dad finds out that his aspiring linebacker is genetically predisposed to developing Alzheimer's. In focus groups that are part of Krantz and Spinner's study, nearly all the parents said they would want to know about every disease risk, even if there's no treatment available. But in groups of bioethicists, lab directors, geneticists, pediatricians and genetic counselors, the majority said only results that could be immediately acted on should be shared with families.

This year, the lab Spinner runs tested a baby with a mysterious illness and found a completely unrelated mutation that indicated that dementia would likely set in at around age 40. Endless discussions followed: Should they tell the baby's parents that their child would probably develop a progressive neurologic disease marked by incontinence, blurred vision and confusion? There is no current treatment or cure. Telling them would all but guarantee that their child would never be able to get disability or long-term-care insurance. "We came around to the realization that we could not divulge that information," says Spinner, who is a genetics professor at Penn's medical school. "One of the basic principles of medicine is to do no harm."

At about the same time, her lab discovered that a 2-year-old with kidney disease carried a genetic risk for a kind of colon cancer. In some cases, polyps have been known to develop as early as age 7. With this patient, withholding the information would have seemed unethical. "We feel good about that one," says Spinner. "Proper screening can make a huge difference."

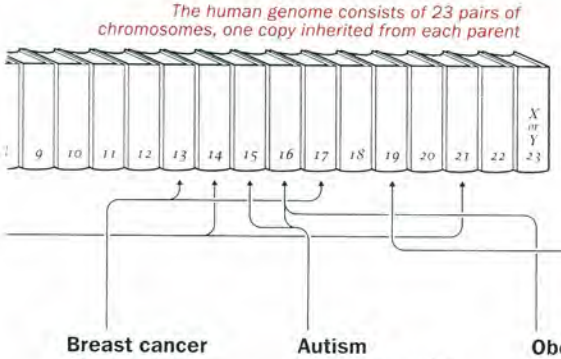
Genome sequencing isn't the first medical development that has forced doctors to grapple with the question of how much to tell patients. There have been cases of physicians' choosing to keep quiet when a test revealed a child's father was not his or her biological father. In years past, doctors have agreed not to share news of a terminal illness with an elderly patient if the consensus was that the knowledge would cause too much anxiety.

But genomes are vastly more complicated. "If you fall off your bike and get an X-ray looking for a fractured rib, the radiologist scans the entire X-ray and automatically reports back to your doctor if something else is going on," says Dr. Robert Green, a geneticist at Harvard Medical School. "More than a few cancers have been picked up this way. The problem with genomics is that everyone could have incidental findings."

Perhaps nowhere is the risk of overreacting to murky results greater than in the field of prenatal testing. This year two groups of researchers announced that they had each sequenced a fetus' DNA from cells gathered from the mother's blood, leading to concerns that in the not-too-distant future, women might abort a pregnancy if they learn their unborn baby has an increased risk for cancer. "Great, we can sequence the genome of a fetus. What the hell does it tell us?" says bioethicist Tom Murray, a visiting scholar at Yale. "Much less than most people probably believe. Probabilities are not the same as guarantees."

Faced with a growing need for protocols, the medical community is trying to hammer out some guidelines. This spring, the American College of Obstetricians and Gynecologists stated that though personalized gene profiles may be promising, they are "not ready for prime time" and should be discouraged. The American Academy of Pediatrics advises against genetic testing for children unless there is clear evidence of beneficial treatment or effective prevention strategies.

The challenge doctors face in determining how much to tell patients—or their parents—is complicated by a steady stream of new discoveries. Test results that are indecipherable today could be lifesaving in 2025. But waiting years to share sequencing



GENOME SEQUENCING
Scanning a person's **entire genetic code** can help diagnose a mysterious illness, but murky results can lead to a lot of anxiety

Breast cancer
Chromosomes 13 and 17
A woman who inherits mutations in either of two genes (BRCA 1 on chromosome 17 or BRCA 2 on chromosome 13) is about five times as likely to develop breast cancer as a woman who does not have such a mutation

Autism
Chromosomes 15 and 16
About 20% of autism cases can be traced to genetic abnormalities, including deletions or duplications on chromosomes 15 and 16. A new experimental blood test looking at 55 genes might help diagnose the condition earlier

Obesity
Chromosome 16
It's a mistake to attribute the obesity epidemic to DNA alone, but dozens of genes, including the fat mass and obesity-associated (FTO) gene on chromosome 16, appear to play a role in weight variation in adults

Alzheimer's disease
Chromosome 19
A common variant of the ApoE gene on chromosome 19 increases a person's risk of getting late-onset Alzheimer's, which develops after age 60. Mutations in several other genes have also been linked to the disease

information is a logistical nightmare, particularly considering that patients may not remain under that geneticist's care and may change addresses many times over. Genomic transcripts are also so massive—labs typically FedEx a hard drive because there's too much data to transmit digitally—that the information is often relegated to a hospital's archives, if it's saved at all.

One possible solution to the problem of what to do with the deluge of data is a new Web-based venture called My46. Named for the number of chromosomes in human DNA, the nonprofit will allow people to store their sequencing results online and choose what they want to know and when. For example, parents of a baby who gets sequenced could opt to learn right away any findings about childhood diseases and put everything else—from unclear results to increased risks of adult-onset diseases—in the digital equivalent of a locked drawer, where it can be stored forever and accessed whenever they want to open it.

"Right now, it's not unusual for researchers to say that they're not returning results because there's no good way to do it," says Dr. Michael Bamshad, chief of pediatric genetics at the University of Washington, who works with Burke and is helping develop My46. Eventually, he predicts, "everyone will have their genome stored in a cloud."

Living with the Results

FOR LAURIE HUNTER, THE NEWS OF HER own cancer risk was not actually a shock. The disease runs in her family. Her mother and aunt had breast cancer, and her brother died of testicular cancer when he was 27. "I'd resigned myself that it was part of my reality, but I didn't think about it being part of my kids' reality—not this young, anyway," she says. One of the genes she's missing increases her risk of extra-adrenal tumors, which can pop up in the head, neck, chest and abdomen. The average age of onset is 30. Hunter is 42. So she scheduled blood tests and a full-body MRI to see if any tumors had started growing. She was thinking not just of herself and Amanda but also of her son Ryan, 4, who has always been healthy, and of her youngest child Kailyn, who was born with a rare genetic disorder unrelated to Amanda's, called Wolf-Hirschhorn syndrome. At 2½, she cannot talk and can barely sit up. "I have two girls, one of whom will never speak, and they need to be cared for by somebody," she says. "I worry about, if something happens to me, who will take care of them." And then there is Ryan. What if she had passed the cancer risk on to him?

"I have shed more than a few tears since I learned about this gene deletion," Hunter says. "I love all my children equally, but I have reconciled myself that neither daughter will ever drive, go to college, get married or live on her own. The hardest part is thinking about my son. I have this one child in whom all my hopes and dreams lie, and now he may have this deletion too."

She considered not testing him. Maybe ignorance would be better than knowing the worst. "But I thought, God forbid, what if he was one of the ones who develops tumors at 10 years old and I didn't know. I'd be consumed with guilt."

Ryan was tested in the last week of September. The waiting was a kind of torment. "We got the results back the other day," Hunter says. "He does not have the deletion. I feel like I can breathe again."

But because of Amanda's increased risk, she is being closely monitored. An MRI found a spot on her neck that turned out to be an enlarged lymph node. The doctors still don't know what is causing her other health problems.

"If all three of my children were healthy and had no issues, I don't know if I'd want to know about those seven missing genes," says Hunter, whose own MRI detected a lesion above her diaphragm. She's waiting to learn whether it's a tumor. "Sometimes what you don't know is easier. I feel completely overwhelmed with information. Now it just feels like a waiting game."

This is often how medicine works. Our powers outpace our principles and protocols, so that we wake up one day to headlines that a sheep has been successfully cloned and have to figure out what that means for the future of reproduction. In the case of genetic testing, there is little doubt that greater knowledge will bring many blessings, but it comes with costs, literal and emotional, and patients entering this territory with imperfect maps need to reckon with the odds of getting lost. ■

latimes.com/news/science/la-sci-fetal-genome-sequence-20120607,0,7625263.story

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Entire DNA of fetus revealed through risk-free testing

Researchers use blood from the mother and saliva from the father to determine a fetus' entire DNA sequence. If refined, the technique could provide a risk-free way to screen for genetic disorders.

By Rosie Mestel, Los Angeles Times

5:44 PM PDT, June 6, 2012

Scientists have pieced together the entire DNA sequence of an 18-week-old fetus without having to use any invasive tests that could result in a miscarriage — an advance that offers a glimpse of the future of prenatal testing.

Using blood drawn from the mother and a sample of saliva from the father, the researchers were able to scan the fetus' genome and determine whether it contained any of the myriad single-letter changes in the DNA code that can cause a genetic disorder. They could even pinpoint which mutations were inherited from Mom, which came from Dad, and which were brand-new.

If the technique is refined and the technology becomes inexpensive — as many experts anticipate — this type of prenatal testing could provide prospective parents with a simple, risk-free way to screen for a broad array of simple genetic disorders, according to the authors of a report in Thursday's edition of Science Translational Medicine.

The work is based on the fact that small fragments of fetal DNA circulate in the blood of pregnant women.

Several biotech companies are developing tests that capture those DNA fragments and screen them for signs of Down syndrome and other disorders that result from having an extra copy of an entire chromosome.

But that type of screening is far easier than searching for single-letter variations in individual genes, said senior author Jay Shendure, a geneticist at the University of Washington in Seattle.

An additional chromosome is "the equivalent of an extra chapter in a book," he said. "What we're trying to do is pick up a typo in a word."

To set about their task, Shendure's team started by sequencing the genome of an anonymous pregnant woman, using a complete sample of her DNA obtained from her blood cells. They also sequenced free-floating DNA fragments extracted from her blood plasma, repeating their work until they had decoded every part of the human genome 80 times.

That plasma contained a mix of 10% fetal DNA and 90% maternal DNA, all in tiny fragments. The scientists needed to be able to tell which pieces were from the mother and which belonged to the fetus.

To solve that problem, the scientists relied on the fact that genetic material is inherited in long strands of DNA, called chromosomes — and that tiny genetic variations on the same chromosome are usually inherited together, in blocks known as haplotypes. If a given haplotype was present in the fetus as well as in the mother, it would be detected in the plasma in extra amounts.

The scientists also sequenced the father's DNA, which was extracted from saliva. This allowed the team to figure out whether genetic variations in the fetus that didn't match the mother were inherited from the father or were new mutations. On average, about 50 new mutations show up in a fetus.

The scientists checked their results against a blood sample taken from the baby's umbilical cord after birth. Their calculations were more than 98% correct, they found, and they had detected 39 out of the 44 new mutations. None of those mutations had known medical consequences, the researchers said.

This approach could be used to devise a single test to screen for the 3,000 known disorders that are caused by mistakes in single genes. Individually, they are rare, but together they affect about 1% of births.

Technology like this could lead to more widespread screening of fetuses for genetic disorders that could benefit from early treatment, said Dr. Joe Leigh Simpson, senior vice president for research and global programs for the March of Dimes in White Plains, N.Y. It might even help doctors identify women at heightened risk for problems such as pre-term birth, he said.

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TIME

Thursday, May. 20, 2010

Scientist Creates Life. That's a Good Thing, Right?

By Alice Park

It's the ultimate science experiment, really — taking a handful of chemicals, mixing them in just the right combination and presto — life!

And after nearly 15 years of such toiling in his labs in Rockville, Md., J. Craig Venter, co-mapper of the human genome, has done just that. Reporting in the journal Science, he describes a remarkable experiment in which he and the team at his eponymous institute have pieced together the entire genome of a bacterium and then inserted those genetic instructions into another bacterium. The cell booted up, and life — by nearly any definition — was created. (See the top 10 scientific discoveries of 2009.)

"We're basically getting new life out of the computer," Venter says. "We started with a genetic code in the computer, wrote the 'software,' put it into the cell and transformed it biologically into a new species. We're still stunned by it as a concept."

With Venter's breakthrough it's now possible to splice and snap together genetic material to create a Legoland's worth of new genetic combinations. Ideally, some of these would have robust industrial purposes, such as manufacturing bacteria that can churn out valuable vaccine components to shorten production times during an epidemic, or co-opting organisms such as algae to pump out new sources of biofuel-based energy. (See TIME's health checkup package on how to live 100 years.)

"Just imagine these cells where all we do is put in a new piece of chemical software and all the characteristics of the cell start changing to become what was dictated by the new software," says Venter. "These are biological transformers."

The paper is the final and most critical step toward realizing what began as scientific curiosity among the scientists at the J. Craig Venter Institute back in the early 1990s, when many of the same researchers first succeeded in sequencing the entire genome of a self-replicating organism, the bacterium Haemophilus influenzae. That led to the generation of the complete sequencing of the smallest known genome, at 582,000 base pairs, belonging to another bacterium, Mycoplasma genitalium. Such smallness was intriguing because it led Venter to the philosophical question that inspired the current research — what was the minimum genome required to create life in the lab? (See the top 10 unusual medical treatments.)

For the study just released, the answer turned out to be about 1 million, and the paper describes how he did it. DNA is made up of millions of paired molecules known as bases, some of which make up genes, that when read by enzymes produce the proteins essential for sustaining life. Venter intended to build his own version of the tiny M. genitalium genome, but the species replicates slowly and that would have caused delays in his study. Instead, he turned to the larger but significantly quicker bacterium Mycoplasma mycoides, with 1 million base pairs. He fed the blueprint of the M. mycoides genome into a computer, mixed together varying combinations of the four basic elements of DNA — the bases adenine, cytosine, guanine and thymine — and pieced them together in three stages. To ensure that the strings of bases were lining up in the correct order, he and his team attached known segments of DNA to the ends of each piece, allowing them to find and link up with their appropriate sections like genetic Velcro joining.

What made the work unwieldy is that even a very small genome has a lot of base pairs and current sequencing machines can handle only 50 to

80 at a time. To align the ever-growing strings of DNA, Venter thus enlisted the help of some natural born synthesizers — yeast and E. coli. These organisms are quite adept at stitching together huge pieces of DNA, and once they did their job, the genome was complete.

See a photo gallery of microscopic organisms.

See the top 10 scientific discoveries of 2008.

But that was only half the goal. The next step was to insert the man-made genome into a cell and see if it could function properly and cause the cell to divide. "The first transplants we did — we usually do them on a Friday and on Monday morning we come back to see if anything grew — didn't work," Venter says. "Then a month ago, I got a text at six in the morning that we had a colony."

Venter is the first to concede that while what he has created is life, it's not new life, since the synthetic genome is a copy of an existing one, albeit with a few modifications. In order to confirm that the genome they generated was indeed entirely manmade, the scientists inserted some genetic watermarks, including their names and three philosophical quotations. Since the four-based genetic code is read in three-letter triplet combinations, the scientists devised a new code in which the 64 possible triplets symbolize the letters of the alphabet and punctuation. One of the quotes, by James Joyce, was especially apt: "First to live, to err, to fall, to triumph and to create life out of life." Says Venter understatedly: "The chances of finding these sequences in the natural genome are close to zero."

Synthetic biology, as the field of man-made biological components such as Venter's is called, is a promising new field that raises as much concern as it does excitement. It's basically genetic engineering writ on a larger, more profoundly amped-up scale. That process could generate valuable new species that can produce vast amounts of much-needed food or pharmaceutical products, and Venter is already at work on such projects. Collaborating with Novartis, he is building a bank of man-made versions of every known influenza strain so that if a new strain, such as H1N1, begins to circulate during flu season, vaccine makers can simply pull the appropriate synthetic segments off the shelf and begin the vaccine making process, cutting the months-long job of sequencing the appropriate strain down to a single day.

Working with Exxon, Venter's team is investigating ways to harness algae to convert carbon dioxide into a hydrocarbon source for biofuel on a scale that would finally make such alternative energy options worth pursuing. "No natural algae we know would do this on the scale needed," he says. "So we have to use a synthetic genome technique to either heavily modify existing algae or devise whole new ones." And the same strategy can be used to build organisms that can clean up pathogens in water or boost nutritional content in foods such as wheat crops.

Those, of course, are the positive applications, but even Venter acknowledges that the approach can have some less useful, and even dangerous outcomes. The same technique could generate unheard of combinations of genes in the form of potentially dangerous mutants. "Somebody could do something, like copy one of the existing pathogens out there," Venter admits, "but the odds of that are extremely low. This is not a trivial process, and isn't something that labs are going to start repeating at the same scale."

As his team was perfecting the technology, Venter invited the National Academy of Sciences and other U.S. government agencies to review the promise and dangers of synthetic biology to ensure, he says that "the science proceeds in an ethical fashion, and that we are being thoughtful about what we do."

It's a discussion that Venter hopes will continue, as the range of applications for synthetic cells becomes clear. "This whole field was theoretical until this experiment worked," he notes. "This is the early beginning showing all that is now possible."

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