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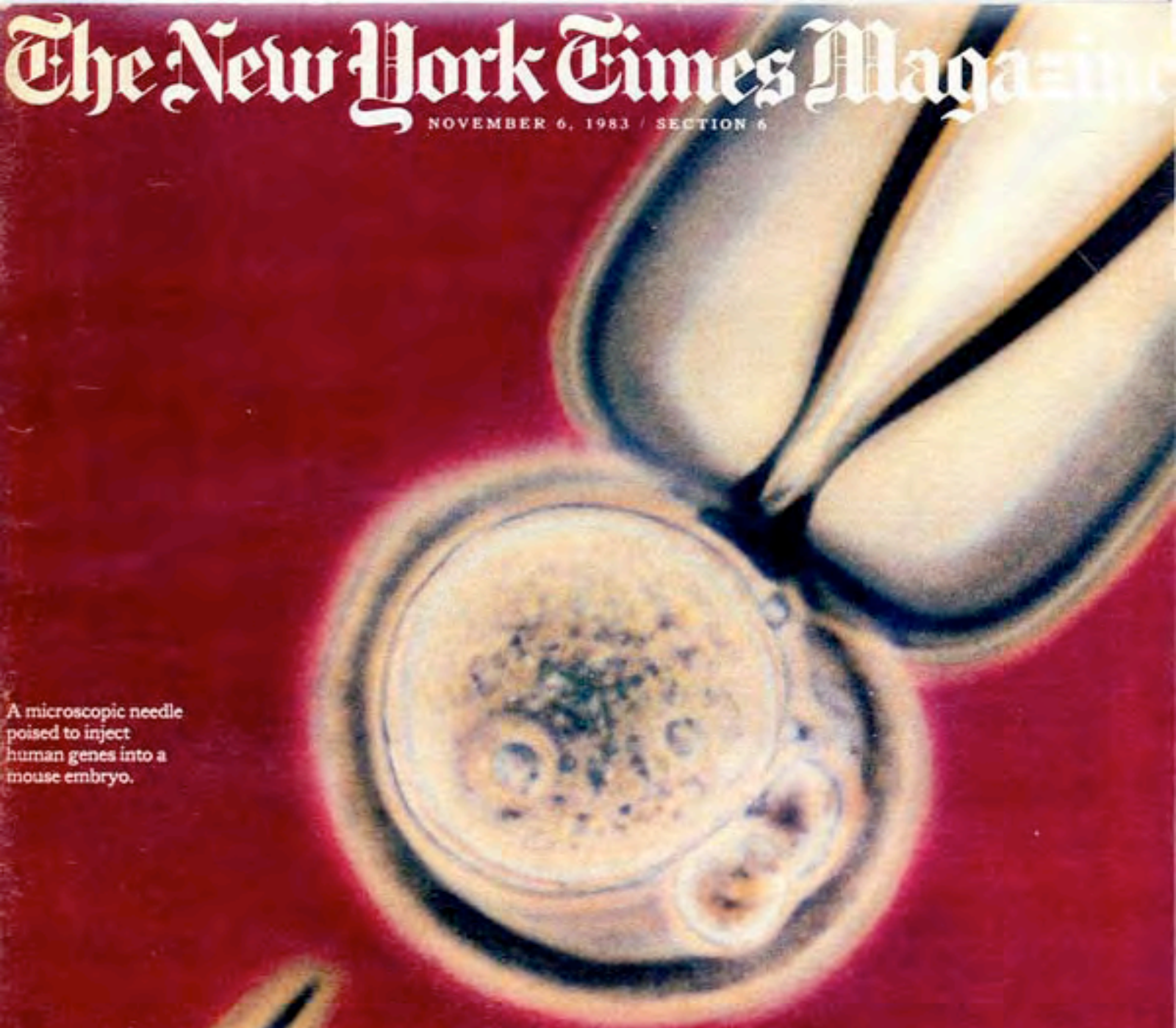

A microscopic needle poised to inject human genes into a mouse embryo.

KEEPING UP WITH

THE GENETIC REVOLUTION

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KEEPING UP WITH THE GENETIC REVOLUTION

Wielding tools of genetic engineering, researchers are cracking the very code of life. Their discoveries may enable scientists to diagnose many diseases before they occur, and to cure them.

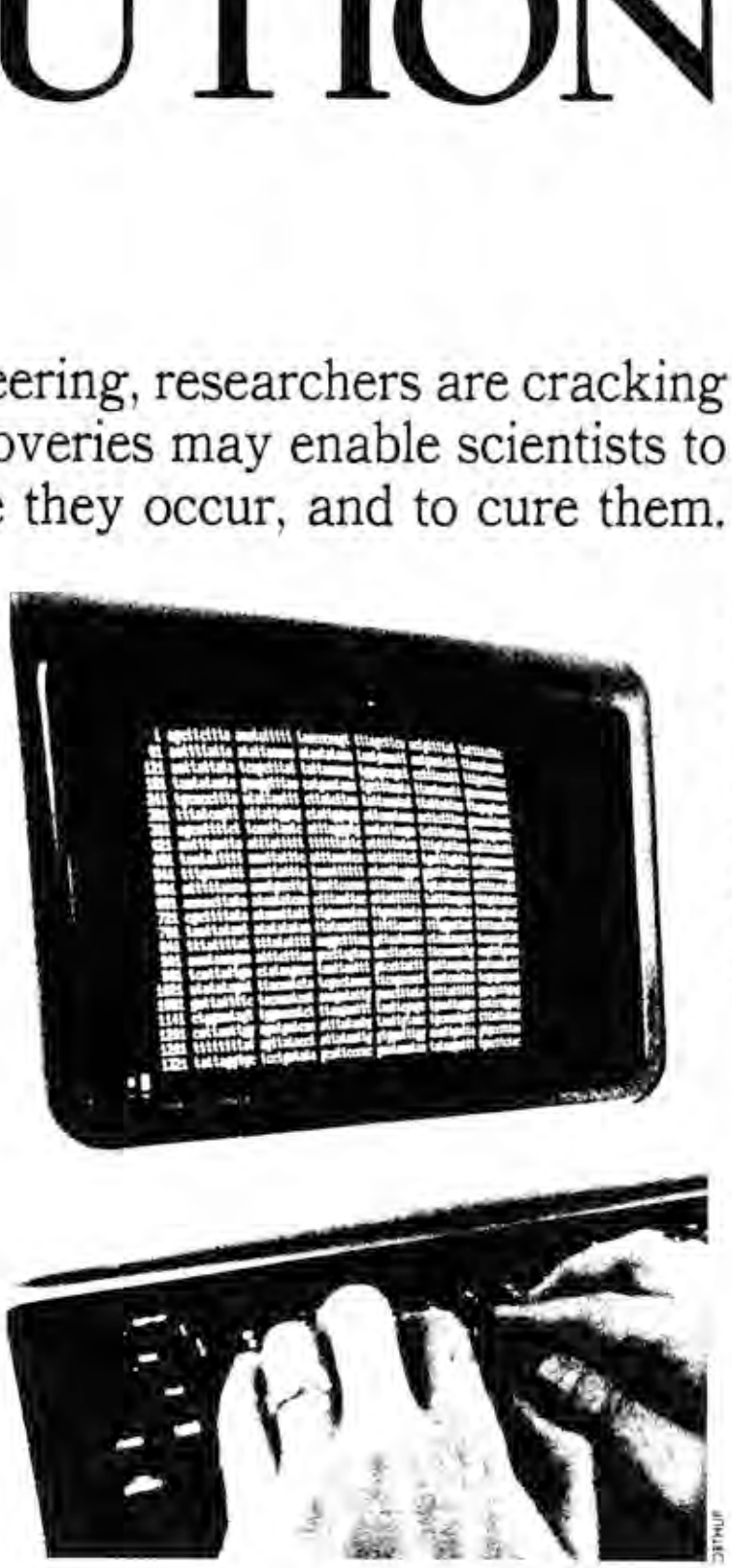
By Kathleen McAuliffe and Sharon McAuliffe

AT THE LOS ALAMOS NATIONAL Laboratory in New Mexico, biophysicist Walter Goad punches a few keys on a computer terminal. Moments later, glowing green type illuminates the monitor in front of him. "ATGGCTACAGGTAAG . . . " begins the message, which goes on and on for almost 2,000 repetitions of A, T, C and G. Dr. Goad, director of the Government-sponsored Genetic Sequence Data Bank, known as GenBank, can read the cryptic language easily. It is an example of the genetic code, this particular procession of characters being the recipe for making a specific protein, the hormone that controls human growth.

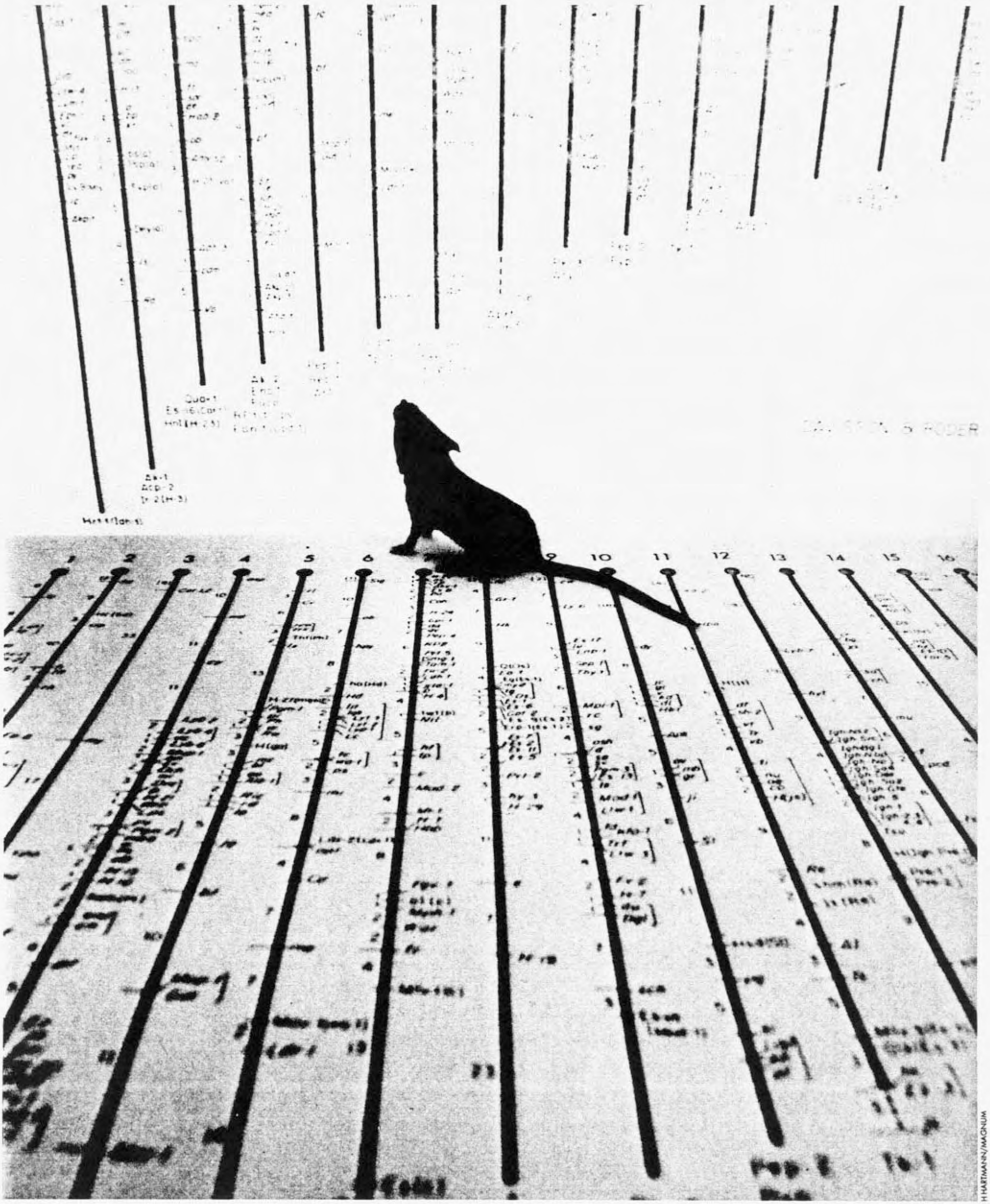
It will probably take more than three billion characters to encode in this way all the chemicals in the body. One day, Dr. Goad hopes, the complete recipe for a human being will be revealed. "Man's entire hereditary code should fit on 30 high-density magnetic tapes, taking up less than a four-foot bookshelf."

Equipped with the tools of molecular biology, scientists like Dr. Goad are participating in an intense study of the genetic basis of human life, racing to unscramble the detailed structure and position of all the genes on man's 46 chromosomes. The major aims are to uncover how these genes are "switched on and off" to promote normal development and to learn just what goes wrong when disease ensues. In one experiment, for example, researchers are trying to understand the functions of human genes by implanting them in the nu-

Kathleen McAuliffe is a contributing editor at Omni maga-



Opposite page: A laboratory mouse on a chart mapping its chromosomes and the locations of some of its genes. Left: A researcher calls up on a computer screen the genetic formula for the hormone that controls human growth.



H. HARTMANN/MAGNUM

cleus of a mouse embryo. (See the photograph on the cover.) By studying how these genes alter the characteristics of the newborn animal, they hope to unravel the fundamental mechanisms of genetic control.

OF THE ESTIMATED 100,000 GENES found tucked up inside a human cell, some 800 have now been tracked to their chromosomal locations, with new genes being mapped at a rate of 200 per year. According to Dr. Frank Ruddle, professor of biology and human genetics at Yale University, this rate will accelerate exponentially over the next few years so that "by the turn of the century, the major outline of the human gene map should be known."

It will probably take several decades more before Walter Goad's genetic bookshelf is realized, but already the molecular cartography of animal and human genes heralds startling advances in health care:

■ Vaccines. Last month, scientists of the New York State Health Department announced they had used the manipulation of genetic material — genetic engineering, as it is commonly called — to develop vaccines that protect rabbits against hepatitis and mice against a type of herpes. They held out hope that tests could begin in three years or so on similar vaccines that might protect humans from the same afflictions. In the same week, a New York City team announced it had isolated the gene for a substance that may cause toxic shock syndrome. A vaccine to guard against that condition, too, might possibly result.

■ Early warning for adult diseases. In the brief interim since the genetic origins of many cancers first came to light, scientists have succeeded in isolating specific snippets of genetic material that may predispose individuals to heart disease and emphysema. Medical sleuths are now hot on the trail of genes that have emerged as likely culprits in diabetes, allergies, peptic ulcers and other common diseases of midlife, a trend that may shift the central thrust of medicine from treatment to prevention.

■ Understanding the basis of inherited diseases. The blood disorders sickle-cell anemia and beta thalassemia, and over a dozen other hereditary diseases have now been traced to specific "spelling errors" in the genetic code, shedding new light on the underlying causes of hereditary afflictions.

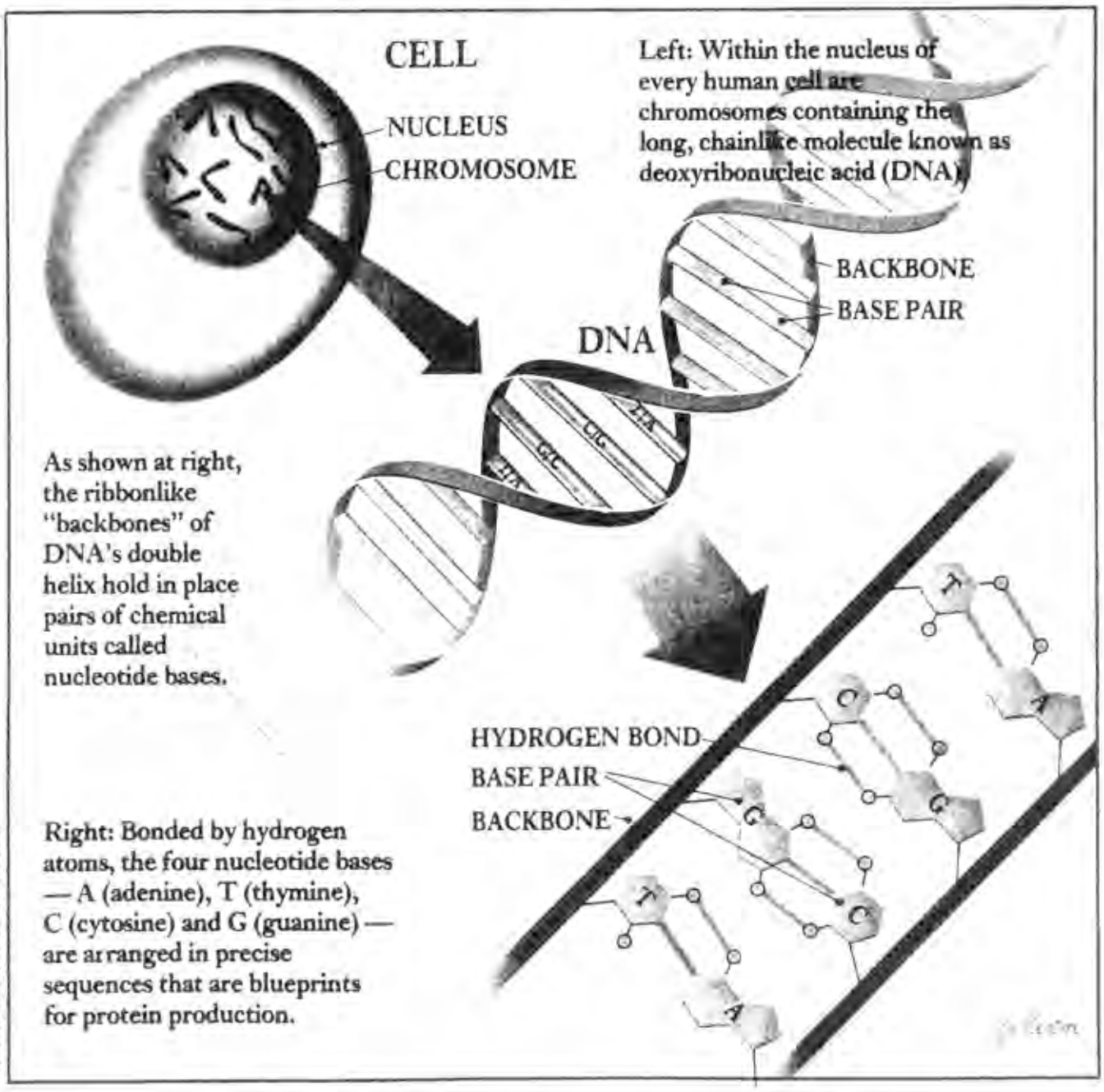
■ Prenatal screening. Old limitations of prenatal diagnosis are being overcome by new techniques that enable clinicians to analyze directly the genetic makeup of developing fetuses. By the late 1980's, experts predict, these methods will permit fetuses to be screened early in pregnancy for such lethal hereditary diseases as cystic fibrosis, muscular dystrophy and Huntington's chorea.

■ Therapy. Within the last year, doctors at the National Institutes of Health in Washington reported using a revolutionary gene therapy to ease the effects of two hereditary blood disorders, a historical first that suggests that the power to alter our biological destinies may be fast approaching.

■ Natural drugs. Genetic formulas are being used increasingly by the pharmaceutical industry to prepare potent natu-

UNSCRAMBLING THE GENETIC CODE

Man's 46 chromosomes contain an estimated 100,000 genes, each a different sequence of four chemical units. Scientists are now unraveling these sequences and tracking genes to their chromosomal locations at a rate of 200 per year.



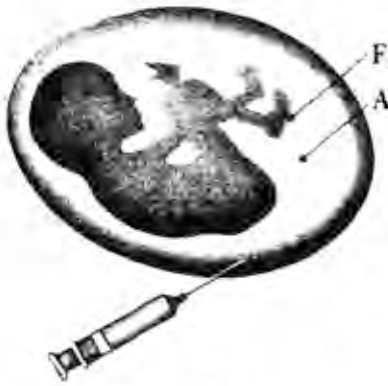
ILLUSTRATIONS BY GEORGE V. KELVIN

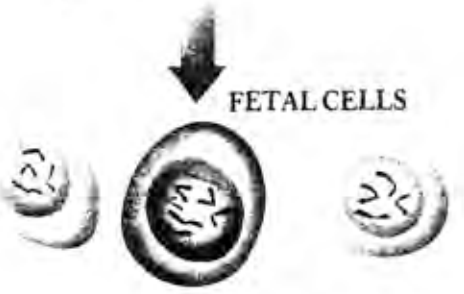
Above: This pair of human chromosomes is the largest in the body's cells and is magnified here more than 4,000 times.

TESTING FOR GENETIC DEFECTS

Sometimes 'misspellings' occur in the genetic code — an error creeps into the chemical sequence. Such defects can be inherited or caused by chemical change, and give rise to disease. Prenatal screening can find faulty genes and identify individuals likely to contract specific ailments.

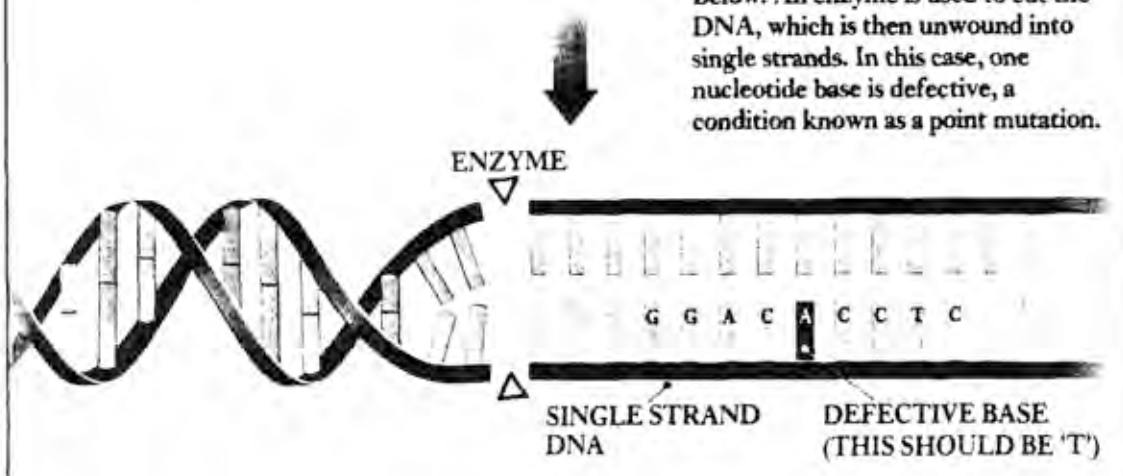
Right: In a prenatal test to determine the presence of the hereditary disease sickle-cell anemia, fetal cells are removed from the amniotic cavity through the process of amniocentesis.

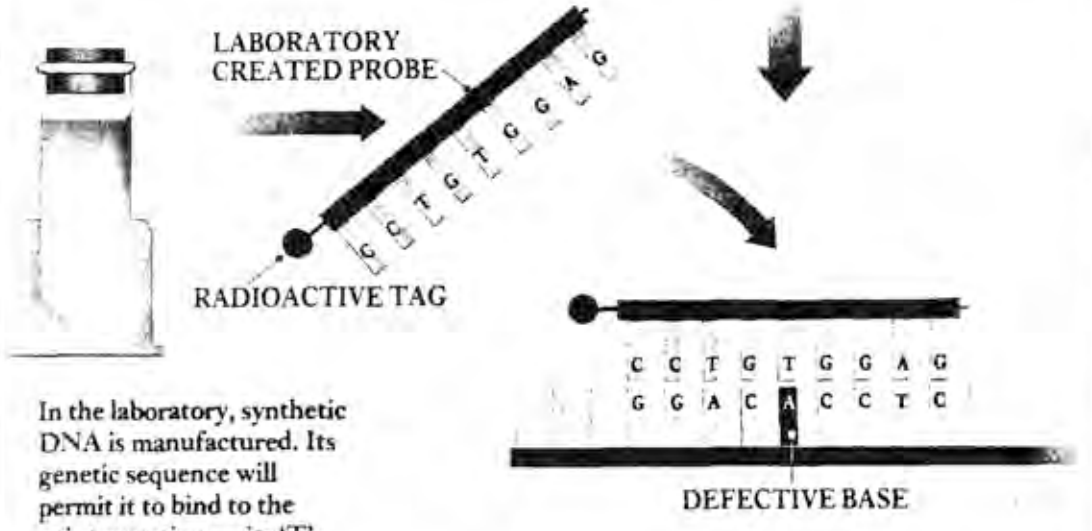




The DNA is removed from the fetal cell.

Below: An enzyme is used to cut the DNA, which is then unwound into single strands. In this case, one nucleotide base is defective, a condition known as a point mutation.





In the laboratory, synthetic DNA is manufactured. Its genetic sequence will permit it to bind to the point mutation — its 'T' with a defective 'A'. A radioactive tag is then attached to the probe.

The probe is mixed with the fetal DNA, and the radioactive tag enables scientists to detect whether the bases bond. In this case, they do, indicating the fetus does have the potential for developing the blood disease.

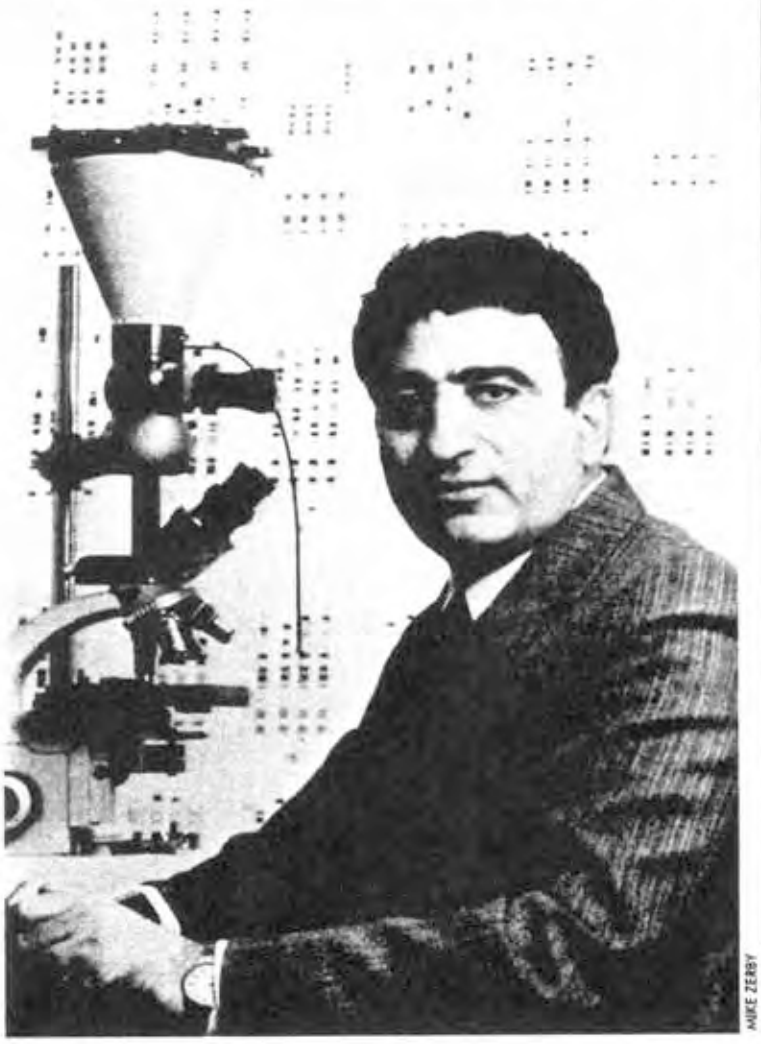
DR. GARY WISE, TEXAS COLLEGE OF OSTEOPATHIC MEDICINE

Normal human red-blood cells shown magnified in top photo are a startling contrast to blood cells deformed by sickle-cell anemia, above. Below: An automated synthesizer, known as a "gene machine," creates DNA from organic chemicals.

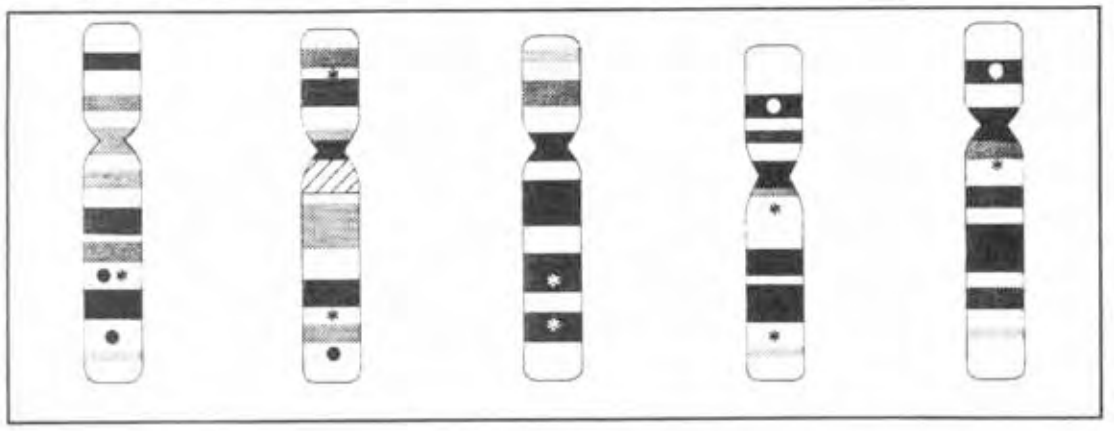
DOUGLAS KIRKLAND/SYGMA

PINPOINTING TROUBLE SPOTS

Most cancers are caused by a mixture of external and internal factors. It is thought that some individuals are born with a certain genetic predisposition to the disease.



Right: Dr. Jorge J. Yunis, a geneticist at the University of Minnesota Medical School, in front of a chart showing his findings regarding "brittle" DNA. Sites where chromosomes are fragile and easily broken (indicated by asterisks in the detail below) are often found in close proximity to cancer genes (dots).



ral medicines never before available for routine clinical use.

Along with the anticipated benefits, however, has come a barrage of worries and uncertainties, including the familiar questions about just where all the ground-breaking research is leading.

Of all the ethical dilemmas raised by genetic science, none is more pervasive than the public's fear that we may soon be tempted to "play God." Last June, a group of 64 religious leaders and several prominent scientists asked Congress to ban experiments that could alter man's inheritable traits. The question of when, or if, it is morally acceptable to modify human genes is certain to remain the focus of debate well into the next century.

Within medical circles, meanwhile, there is concern that people may come to expect too much too soon. Specialists point out that the age of genetic discovery is still in its infancy; major obstacles will have to be overcome before our newfound knowledge is translated into treatments and other useful applications. Others observe that advances in genetic science may tend to

AT THE CENTER OF ALL THESE advances and concerns is, of course, the long, chainlike molecule known as deoxyribonucleic acid (DNA), found bundled up inside each cell's chromosomes. The DNA chain is made up of chemical subunits, groups of atoms known as nucleotide bases. (See illustration on page 42.) A string of thousands or more of these comprises a gene. What matters about these nucleotide bases, it turns out, is their exact sequence along the "backbone" of the DNA molecule. The chemicals' arrangement can be likened to a genetic Morse code that uses four nucleotide bases — denoted by the letters A (adenine), T (thymine), C (cytosine) and G (guanine) — in place of dots and dashes. This simple alphabet spells out all the instructions the body needs for manufacturing proteins, the key administrators of the processes of life. Genes, by providing a blueprint for protein production, ultimately determine why a man is unlike a mouse or a moose or any other species on earth — and why an individual man or woman is unlike any other man or woman on earth.

Not long ago, the messages encoded in DNA were considered inscrutable. But the picture changed drastically when genetic engineering provided the instruments to dissect man's DNA. Using chemical catalysts known as enzymes to break molecular bonds and thereby cut the DNA into gene-sized segments, molecular biologists could begin to ascertain the order of the A's, T's, C's and G's — a process known as sequencing. And once deciphered, the formulas could be used to reconstruct genes synthetically in the laboratory from organic chemicals. From GenBank and other DNA repositories around the globe, researchers can now call up the recipes for dozens of vital body proteins. Then, by manufacturing the genes synthetically and splicing them into fast-growing bacteria cells, the scientists can induce the cells to churn out prodigious amounts of human chemicals.

The first genetically engineered protein, or natural drug, to reach the marketplace was Eli Lilly's human insulin, Humulin, introduced earlier this year. It will soon be followed by Genentech's human growth hormone for the treatment of hypopituitary dwarfism. In the next two years, still other drug manufacturers plan to market a blood-clotting factor for the treatment of hemophilia and the antiviral compound interferon, which may also be applied to certain cancers. Data banks also list the genetic codes for many other intriguing body and animal substances that may soon be targeted for commercial production. These include a dozen variants of interferon; encephalins, the brain's natural painkillers; key components of the body's immune system, and protein components of microorganisms that may be used in the manufacture of vaccines against hepatitis B, genital herpes, toxic shock syndrome and other microbial infections. But as Dr. Goad likes to point out, today's computerized catalogues offer only a glimpse of what is to come. Of the 50,000 proteins (exclusive of antibodies) synthesized by the body, less than 2 percent have been identified. As the sequencing of human genes progresses, it should be possible to grow many more rare proteins outside of the body and for the first time obtain large enough quantities to test their medical properties.

DNA SEQUENCING IS ALSO HELPING TO UNCOVER the underlying causes of many disorders, including diseases not normally thought of as hereditary because of their late onset. In this way, genetic data can enable doctors to identify individuals who are most likely to succumb to specific ailments.

For example, a team at the Baylor College of Medicine in Houston recently uncovered a mutation that can dramatically increase susceptibility to emphysema in adults. What prompted their search was an earlier epidemiological study that showed that people who develop emphysema often have insufficient amounts of a lung-protecting protein. Using radioactive probes, they were able to extract some of this protein from a patient's cell at a stage when it was still attached to the gene that controlled its production. Once the key gene was isolated, the sequence of its nucleotide bases could be determined, and, surprisingly, the patient's gene was found to differ from a normal one by only a single changed letter in the hereditary code. This abnormality, known as a point mutation, turns out to be most prevalent among people of

GENETICS

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population, it is estimated that one out of every 2,000 persons will be afflicted with emphysema, often dying within a few years after the first symptoms appear. An individual who knows he has the genetic abnormality can be extra cautious. The Baylor team leader, Savio Woo, says, "The onset of emphysema can be delayed by as much as 30 years if the person's condition is not irritated by cigarette smoke or polluted air."

More recently, Dr. Michael S. Brown and Dr. Joseph L. Goldstein, geneticists at the University of Texas Health Science Center in Dallas, used a similar approach to pinpoint several mutations that underlie one of the leading killers in the United States — hardening of the arteries, also known as arteriosclerosis.

"It's an insidious disease that begins in the teen-age years," says Dr. Brown, "but usually causes no symptoms until middle age, when heart attacks begin to occur." The faulty gene, present in one out of every 500 people, interferes with the normal cellular function of absorbing and breaking down excess cholesterol. In affected individuals, this substance builds up, clogging arteries and leading to premature death. When scientists learn how various mutations cause the malfunction, Dr. Brown is confident that much better treatments for arteriosclerosis will follow. "In fact," he says, "a drug is already being clinically tested."

Armed with genetic-engineering technology, medical researchers are also gaining insights into the deep-rooted causes of cancer. The kernels of the disease appear to lurk within us all, and normal cellular genes can quickly be changed into cancer-causing agents known as oncogenes (from the Greek word *onkos*, meaning mass). At least 18 oncogenes have already been discovered, but experts estimate that as many as 50 may underlie all the different forms of cancer.

Oncogenes are the result of alterations in DNA caused by radiation, chemicals, certain

viruses and other poorly understood factors. British and American studies published in the last few months suggest that at least two distinct oncogenes must become activated if cancer is to occur. Dr. Robert A. Weinberg at the Massachusetts Institute of Technology speculates that one oncogene stimulates a cell to grow indefinitely. A second acts to allow growth even though the cell's normal growth stimulus is lacking.

Exposure to chemicals or radiation is not, however, the whole story of cancer-producing genetic change. Dr. Jorge J. Yunis, a geneticist at the University of Minnesota Medical School in Minneapolis who has introduced innovative techniques for studying the detailed structure of chromosomes, reports that some individuals are born with "brittle" DNA. The molecules contain regions that are unstable and prone to breakage. If the fragile site is in the neighborhood of an oncogene, the person's risk of contracting cancer is probably heightened. Dr. Yunis has positively linked at least eight leukemias and non-Hodgkins lymphomas to brittle DNA. "In all likelihood," he says, "a combination of internal and external factors sets the stage for tumor formation. For example, the chemicals in tobacco frequently do damage to the short arm of chromosome number 3, so anyone with an inborn weakness in this area should stay away from cigarettes if they don't want to get lung cancer."

Along with academic institutions, many pharmaceutical companies and biotechnology firms are launching major research projects to pursue these findings. A common aim is to silence oncogenes by drugs or other means, or at least to deactivate the genes' protein products. Although no one expects to find any cures in the near future, there is widespread optimism that these quantum jumps in understanding the disease will speed progress toward the goal. "The discovery of oncogenes," declares Frank J. Rauscher Jr., senior vice president for research at the American Cancer Society, "is unquestionably the single greatest breakthrough in all our years of cancer research."

There is another group of genes that can bode ill. Found on chromosome number 6, these genes determine the precise configuration of the human leukocyte antigen (HLA) system — a chemical "fingerprint" etched on the outside of all the cells in the body. This molecular monogram permits the immune system to distinguish "self" from all foreign matter and was initially of greatest interest to transplant surgeons seeking to match the tissues of an organ donor with a recipient. But in recent years, immunologists have begun to discern a statistical correlation between genes in the HLA system and certain illnesses. For reasons that are still not entirely clear, the genes can sometimes be prognosticators of disease.

Take, for example, the HLA gene referred to as B-27. It is present in 95 percent of all people with ankylosing spondylitis, a chronic arthritis of the lower spine common in adult men. Roughly one in every four males with B-27 eventually develops back problems, ranging from minor aches and pains to full-blown symptoms of arthritis. Or consider the HLA D-7 gene. While it is represented in 15 percent of the normal population, it is found in almost 75 percent of the victims of multiple sclerosis. In addition, HLA genes have been more loosely associated with some 75 other disorders, including hay fever, lupus, juvenile onset diabetes and chronic active hepatitis.

Researchers stress that most of these correlations are too low to be of much predictive value. But as HLA data is added to our increasing knowledge of oncogenes, brittle DNA and other genetic abnormalities, science's ability to forecast the future may be greatly enhanced. It is likely that many more diseases will be detected earlier — or before they even arise. In fact, there no longer seem to be any insurmountable obstacles to screening fetuses for predilections of diseases that strike in early adulthood, or even later in life.

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The ability to spot health risks far in advance of symptoms represents the latest advance in genetic screening, a practice that got its biggest boost in the early 1970's with the introduction of amniocentesis. This technique, usually carried out in the fifth month of pregnancy, entails inserting a syringe into the mother's womb to withdraw fetal cells that have been shed into the amniotic fluid. These are then subjected to a battery of tests. Today, amniocentesis is frequently done in conjunction with ultrasonagraphy — a method of acquiring a description of the developing embryo by using sound waves. Together, these two approaches permit the detection of more than 190 chromosomal aberrations and hereditary disorders within the first 20 weeks of life.

As impressive as these advances have been, countless mutations continue to go undiagnosed in fetuses because they can be revealed only through a careful analysis of the finer structure of genes. In these cases it is not enough to run tests on the biochemical products manufactured by human cells, or to examine their chromosomes under a microscope — the standard procedures for detecting trouble. The majority of defects, in fact, are difficult or impossible to uncover unless the DNA itself is analyzed directly. It is in this area that recombinant DNA technology promises to make its greatest contribution to genetic screening.

At the City of Hope National Medical Center in Duarte, Calif., a research team is creating radioactive probes

made of synthetic DNA. These can bind themselves in a complementary fashion to DNA extracted from a donor's cells. If there is a point mutation in the donor's DNA (point mutations are those instances when only one letter of the genetic code has been altered), the radioactive probe will indicate an area of instability at that location. The researchers can then be certain that the mutation exists. (See the illustration on page 43.) Some half-dozen probes are now being applied in the prenatal diagnosis of sickle-cell anemia (a blood disorder that affects many blacks) and other inherited blood diseases, but this number is expected to double over the coming year. "As new genes are sequenced," says Dr. Brenda Conner, one of the scientists heading the hospital's new clinical program, "we can plug the information right in and use it to develop new screening tests." Not surprisingly, the investigators have recently made oncogenes the target of their probes.

Will it soon become commonplace to run everyone through a battery of these genetic tests? "No," says Dr. Conner. "Because only a small percentage of the population is at risk for any given disease, it just wouldn't be a cost-effective form of preventive medicine. But if familial history suggests that the illness could occur, then it is certainly worth the time and expense." The tests are currently available on an experimental basis. The price is about $1,050, or $300 on top of the $750 usually charged for amniocentesis.

Still other researchers are working on an alternative method of screening in families with a history of hereditary problems. When enzymes cut DNA into pieces, fragments called "variants" are often produced. These have been found to indicate the proximity of a defective gene and can be thought of as red flags, markers that signify trouble nearby. Within three to five years, authorities predict, they may be able to test for these markers and make prenatal diagnoses of Duchenne's muscular dystrophy (a wasting disease that afflicts thousands of American males), cystic fibrosis (the most common lethal hereditary disease), Huntington's chorea (a debilitating neurological syndrome) and hemophilia (the hereditary blood-clotting disorder).

"To detect every genetic disease known to mankind," says Dr. Arno G. Motulsky, director of the Center for Inherited Diseases at the University of Washington in Seattle, "it has been estimated that you would need around 400 variants randomly distributed throughout our chromosomes. The beauty of this strategy is that you don't have to know the nucleotide sequence of the defective gene. Once a marker is identified in an affected family, you should theoretically be able to diagnose the genetic disease, regardless of whether or not you understand what's gone awry in the hereditary code. That's a big leap forward."

Dr. Motulsky and others stress that research in this area is still at a preliminary stage; no one is about to go into a doctor's office for a complete genetic physical. Nonetheless, a Presidential ethics commission concluded last February that "genetic screening and counseling are certain to become major components in both public health and individual medical care" by the end of the century. In its report, the commission noted that a time "can already be envisioned" when all information about an individual's genetic constitution would be readily accessible. The report also urged the medical profession to get ready for a "huge demand" for screening tests to determine the future health of unborn children and to identify adults who are susceptible to disease or whose offspring may be. Dr. Motulsky says, "Diabetes, high blood pressure, allergies, peptic ulcers — these and many other diseases of middle life are now being found to have genetic determinants. By finding out what these are, we can begin to identify populations at much higher risk for various disorders, and then direct preventive measures at these people in a more concentrated way."

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Progress is inevitably accompanied by growing pains — and the development of genetic science is no exception. Because of our newfound ability to spot disease susceptibilities, screening has entered a murky realm governed by statistical probabilities. Not surprisingly, genetic counselors worry that their warnings of possible future diseases could be misconstrued as inevitable outcomes. If so, couples might perceive relatively minor risks to the fetus as grounds for abortion. Similarly, dietary changes, exercise and other preventive measures

might be abandoned on the assumption that it is futile to fight what is in the genetic cards, so to speak. The very latest scientific advances could be used to revive the ancient idea of inexorable human destiny.

Even more troublesome is the potential for outsiders to misuse genetic data. It is not inconceivable that insurance companies could demand such information in fixing a customer's premium rate. Likewise, prospective employers could use genetic screening as one means of selecting job applicants. According to a survey conducted in 1982 by the Government's Office of Technology Assessment (O.T.A.), half-a-dozen major corporations in the United States employ genetic testing to spot employees who are likely to react adversely to toxic substances in the work environment. In addition, another 59 companies report that they are considering adopting such a policy within the next five years.

Although this practice is still very limited, it has already engendered enormous controversy on two main battlefronts. First, the validity of the tests has been disputed, and, in fact, none evaluated by the O.T.A. meet established scientific criteria for routine use. Secondly, labor unions have voiced concern that industry, in the name of protecting the worker, will only succeed in creating a group of "genetically unemployed." They fear that corporations, rather than cleaning up the work place, will be able to shift the burden of blame and responsibility onto the worker by labeling him or her unfit.

Blue-collar laborers are not the only group who could find themselves denied work as a result of screening technology. The up-and-coming executive in a high-pressure business could be passed over for promotion if identified as someone likely to fall prey to coronary attacks at a young age. Because genes are unevenly distributed among people of different sex and ethnic origin, there is the additional worry that genetic testing could be used to discriminate against minorities. Although it appears that companies have so far tried to offer alternative work to those deemed at risk, there have been a few documented cases of women and blacks being refused jobs because of current thinking about hypersusceptibility.

"Unless applied with great care and sensitivity, genetic screening could be perceived

as a threat to the egalitarian ideals we cherish in a democracy," cautions Dr. Thomas H. Murray of the Hastings Center Institute of Society, Ethics and the Life Sciences. "Until now, it has been widely assumed that ability, effort and ambition are the three key ingredients for getting ahead in this country. So it's threatening to think that jobs and other rewards in society might depend on one's genetic fitness. After all, the one thing we can't alter about ourselves is our genes. If you're overweight you can diet. If you're a slow reader you can go to Evelyn Wood. But if you're genetically unqualified, effort can't make up the difference. Genetic screening types you in a way that is utterly outside your control. For that reason alone, it would be wise to proceed cautiously in this area."

At Yale University, Dr. Ruddle underscores still another reason to proceed with care. "Right now," he notes, "our diagnostic ability is outpacing our capacity to treat a whole range of conditions. So what good does it do to tell someone that they're susceptible to a serious disease that can neither be prevented nor cured? One might even argue that you were doing that individual more harm than good. Of course, this line of research should eventually lead to improved therapy, but until such time, there's apt to be an uncomfortable hiatus."

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Ironically, the much more futuristic technology of gene therapy poses, by comparison, only minor ethical dilemmas. Banner headlines notwithstanding, the first attempts at transplanting healthy genes to impaired human cells do not represent a radical departure from other therapeutic modalities. As Dr. Motulsky in Seattle points out: "So long as the patient's sex cells — eggs and sperm — are not modified, gene therapy is conceptually no different from other forms of medical intervention such as surgery or drugs, where the aim is simply to repair an abnormality. Only the individual being treated is actually affected by the manipulation — the genetic alteration will not be passed on to the next generation."

To date, corrective measures have been directed only at hereditary disorders that result from a defect in a single gene. This is as far as technical skills have progressed, and, even in this limited realm, immense obstacles remain to be hurdled.

The first clinical trials were undertaken in the summer of 1980 by Dr. Martin J. Cline, then head of the hematology and oncology division of the department of medicine at the University of California School of Medicine in Los Angeles. This early research was a failure on two counts: The patients showed no signs of improvement, and Dr. Cline was heavily censured for failing to get proper authorization for the experiment.

Dr. Cline's general research strategy, however, illustrates one approach to gene therapy that many scientists believe could eventually come into use. In Israel, Dr. Cline attempted to replace the defective genes carried by two victims of beta thalassemia, a painful and deforming hereditary blood disorder that usually kills its victims by early adulthood. Because red blood cells are manufactured in the bone marrow, his strategy was to remove this tissue from the patients' thighbones and treat the marrow cells in such a way as to induce them to incorporate copies of the normal gene for hemoglobin. This step completed, he reimplanted the marrow into the thighbones, where he hoped the healthy cells would replicate and replenish the blood supply.

By the following autumn, when the research was heavily publicized, it was clear that neither patient had been helped by the operation. Investigating the matter, both Dr. Cline's home institution and the National Institutes of Health (N.I.H.), the major funding body for biomedical research, deemed the trial premature in light of insufficient animal studies. Dr. Cline's punishment for his offense was severe: He remained at U.C.L.A., but lost his chairmanship and close to $200,000 in Federal research funding.

Even if Dr. Cline's approach eventually becomes successful, it will only be applicable to tissues that normally regenerate themselves — such as skin, blood and the lining of the intestinal tract. Otherwise, the genetically engineered cell will not be able to multiply within the body to supplant defective cells with healthy ones. The brain, for example, does not grow after birth, so this method offers little hope for victims of such neurological syndromes as Tay-Sachs disease and Huntington's chorea.

Ever since Dr. Cline was formally censured, no other

medical researchers have attempted human experiments that pick up where he left off. But that is not to imply that gene therapy has come to a standstill. In one recent clinical trial, a brand-new approach to the treatment of blood disorders yielded exciting results, demonstrating that genetic engineering has reached the bedside.

This latest effort marks a major divergence from treatments based on gene replacement. The strategy was inspired by the observation that the body carries a gene that triggers the production of fetal hemoglobin. The gene becomes dormant slightly before birth, when a second gene for the adult form of hemoglobin takes over its function. If the adult hemoglobin gene is faulty, it was reasoned, perhaps the fetal gene could be reactivated.

In the last few years, research has hinted that a drug called 5-azacytidine might be the secret to reawakening the long-dormant gene. The compound seems to keep DNA free of certain chemical groups that bind to the genetic material and prohibit gene expression. At N.I.H., a team of researchers led by Timothy J. Ley and Arthur W. Nienhuis decided to put the compound to the test, selecting three people with beta thalassemia and two with sickle-cell anemia for the first trial.

The result: The blood of all five patients showed a striking improvement over the course of the one-week therapy, with the beneficial effects sometimes lasting for up to a month. By stirring the fetal hemoglobin genes into action, red-blood-cell formation was enhanced and anemia reduced.

It is still too soon to say whether this simple, straightforward technique of gene manipulation will live up to its initial promise. Although none of the patients developed adverse side effects from the chemotherapy, researchers fear that prolonged treatment might heighten the risk of contracting cancer. While the ultimate value of this approach can only be ascertained with further tests, the preliminary results have been enthusiastically received by the medical profession.

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Almost everyone agrees that genetic surgery remains a distant prospect. Yet to a large number of clerical leaders and a handful of scientists, the possibility looms large enough on the horizon to pose a serious threat. Their fears about the present direction in which gene therapy is headed prompted them to endorse a recent resolution that calls upon Congress to prohibit changes in reproductive cells that control inheritance.

The rationale behind this action stems from the belief that gene therapy will ultimately lead to gene enhancement if the Government ever tolerates the modification of human eggs, sperm or embryos. The distinction between the correction and perfection of genetic traits can sometimes blur. Seeking the humane goal of eliminating disease and suffering, the argument goes, we nevertheless may soon find ourselves embarking on a eugenics program and irreversibly altering the human germline for generations to come. Moreover, the outcome of all this tinkering could be the transformation of man into an entirely new species, which may be — to quote the theological letter accompanying the resolution — "as different from Homo sapiens as we are to the higher apes."

Truth to tell, the rudimentary state of human gene therapy today could scarcely have inspired such a frightening scenario. A much more likely impetus behind the current movement for restrictive legislation is a series of trailblazing animal experiments. Late last year, in one of the most spectacular demonstrations to date, scientists succeeded in creating a group of giant animals. The "Mighty Mouse" experiment, as it was dubbed by the media, involved the injection of multiple copies of a rat growth-hormone gene into mouse embryos. Six of the resulting animals eventually grew into extremely large adults — some close to twice the size of a normal mouse. Furthermore, many of their descendants also grew into giants, showing that the foreign genes had been passed on.

At about the same time, another breakthrough was announced. By introducing new genetic information into insect embryos, a mutant population of adult fruit flies achieved the status of normality within a single generation. In this case, their eye color changed from abnormal brown to healthy red.

It is worth observing that the scientists who carried out these experiments were not attempting to lay the groundwork for gene therapy in man. Rather, they were interested in studying basic problems in biology. To the public, however, these genetic engineering feats are perceived as transferable to the human germline. If scientists can manufacture Mighty Mouse today, then why not Super Man tomorrow?

According to Yale's Dr. Ruddle, whose laboratory remains at the vanguard of gene-transfer research, the modification of animal embryos is far from a refined, carefully modulated process. Mice, for example, normally manufacture growth hormone in their pituitary gland. But in the genetically altered strain, the liver became the chief production site for the chemical. In addition, the gene implants are only successful in about one in every 20 embryos treated; the rest usually do not survive the microinjection.

"I can't see gene therapy being administered to human germ cells in the foreseeable future," says Dr. Ruddle. "For one thing, you'd have to select diseases which are sufficiently serious to warrant that kind of intervention. And probably the best way of handling those conditions would be to screen for the defect at the fetal stage and allow for elective abortion. So prenatal diagnosis will probably be the solution to those types of problems, especially when we have no guarantee that genetic therapy would actually succeed in correcting the abnormality."

As for going beyond gene therapy to the remodeling of man, most of the characteristics likely to be targeted for improvement — health, intelligence, longevity — are not controlled by a single gene. They result from the cumulative effect of dozens, hundreds or even thousands of genes interacting with the outside environment. The manipulation of such complex and poorly understood systems has yet to be broached in animal research, and may not be unraveled for many years to come.

Will we ever reach that level of technical expertise? And if so, will we seek to apply the technology to man? It is already clear that with every new insight into how we came to be, the skills for predicting and even altering certain aspects of our futures are likely to follow. As to the second question, that is more difficult to foresee. But as Dr. Ruddle and other scientists acknowledge, "Morality changes as the times change. What we deem unacceptable today could be embraced by generations in the future." ■