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BIOTECH COMES OF AGE

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HIGHLIGHT: MORE THAN 100 GENE-SPLICING COMPANIES LAUNCH A BARRAGE OF PRODUCTS

Just nine years ago, a worried group of U.S. and foreign scientists met at Asilomar, the conference center near Monterey, Calif., to decide whether altering living organisms was too perilous a research path for them to pursue. Never before had scientists felt the need to make such a decision, but researchers had for the first time moved a gene from one living organism to another. And the scientific community feared that further experimentation would be opening a Pandora's box -- deadly, artificially made organisms could escape from the laboratory, triggering worldwide epidemics. But after a heated three-day debate, the scientists decided to continue this work, although under strict safety guidelines: The potential benefits of recombinant DNA, or gene-splicing, were too great to ignore.

Their decision to go ahead has sparked a technological revolution that may rival even the development of the computer. From the beginning, the progress of gene-splicing has outdistanced even the most optimistic forecasts. No one could have suspected nine years ago that by 1984 an incredible $2.5 billion would have been invested in setting up more than 100 new companies dedicated to pioneering new products from biotechnology.

Clearly, those startup companies are now coming of age. Biotechnology sales are beginning to build fast, with some of the leaders even predicting billion-dollar annual revenues within the next few years. And five of the biotech startups (boxes) now dominate the business as well as the research -- not only in the U.S. but throughout the world.

IS IT REAL? The products of gene-splicing are beginning to hit the marketplace en masse. Diabetics are now treating themselves with human insulin that was produced by modified bacteria in fermentation vats rather than with animal insulin. The Food & Drug Administration is on the verge of approving the marketing of human growth hormone to counteract a deficiency that causes some children to become dwarfs. Nearing FDA approval, too, is alpha-type interferon for treating several kinds of cancer. Newborn calves are now being vaccinated against a fatal disease called scours. And greenhouses are being filled with new varieties of corn and tomatoes that are hardier and more nutritious because they were genetically modified.

"The fundamental question -- 'Is the technology real?' -- has been settled: There is no doubt gene-splicing can produce useful products," points out Janice M. LeCocq, a biotechnology analyst for Montgomery Securities in San Francisco. Most experts are now convinced that sales from biotechnology will increase dramatically over the next decade. Congress' Office of Technology Assessment (OTA), for example, predicts that sometime before the turn of the century, annual sales of chemicals and drugs that are produced by gene-splicing could top the $15 billion mark. And sales of products growing out of gene-splicing will come from virtually every area of manufacturing:

* Drugs. Gene-splicing is causing a fundamental shift in the research and development being done in the $15 billion pharmaceutical industry. Instead of testing one chemical after another to determine which would make a useful drug, scientists are identifying the substances that form the body's natural defenses so that manufacturers can turn them out commercially. Products with mysterious names -- interleukin-2, tissue plasminogen activator, and factor VIII -- are

beginning to move through the FDA's clinical testing procedures. Respectively, these chemicals help regulate the body's immune system, dissolve the blood clots in a heart-attack victim, and clot the blood of a hemophiliac.

A broad variety of faster, more accurate diagnostic tests is reaching the market, some for such difficult-to-diagnose diseases as prostate cancer. Less costly, more effective, and safer **vaccines** are being developed for diseases such as hepatitis B. A **vaccine** against herpes infections is being tested. Scientists believe they may even be able to cure such genetic diseases as sickle-cell anemia.

* Chemicals. Nearly $50 billion worth of products are sold annually by the chemical industry, and all but a tiny fraction are derived from oil. But many important chemicals could be made -- possibly more cheaply -- with the water-based chemistry of living organisms. For example, indigo dye is being made experimentally by inserting several genes from two different organisms into bacteria rather than using the synthetic chemistry that now produces the dye in commercial quantities. Even sugar-free soft drinks are being sweetened with the products of biotechnology. A key substance used to make G. D. Searle & Co.'s **aspartame** sweetener is being produced by genetically engineered bacterial enzymes. And experts believe that even high-volume chemical feedstocks such as ethylene -- which is used to make plastics -- could be made commercially with biotechnology.

* Agriculture. Growth hormone for cows, a future product that promises significant increases in milk production, is being field-tested by several companies. **Vaccines** for several animal diseases -- hoof and mouth, for example -- are under development. And bovine interferon is being tested on cattle as a means of preventing deadly "shipping" fever.

In plant genetics, scientists are now manipulating the genetic makeup of single plant cells so that they can then be grown into complete plants with new traits. Already researchers are developing new crop varieties that are resistant to herbicides, grow in drought conditions, or thrive in high-salinity soil. The chemical composition of plants is being modified, too, to improve their nutritional value. This could become a giant business. L. William Tewles, a Milwaukee agriculture consultant, predicts that the value of genetically manipulated seed for new plant varieties will grow from a mere $8 million predicted for 1985 to $6.8 billion by the year 2000.

This impressive list of new products is coming from an unlikely collection of startups, which have fostered an atmosphere that combines basic university research with the product-oriented R&D of industrial laboratories. The huge outpouring of money invested to date has built some of the best-equipped laboratories in the U.S. and has attracted a new breed of young, entrepreneurial scientists, who almost always own stock in their fledgling companies. They have swamped the U.S. Patent & Trademark Office in recent years with nearly 1,000 patent applications in biotechnology.

Such scientists have turned recombinant DNA technology from a scientific feat of the highest order into what is now almost a routine laboratory procedure. "The technology is becoming no more mysterious than any organic chemistry," says Jon P. Miller, director of the biotechnology research at SRI International. With highly specialized enzymes, researchers can snip individual genes out of the mass of DNA that controls the heredity of living organisms. Those genes, containing the code that directs biological processes, can then be implanted in other organisms -- such as bacteria. By growing those bacteria in vats, scientists can obtain large amounts of such things as hormones and enzymes that exist in minute quantities in the human body.

The amazing variety of products about to hit the market has now dispelled any notion that the forecast of a "biotechnology industry" is nothing more than a giant hype. It has also put to rest the widely held belief -- which swept through Wall Street in 1982 -- that biotechnology startups were headed for a catastrophic shakeout. While several of the companies brought in professional managers and sent their founder-scientists back to the lab, only 3 of the more than 100 small companies have actually failed. "Most companies are past the foundering stage," observes Geoffrey Karny, a lawyer who formerly watched biotechnology for Congress.

BLOCKBUSTERS? Most analysts now agree that the companies already in the field have sufficient capital to keep developing new products for years to come. "There is plenty of money around. Some companies don't have to have a product out for five years," says Nanette Newell, who directed for OTA a study of biotechnology that will soon be

published. And industry observers believe that some of the products now on their way to market -- such as gammatype interferon, a more promising interferon than the earlier alpha-type -- could be $1 billion-a-year blockbusters.

No more than a handful of these start-up companies, however, are expected to succeed in building the necessary marketing expertise and manufacturing capability to grow into major companies. But "very few" of them will disappear, predicts Nelson M. Schneider, a vice-president at E. F. Hutton & Co. who believes that as many as two-thirds of the biotechnology companies will merge together or be acquired by one of the drug or chemical manufacturers.

The first such acquisition took place in 1982, when Schering-Plough Corp. spent $29 million to buy DNAX Research Institute. The first biotechnology merger occurred last September when venture capitalist Frederick R. Adler combined troubled Bethesda Research Laboratories with Gibco Corp. to form a company called Life Technologies Inc.

One way the startups can remain independent and still gain access to marketing and manufacturing expertise that they lack is by forming joint ventures with large drug or chemical companies. "Companies need not go under if they play it right; all they need to do is find the right partner," says Zsolt Harsanyi, an E. F. Hutton vice-president who predicts that at least a dozen joint ventures will be formed this year. Almost all the startups licensed their first products to established companies to provide sufficient revenues to get them rolling.

Joint ventures, however, allow the small companies to retain a greater share of their revenues than does licensing. Genentech, for example, licensed its human insulin to Eli Lilly & Co., but it now has set up several joint ventures -- the most recent with Baxter Travenol Laboratories Inc. to develop diagnostic tests. And Collaborative Research Inc. is in the process of forming a joint venture with American Hospital Supply Corp. to develop, rnanufacture, and market medical diagnostic tests.

While the giants may make good partners for the startups, they are also becoming increasingly determined competitors. Although they have invested heavily in the new biotech businesses, the big companies have already spent more than $2 billion on biotech R&D in the past few years, and they are boosting the amount of this money that goes into their own R&D labs. This spending -- and the startups' success in making gene-splicing a routine procedure -- is starting to break the small companies' hammerlock on the technology.

Also helping to make it easier for the larger manufacturers to move into the startups' turf is the growing abundance of biotech-trained scientists. In fact, some observers predict that there will be a glut of these people because the startups have finished staffing their labs and are adding sales and marketing departments instead.

As a result, says SRI's Miller, "it's getting easier for companies not involved in biotechnology to recruit." And recruit they are: A recent issue of Science, a leading scientific journal, carried job offerings from such giants as Abbott Labs, Eli Lilly, Upjohn, Monsanto, Celanese, Du Pont, Bristol-Myers, and Allied. Most of these companies have stopped thinking of biotech as being too speculative for them. Now, says L. Patrick Gage, vice-president for biological R&D at Hoffmann-La Roche Inc., "It is risky not to be in the business."

Several drug and chemical companies already have research efforts under way that rival those of the largest biotech startups. Du Pont Co., for one, is exploring a broad range of projects from pharmaceuticals and improved plant varieties to pesticides and chemical feedstocks. Biotechnology accounts for "an ever bigger share" of Du Pont's R&D, says David D. Mooberry, group vice-president who heads the company's Biomedical Products Dept.

Du Pont's arch competitor is not far behind. "We see this as a direct part of our chemical activities," says Howard A. Schneiderman, Monsanto Co.'s senior vice-president for R&D. The St. Louis company has a portfolio of products that it expects to begin marketing by 1986. It is now completing a huge research lab in Chesterfield, Mo., that will house 1,000 scientists when it is going full tilt by the end of the year.

These chemical giants believe it will be easier for them than the startups to move new products out of the labs. They argue that many of the smaller companies will find it difficult to finance the cost of getting drugs through the

lengthy regulatory approval process. "This is not an easy marketplace to move towards," points out Ralph W. F. Hardy, director of life sciences in Du Pont's Central R&D Dept.

THE GIANTS' EDGE. Grafting a production line to their research labs also is a costly proposition for the startups. "You don't go into the fermentation business for under 40 million bucks," claims R. Anthony Laughrey, president of Cell Products Inc., which does fermentation work for other manufacturers.

Fermentation is something the large companies claim they know very well. "We've always been in these areas. We do them routinely," says David V. Milligan, divisional vice-president for R&D at Abbott Laboratories. Because the big companies have the production capability, says Cell Products' Laughrey, "they will be the ones that commercialize the technology, not the innovators."

Paralleling the growing role of the large companies is the declining role of venture capital in biotechnology. The big rash of startups seems to have passed. "The major players have already staked out the territory," figures C. Richard Kramlich, partner in New Enterprise Associates in San Francisco, which made its last investment in gene-splicing more than two years ago.

What little venture capital activity remains is being aimed at highly specialized companies. "You have to go out there [now] with a rifle, not a shotgun," says Robert F. Johnston, managing director of Johnston Associates Inc., who set up Genex Corp. "We would not dream of starting a company today as broad as Genex." Following his own advice, Johnston recently set up two new niche companies: Cytogen Corp., to commercialize tagged antibodies for cancer therapy, and Ecogen Inc., to develop new biological pesticides.

A CLOSED WINDOW. Wall Street's current lack of enthusiasm about almost any high-tech stock is also helping to cap the growth of biotech startups. Like most technology stocks, shares of the biotech companies began to fall sharply last summer and are now selling far below their yearly highs. As a result, some companies have shelved plans to go public. Venture capitalist Adler, for one, canceled an October stock offering of Life Technologies. "The public-offering window is closed," says George B. Rathman, president of Amgen, which went public in June at $18 a share only to see its price quickly fall to $6 a share.

But the initial outpouring of venture capital into startups has already made the U.S. far and away the world leader in gene-splicing. Biotechnology is certainly not a U.S. monopoly, however. Growing competition is coming from both Japan and Europe. In Japan, an estimated 160 companies spent more than $200 milllion last year in genesplicing research.

The Japanese are also buying gene-splicing technology from U.S. companies that are seeking an entree into the huge Japanese pharmaceutical market. U.S. companies already have signed about 15 technology-transfer agreements that give the Japanese marketing rights in return for royalties. For example, Shionogi & Co. is getting gamma-type interferon technology from Biogen. And two other Japanese companies, Toray Industries Inc. and Daiichi Seiyaku Co., contracted with Genentech to develop the same substance. Biogen also has licensed to Suntory Ltd. manufacturing rights for a pharmaceutical that might be used to destroy cancer tumor cells.

At the same time, U.S. companies are reaping some benefits from Japanese research. Schering-Plough has licensed gamma-type interferon technology from Suntory. Other U.S. companies are tapping into Japan for the expertise to grow bacteria -- a field in which some experts say the Japanese excel. "The lead [in fermentation] is shifting to Japan," wans Luther H. Smithson, senior health economist at SRI.

European companies are also trying hard to catch the U.S. in biotechnology. Even though European universities employ some of the world's leading biotechnology researchers, the lack of venture capital to form new companies has slowed the development of a local biotech industry. With the exception of a few large companies, Sweden's Novo Industri, for example, such work is being done by no more than a handful of new European companies.

But now the European governments are trying to close the gap. Britain's Trade & Industry Dept. is spending nearly

$17 million to help small companies move into biotechnology, and the country's industry and science agencies have dramatically stepped up their spending on biotech research. The French government is trying to create its own Silicon Valley by helping to set up high-tech companies near major academic centers. And West Germany will spend $25 million on this research, more than double its budget of two years ago.

STILL CONCERNED. In addition to this new competition developing offshore, U.S. biotech companies have at least two other problems to worry about. Although the scientists who met at Asilomar decided to plunge ahead with gene-splicing, there is still some concern that it could be hazardous. After lengthy congressional hearings last summer on the ethics of biotechnology, Representative Albert Gore Jr. (D-Tenn.) introduced a bill that would set up a 15-person federal advisory commission to monitor genetic experiments on humans.

Similar concern led author Jeremy Rifkin and several environmental groups to file a lawsuit last September against the National Institutes of Health's Recombinant DNA Advisory Committee, which was set up as result of the Asilomar meeting to insure the safety of gene-splicing research. They took that action because the committee had just approved an experiment by a University of California researcher that involved releasing modified bacteria into the environment. Rifkin calls such tests "ecological roulette." And industry, he says, "is talking about thousands and thousands of such experiments. All it takes," he says, "is for one of those experiments to go haywire."

While the first gene-splicing products are huge technological successes, they are not likely to transform startups into billion-dollar companies overnight. "The first products were teasers for investors," maintains Anthony J. Dennis, manager of medical and molecular biology at Battelle Memorial Institute. "They are not remarkably well thought out." Actually, many of the early development projects were simply experiments, undertaken by university scientists with no thought of the commercial potential. And some products -- such as interferon -- are reaching the market before their usefulness has been fully determined. To make matters worse, at least six companies are seeking FDA approval for interferon. This kind of heavy competition has been occurring across the board. "Everyone is going after exactly the same products," observes Milligan of Abbott Labs.

The upcoming wave of new products, however, is not going to have these kinds of problems, as far as the leading U.S. biotechnology companies are concerned. These aggressive startups are still confident that they will be around to reap the profits from their science. And despite the major corporations' massive move into biotechnology, the small companies are convinced that they will continue to attract the best of a new breed of entrepreneurial biologist. The startups also believe that they have barely begun to achieve what is possible with biotechnology. "We are in a race, and we feel the pressure," says Biogen Inc.'s president, Mark B. Skaletsky. "The key is the technology, and we will stay on the cutting edge."

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