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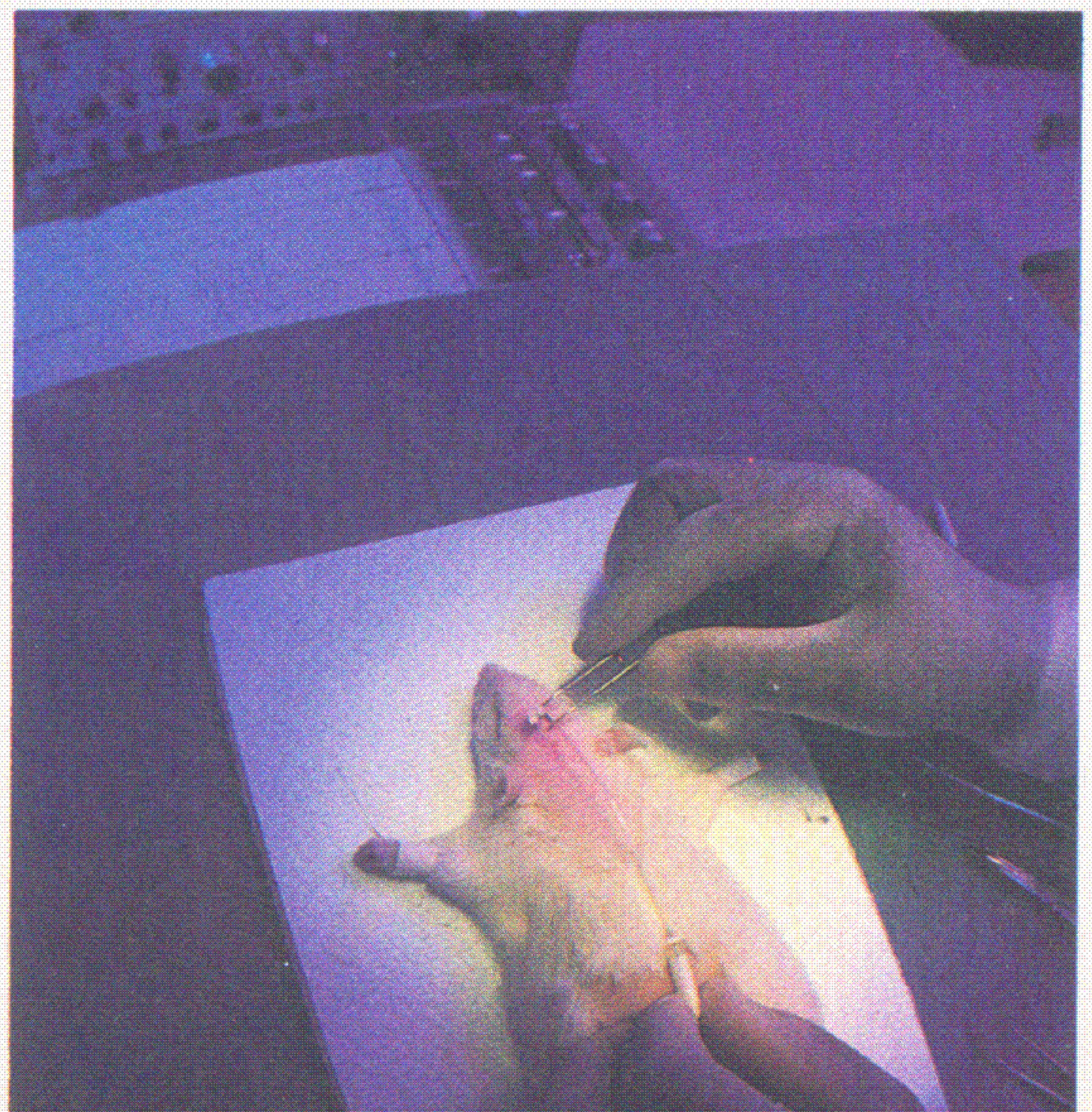
From a chilled beaker, a scientist clad in white gently spools spaghettilike threads of DNA onto a glass rod. He is about to treat it with enzymes that will clip away all but a chosen gene, then insert it into the genetic material of a bacterium called *Escherichia coli*, endowing the microbe with powers that nature never gave it.

Not long ago experiments with recombinant DNA stirred visions of strange, artificial diseases against which humanity would have no natural defense; such experiments provoked sharp controversy over whether scientists should be allowed to tamper with life itself. Today most of the fears have died down, and biotechnology is filling the heads of businessmen with visions of immense profits.

In the past ten years or so, dozens of new companies have begun to harness the life processes and put them to work in industry. Quietly, almost unnoticed in a world dazzled by innovative electronic products, these firms are fomenting a technological revolution that promises to shake the foundations of medicine, agriculture, food processing, energy production, and the chemical and pharmaceutical industries.

Already included among biotechnology's success stories are bacteria engineered to produce human insulin, drug-delivery systems that



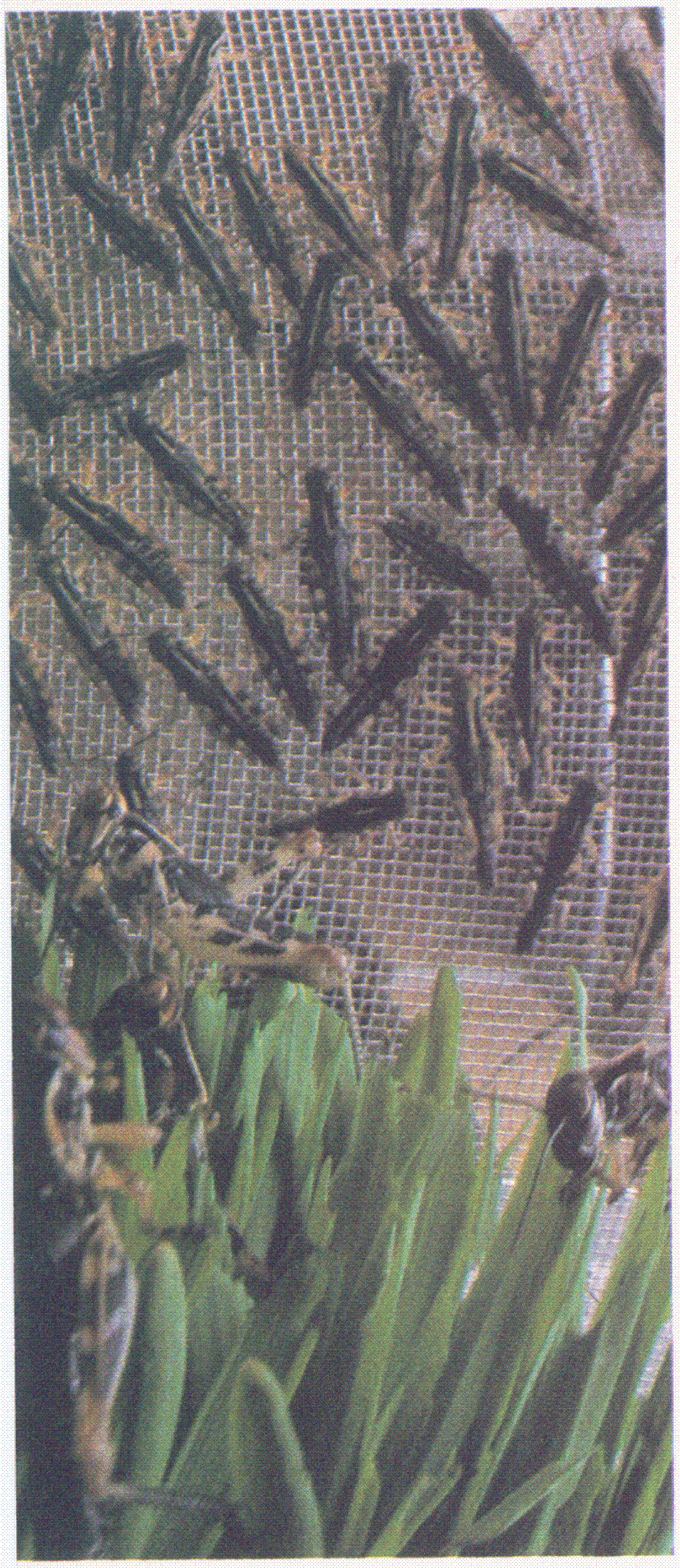
THE GENE TRUST

BY KATHLEEN AND SHARON McAULIFFE

Science and business join forces to exploit the machinery of life

PHOTOGRAPHS BY DOUGLAS KIRKLAND

At Cetus, a scientist tricks the cellular components of a frog's egg into synthesizing protein by injecting foreign genes (above); the artificial gland being implanted underneath the rat's skin is an Alza prototype for a drug-delivery system in humans (right).



To prevent grasshoppers from doing damage in their juvenile stage, Zoecon seeks to isolate a hormone antagonist that will accelerate insect metamorphosis (far left). Long, slender threads of DNA are spooled onto a glass rod (left) inside Cetus's containment facility, which protects the outside world from the living products of genetic engineering (below).

faced major problems in getting started.

"When we went out to sell our insights about molecular biology, we ran into brick walls," Cape says. "We were told we were dreamers. Now, eight years later, everybody's racing like hell to spend money in this area, and we're racing like hell to spend money faster to stay in the front line. It's difficult to believe how many people told us we didn't know what we were talking about."

One of Cetus's first goals is to develop a renewable energy source. With the world's oil supply dwindling rapidly, converting plant biomass into fuels and valuable chemicals is increasingly attractive. Sugarcane and sorghum, for example, trap up to 6 percent of the sun's energy that falls on their leaves. When these major food crops are harvested, however, millions of tons of bagasse, the leftover stalks, is thrown away. To convert this debris into ethanol for gasohol, Cetus intends to exploit the ravenous appetite of certain microorganisms.

"It's a coupling reaction," Cape explains. "The biomass becomes their food, and we use them as little chemical factories to convert it into alcohol."

The process now requires two kinds of microorganism: one that converts the cellulose in the biomass to glucose and another that turns the glucose into alcohol. Using recombinant-DNA technology, however, Cetus hopes to stitch the necessary genes from both microorganisms into one "superbug," which will perform the entire reaction.

MAN-MADE MICROBES

Although recombinant DNA enters into almost all research at Cetus, the company was not founded solely to exploit this technology. It was not until 1973, two years after Cetus was established, that Stanford University's Dr. Stanley Cohen and others began developing means to transplant genes from one microorganism to another. The original plan was to harness the astounding versatility of natural microbes, which had been all but ignored by commercial enterprises. The unexpected advent of recombinant-DNA techniques simply speeded their progress. Suddenly scientists could endow their "bugs" with entirely new abilities, tailoring them to fulfill industry's needs.

Within Cetus's eight buildings, dozens of breeds of bugs are rapidly multiplying. They may well become an indispensable work force in the future. Huge amounts of single-celled protein may be continuously harvested in one lab to provide livestock feed for countries that lack soybeans. Another microorganism can convert ethylene to ethylene glycol, a principal component of antifreeze. Recombinant-DNA technology may induce still other microbes to produce a sticky, jellylike substance that will coax oil in abandoned wells through the surrounding rock and up to the surface. (After a well has gone "dry," close to 60 percent of the oil may still remain in the ground.)

"We've devoted ourselves to trying to do things for industry that industry hasn't yet been doing for itself," says Cape, whose microbial army is set to make a wide range of chemical products—from plastics to fertilizers—now derived from oil and gasoline. Biological production would save energy, according to Cape, and would reduce pollution and lower the operating costs of traditional chemical synthesis.

One naturally occurring bacterium has already proved its cost-effectiveness in extracting valuable metals from low-grade or inaccessible ores. Mining companies in Canada, Australia, and the United States are investigating the possibility of using microbial processes to supplant conventional mining methods altogether.

Microbes hold even brighter promise for medicine. The body's most potent chemicals exist in minute quantities and are extremely difficult to extract and purify. The scarcity and exorbitant cost of these substances prevent their use by doctors.

Interferon, for example, has been available only to a handful of medical researchers. Even if it should prove to be a powerful weapon against cancer, as researchers suspect, who will benefit when its current price is $22 billion a pound? However, Cape is confident that genetically engineered microbes will solve this problem—and in the not-too-distant future. "I think we'll be getting useful amounts of interferon into people's hands within the next two or three years, at a much lower price than they have to pay now," he reports.

DNA FACTORIES

Although gene grafting was first carried out between breeds of bacteria, it soon proved possible between widely different organisms. When mammalian genes are spliced into bacterial hosts, these microscopic factories can be tricked into producing large quantities of natural body substances—hormones, enzymes, and antibodies—which are difficult or impossible to obtain synthetically.

For the pharmaceutical industry, this development marks the beginning of a new era, and Cetus is not alone in seeking to cash in on it. In South San Francisco, California, Genentech has announced the first synthesis of human hormones in recombinant bugs. A much smaller company than Cetus, Genentech has as its exclusive goal the commercial development of recombinant DNA. Starting with only $1 million in venture capital, president Robert Swanson was able to launch into business quickly by hiring researchers in universities and private institutions to take on projects for Genentech in their own laboratories. While hunting down scientists willing to do commercial work, Swanson met Herb Boyer, a biologist who has made some of the most important discoveries in recombinant-DNA research. The two readily formed a partnership.

The big payoff came scarcely a year later, when Genentech scientists, working with the City of Hope Medical Center in Los Angeles and Boyer's laboratory at the University of California, succeeded in coaxing a strain of *E. coli* to produce the brain hormone somatostatin. Genentech has patented the process, which is expected to lower somatostatin's price from $300,000 a gram to $300 a gram.

Following this breakthrough, Genentech announced two more genetic engineering feats: microbial production of insulin and, more recently, growth hormone, used to treat pituitary dwarfism in children.

From a commercial standpoint, insulin so far is Genentech's most spectacular success. The American insulin market is estimated at $137 million, 80 percent of which is controlled by the pharmaceutical house Eli Lilly. Genentech has signed a contract with Lilly to market human insulin. Most insulin is extracted from the pancreas of pigs and cattle, but one diabetic in 20 is allergic to the animal hormone. This new source will save the life of such patients.

While genetic engineers have been refining their methods in the last decade, other scientists have been finding new body chemicals that might revolutionize medical therapy. Particularly exciting are enkephalin and beta endorphin, opiatelike substances produced by the brain that emerged as powerful pain suppressants during recent clinical trials. Like interferon, these intriguing compounds have become a target for recombinant-DNA researchers at Cetus, Genentech, and elsewhere.

In the last year or so at least three more companies have entered the race to exploit genetic engineering: Bethesda Research Laboratory and Genex, both in Maryland, and Biogen, in Luxembourg. In addition, some larger and longer-established companies are now setting up their own research and development programs.

It will probably be several years before the products of genetic engineering reach the market. Once a discovery is patented, its manufacturer must test the product rigorously to meet the standards laid down

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by government watchdog agencies. In evaluating the first drugs ever obtained from recombinant bugs, the Food and Drug Administration is likely to be exceptionally cautious. This could mean five to ten years of testing and up to $50 million in costs before the product goes on the commercial market.

Yet industry on the whole has not tried to resist these precautions. Although most scientists now believe the potential hazards of recombinant-DNA research were grossly overestimated, public alarm over the safety of such research is a good enough reason for industry to regulate itself voluntarily. According to the Pharmaceutical Manufacturers Association, its half-dozen member firms engaged in recombinant-DNA work have all agreed to abide by the National Institutes of Health guidelines, which now apply only to nonindustrial research. The guidelines stipulate, among other things, that dangerous recombinant-DNA experiments be carried out in containment areas, the so-called P-4 facilities.

"Most people don't realize how conservative business is," says Byers, whose venture-capital firm has been closely watching ongoing developments. "The fear of liability is enormous. It could ruin a company overnight. So it is perfectly rational for businessmen to spend the money to ensure maximum safety."

GENE GAMBLING

Another way to mix the genes of different microorganisms—cell fusion—so far has escaped the controversy whirling around recombinant-DNA research. Cell fusion mates the unmatable, combining the cells of organisms that don't ordinarily breed. Cetus and some of the larger pharmaceutical companies are experimenting with the new technique.

"There are times when you simply want to play a crap game with the genes without being as directed as recombinant DNA is," Cape says. "In other words, just push all the genes in two different cells together and sort out what happens. It's a lot more efficient toward certain goals." Research contracts prohibited him from revealing what projects are under way at Cetus, but it was cell fusion that allowed Otis Godfrey, of Eli Lilly, to fuse two antibiotic-producing microorganisms last year. The result was a hybrid capable of synthesizing a new antibiotic unlike those of either parent strain.

Cell fusion is still in its infancy, but at least one innovation based on it has already been heralded as an advance no less important than recombinant-DNA technology. In 1975 Dr. Cesar Milstein and his colleagues at the Medical Research Council laboratory, in Cambridge, England, stumbled on a way to fuse a myeloma (skin cancer cell) with an antibody-producing white corpuscle. The result, called a hybridoma, began to turn out pure specific antibodies. Moreover, the relentless growth of the myeloma gave the hybrid cells virtual immortality.

Until Dr. Milstein's discovery, the only way to obtain antibodies was to trigger their production in laboratory animals. But harvesting antibodies from the animal's blood serum produces a mixture of antibodies in which some are more specifically directed against the intruder than others. Milstein's technique, however, enables scientists to separate out the hybridoma whose antibodies can distinguish the intruder from all other cells and then to mass-produce them by cloning. His research offers the long-sought "magic bullet" that will destroy viruses and cancer cells without damaging healthy tissue—the major drawback to the "shotgun" therapies now employed.

Hybritech, a year-old firm in La Jolla, California, is already producing antibodies using hybridoma. According to president Howard E. Greene, its early goal is to provide antibodies for clinical diagnostic tests, with a potential U.S. market of about $200 million a year. The company's first product, now being sold for experimental use, is a series of antibodies for detecting hepatitis B. Also under development are antibodies that will aid in the diagnosis of such hard-to-pin-down diseases as heart attack and cancer of the prostate and colon.

Diagnostic materials are less strictly regulated than drugs, and Hybritech plans to consolidate its earnings from test kits before expanding into therapeutics in about five years. The hope for the future is to inject antibodies directly into the body to cure numerous diseases ranging from hepatitis to influenza to cancer.

"Many scientists view cancer as occurring because the immune system can't recognize malignant cells," Greene says. "In other words, certain individuals may fail to generate antibodies against cancer." If hybridomas can be created from the white blood cells of people who can produce such antibodies, Greene says, "You ought to have one of the best possible forms of cancer therapy imaginable—one that's based on our natural defense mechanism."

NATURE'S BLUEPRINT

Genetic engineering and cell fusion are not all there is to the biotechnology revolution. The new life manipulators are developing many other exciting medical and industrial techniques modeled on nature's blueprint. At Alza Corporation, in Palo Alto, California, researchers are designing sophisticated drug-delivery systems that will help doctors use human insulin, the brain's opiates, and other body chemicals.

These substances are extremely powerful and, at high concentrations, can be toxic, even fatal. The problem is that after an injection or tablet, drug levels in the patient's body peak rapidly, then dwindle.

"I said, 'I'm not getting through to you, am I?' "

This fluctuation is a major cause of many dangerous drug side effects.

To prevent this, Alza is mimicking the endocrine system, where each gland secretes its hormones at a controlled rate, without unwanted side effects. Devices now under development deliver medication slowly and only where it's needed—in the eye, uterus, or circulatory system, for example. One mimics the pancreas, continuously releasing tiny amounts of insulin that can be fine-tuned to meet the diabetic's individual needs.

Alza recently received permission to market a three-year birth-control system in Mexico. Placed in the uterus, the device continuously releases progesterone, a natural birth-control hormone. Because the progesterone is released slowly, the device avoids the unwanted side effects of the Pill.

One of the most promising drug-delivery systems being tested at Alza is an "osmotic minipump," a capsulelike unit that can be implanted, injected, or swallowed. Activated by water, it can dispense several drugs at varying rates, either simultaneously or in succession. Eventually physicians will be able to make up a whole two-week drug program and install it in the patient. Such complex and reliable drug schedules will make many common medications much more effective.

"We are also talking of a sampling device, a sucking device," reports Dr. Alejandro Zaffaroni, the company's founder. Instead of dispensing medication, it would take repeated blood samples for up to two weeks or so, preserve them, and send them into a machine for analysis.

"I believe it will give a whole new dimension to medicine," Dr. Zaffaroni says. "Instead of analyzing just one blood or urine sample gathered during a physical exam, you'll get a complete picture of how the patient functions in his daily life. A person might, for example, seem to have normal blood pressure in the doctor's office, yet have episodes of very high blood pressure. That patient is at risk and should be considered for treatment."

Another Zaffaroni enterprise, Dynapol, is working to eliminate the possible hazards of food additives. In light of the recent saccharin scare and the dwindling list of food dyes now approved by the FDA, Dynapol set out to develop dyes, sweeteners, and preservatives that would not pass through the wall of the intestine and into the body.

Dynapol has found a way to leash small food-additive molecules to larger, indigestible polymers. The resulting macromolecules, unaffected by storage, cooking, and the digestive processes, will enter the market in 1981.

PETER PAN HORMONE

At Zoecon Corporation, another research program has led to the world's first commercial insect-growth regulator. Known as methoprene, it interrupts an insect's normal life cycle by blocking maturation. This regulator, a synthetic imitation of a natural insect hormone, is a most effective pesticide.

According to John Diekman, vice-president in charge of research and development at Zoecon, "Insects go through dramatic metamorphoses from wormlike larvae to hard-cased pupae and then on to the adult stage, with full wings. Zoecon and other university researchers set out to isolate the growth chemical turned on and off by the brain during this process."

The natural hormone had problems. It was not powerful or selective enough, it was too expensive, and because it was natural, it couldn't be patented. Zoecon overcame all these drawbacks by synthesizing a chemical that mimics it.

Methoprene works by keeping insects that are problems in the adult stage, such as mosquitoes and the hornfly (a major cattle pest), from fully maturing. It is completely unlike conventional pesticides. "We call them insect-growth regulators," Diekman explains, "because it's not a hard pesticide. If you spray it on a bug, the bug does not immediately drop dead. The methoprene affects the insect's hormone balance, and when the bug is ready to mature, it can't, and it dies."

> *The commercial development of modern biology really began only in the early Seventies. By the mid-Nineties, the applications will have proliferated in ways we just can't imagine.*

The insect-growth regulator is so unusual that Zoecon was one of the first firms Chinese scientists requested to visit when Henry Kissinger's exchange programs began. "I'm sure Kissinger and Nixon had no idea what the heck an insect-growth regulator was," Diekman comments.

Methoprene is now the safest pesticide available. It is biodegradable and nontoxic to other organisms. Indeed, it is so safe that it is fed directly to cattle. When consumed, it passes through the animal's digestive tract and comes out in the manure, where the flies breed. "Instead of going around the King Ranch and trying to spray every manure pile," Diekman says, "you can use the cattle as your applicators, and the maggots die in the manure."

Ironically, the product's safety became a real headache for Zoecon when the firm set out to obtain regulatory approval. The Environmental Protection Agency demands to know what happens if you overdose an animal on a pesticide. Zoecon's problem: Methoprene is so safe that an animal can't overdose.

Zoecon is trying to develop a juvenile hormone antagonist, methoprene's mirror image. Instead of retarding growth, this antagonist would accelerate it, turning insects that, as juveniles, cause tremendous crop damage prematurely into pupae.

Diekman says, "We don't think the Environmental Protection Agency creates incentives for the type of novel research we've done here, and we've been vocal about this. Dr. Carl Djerassi, our chairman, has met with all the important regulatory agencies. But we're tired of fighting. We'll continue to increase our budget for insect control, but we're faced with long lead times, heavy investment, and a moderate success rate." So Zoecon has decided to branch out into other biotechnologies.

Zoecon's long-term plan is to explore plant genetics. Using genetic engineering, Zoecon hopes to produce better plants, strains that are more disease- and insect-resistant, with higher yields. Researchers will attempt to do in the laboratory what takes years, or may even be impossible, using classical plant-breeding techniques.

THINKING BIG

The history of biotechnology, though short, is repeating the pattern of innovation in this country. Over and over again the trendsetters have been fledgling firms willing to risk their money. Dr. Cape says, "The large companies, with very few exceptions, have been caught flat-footed by these rapid developments in biology. The same was true for the semiconductor field.

"When new technologies come along, the people who should throw themselves in, hook, line, and sinker, don't. You would have imagined that Bell Laboratories, General Electric, and RCA would have jumped at the opportunities presented by transistor and semiconductor technology to become the big powers in the industry today. They're not. None of them are. Texas Instruments is, Motorola is, Fairchild is, Intel is, National Semiconductors is. They're the upstarts that came in to fill the vacuum."

Will Cetus, Genentech, Zoecon, and the other pioneers of biotechnology become the corporate giants of tomorrow? It is still too early to say. But the industry as a whole is entering a period of massive growth. Even its most optimistic proponents have been awestruck by how rapidly their dreams have been transformed into financially rewarding undertakings. Few people in industry remain unconvinced that there is big money to be made.

Biology's leap from academia to the commercial world may have come later than that of either physics or chemistry, but its impact on our lives promises to be just as far-reaching. In the next 20 years it will dramatically change everything from the practice of medicine to the world's supply of food and energy. We have only begun to unlock biology's secrets—the technology of life itself. OO