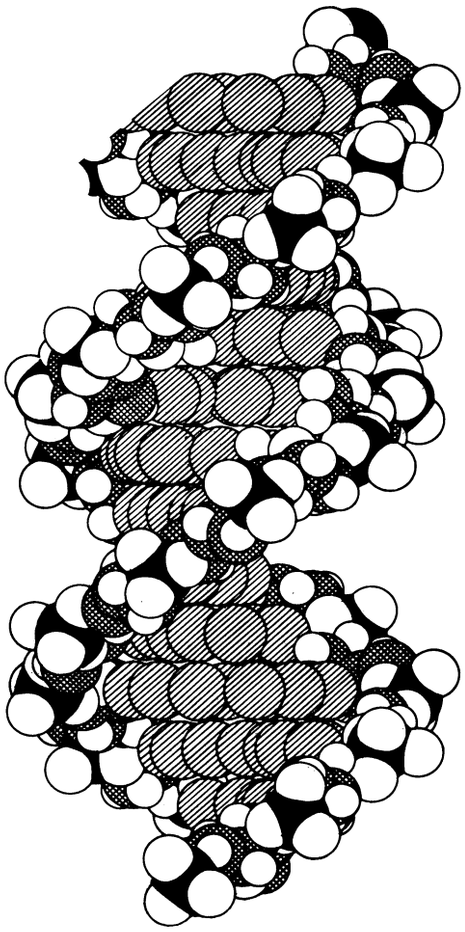
SPLICED GENES



Chemical and pharmaceutical industries are in a frenzy over the commercial possibilities of recombinant DNA technology

BY JULIE ANN MILLER

It's not often that a successful experiment in a molecular biology laboratory is reflected by a price change on Wall Street. Nor is it common for investors to telephone their brokers hoping to put money behind a biochemical technique. Yet that is what has been happening in the past few months as recombinant DNA technology, also called gene-splicing and genetic engineering, has attracted the attention of the business world.

"The technique probably can't do everything that is being suggested, but it sure as hell can do enough," says Nelson M. Schneider, a drug-industry analyst for the investment firm E. F. Hutton. Schneider has followed recombinant DNA developments for years and he says, "The most conservative realistic estimate of its potential is only totally mind boggling."

Applications of genetic engineering projected last year by the U.S. Congress's Office of Technology Assessment include ten categories with numerous subdivisions. Although the major achievements announced so far by laboratories are all in the area of pharmaceutical products, the OTA list includes manufactured and natural foods, scavengers of pollutants, concentrators of scarce materials and products from biomass.

Remodeling the genetic makeup of cells is the goal of the new technology. For more than a century, plant and animal breeders, as well as microbiologists, have used slower, less direct techniques to acquire organisms with commercially desirable traits. But they were limited to selecting among the traits naturally in a species' genetic repertoire. With the newer methods, in which scientists can directly insert DNA into living cells, they bypass that limitation. A bacterium, for example, may be provided with a gene that exists naturally only in yeast or rats or humans. The bacterium then will follow the foreign gene's instructions and produce a yeast, rat or human product.

Besides turning microorganisms into producers of commercially desirable substances, the gene-transfer technique may eventually introduce novel, useful characteristics into higher plants and animals. An obvious possibility, already the focus of much research, is a transfer of genes to allow plants that now require nitrogen fertilizer to "fix" nitrogen directly from the air. Another possibility is to improve the food value and increase the productivity of crop plants.

During the past four years, since the experiments that laid down the basics of the technique (SN: 3/20/76, p. 189), the research and development has spread, not always smoothly, from university labs to small private companies and finally into the giant corporations. The first company to spring up in response to the technique was the South San Francisco firm called Genentech. It started as a partnership between Herb Boyer, a scientist who had done important pioneering work on the recombinant DNA technique at the University of California Medical Center at San Francisco, and Robert Swanson, a businessman who was convinced early of the commercial value of the technique.

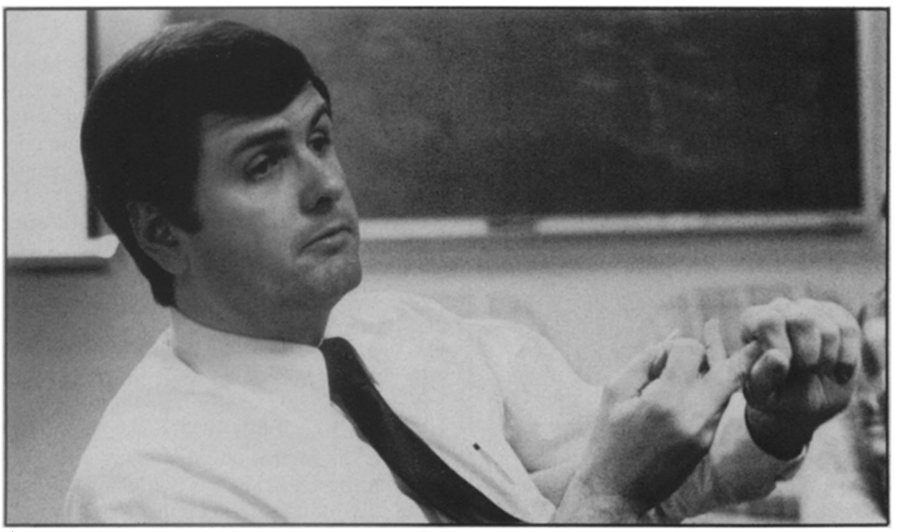
Many academic scientists greeted the Genentech venture with surprise and indignation; they were shocked that a member of their exclusive club would attempt so blatantly to turn scientific research into profit. In Genentech's earliest operation, before it established its own laboratory facilities, the firm funded research in university laboratories. The secrecy required for business success, to ensure potential patent rights (see box), raised resentment in Boyer's university department. Suspicion arose over exactly who had done what and with whose funding. One UCSF scientist bitterly termed the situation "the coming of age of molecular biology."

Ironically, those exact same words are used as a rallying cry by those committed to commercial application of the gene-splicing technology. To them, applying laboratory skills to creating new drugs and other valuable products is a humanitarian, as well as potentially lucrative, venture. "I think a lot of people here want to see the research applied to benefit other people very quickly," says Mike Ross, a young scientist at Genentech, which now has 70 employees, including 30 Ph.D.'s, in a continually expanding laboratory and pilot plant facility. Many technology observers believe that if development of gene-splicing were left to the universities, or the large drug companies for that matter, the fruits of recombinant DNA research might never reach the public marketplace.

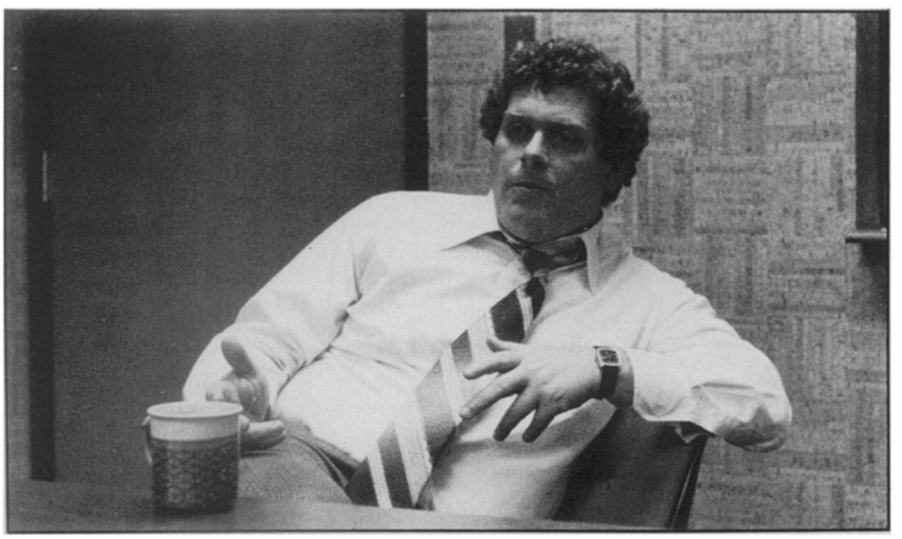
"All major new technologies have been promoted and fostered by small companies," says Hutton's Schneider. "The small guys only have the opportunity because the bigger guys ignore it. The big companies, the players in the market, can't see the forest for the trees. They choose not to participate because of their own ingrown bureaucracies."

These sentiments are echoed by the

GET DOWN TO BUSINESS



Byrnes of Genentech: Goal is to become fully integrated, independent company.



Farley of Cetus: There are few people in industry who can interpret science.

Ross of Genentech: Research applied to benefit other people very quickly.

Photos: J.A. Miller

businessmen of the small companies. Cetus Corp. in Berkeley has been applying molecular biology techniques to agricultural and industrial products for nine years. It now has more than 200 employees, 40 with Ph.D.s. Currently, almost half of its work involves recombinant DNA. Peter J. Farley, president of Cetus, calls the larger companies "entrenched" and "hidebound." "There are few people in industry who can interpret science," Farley says. "They have to read about it in the Wall Street Journal."

Today's small companies, of course, do not intend to remain fledglings forever. They have ambitions of their own. Farley says, "It's biology's turn now. We actually saw it coming, and we were determined right from the onset to become a major company. It's not a get-rich-quick scheme; we expect to be around 50 years from now as a major corporation." Similarly, Robert Byrnes, a vice president of Genentech, says their goal is to become a fully integrated, independent company including manufacture and marketing as well as research and development.

At least two other small companies have crystallized around the gene-splice technology. Biogen came to public attention last January when it announced the production in bacteria of a human interferon —a substance in great demand for clinical tests as an antiviral agent and as a cancer treatment (SN: 1/26/80, p. 52). Many groups have been attempting interferon production in bacteria, but Biogen was the first to claim success.

Biogen is the most international of the companies — it was incorporated in Luxembourg, has its headquarter laboratory in Geneva and also funds scientific work in university laboratories. Biogen's scientific board includes researchers from five countries (the laboratory that produced interferon is in Zurich). However, much of the financial backing for the company, which currently has 30 employees (18 Ph.D.s), comes from the United States and Canada.

The fourth company is firmly based in the United States, in Rockville, Md. Like Cetus, Genex is concentrating less on pharmaceuticals and more on using recombinant DNA techniques to benefit the chemical industry. Leslie Glick, president of Genex, believes that over the next several years it can develop new processes to sharply reduce manufacturing costs of widely used chemicals. Glick has analyzed the synthesis of various chemicals and has concluded that for about 40 percent ($12.4 billion in 1977 sales) of the organic chemical market, the potential impact of recombinant DNA technology is high and for

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more than 50 percent of the market it is moderate. Medicinal chemicals, flavor and perfume chemicals, cyclic intermediates and surface-active agents are included in the high potential impact group.

"The chemical industry is in for some shocks," says Cetus's Farley. And the others agree. Bacteria could be used to make new products or to make current products more cheaply — for instance, by providing crucial intermediates or enzymes for new production schemes. Those strategies have the advantage, well appreciated by Glick and Farley, that industrial operations could get underway without the long-term testing required for introducing a new drug. Some scientists working with recombinant DNA estimate that the technique, in the long run, will reduce capital, energy and related costs by 30 percent to 50 percent for manufacturing chemicals and pharmaceuticals.

While none of the successes of genetic engineering are yet on the market, some are nearing clinical trials. Genentech — and Eli Lilly & Co., with whom Genentech has contracted — are making large amounts of human insulin bacteria. Genentech also plans to set up a pilot plant in their laboratory and produce enough human growth hormone to meet the world's needs. Genentech recently requested permission from the NIH committee on recombinant DNA research to scale up production to 750 liters for several substances, including a newly achieved product called thymosin alpha-1 (SN: 3/15/80, p. 165). Thymosin alpha-1 seems to play a role in stimulating the body's immune response and as such may be an effective cancer therapy.

By now, the larger companies are not sitting by idly waiting for Cetus, Genentech, Genex and Biogen to revolutionize chemical and pharmaceutical production. Schneider reports a frenzy of industrial interest and action: "All over the place, companies are worried that they are not in it or that they are in it and they want to do more. No one is satisfied with their position. They're all worried about the competition."

Some of the industrial giants have teamed up with the small genetic engineering specialists through contracts on specific problems. Others are major investors in younger firms, and some even own portions of several of the genetic engineering ventures. Many large companies have begun their own recombinant DNA research groups. According to Schneider, the firms with active "in-house" genetic engineering teams include Du Pont, Dow Chemical, Monsanto, Exxon Chemical, Pfizer, Merck and Co., Eli Lilly & Co., Abbott Laboratories, Upjohn Co., General Electric Co. and Corning Glass Works.

Schneider sees recombinant DNA opening up areas of chemical production that had been fenced off by large firms through their huge investments. The gene-splicing technology could allow a newcomer to slip into business without putting up the money to directly compete with the giants. "Anything you look at in the area appears producible at lower cost," Schneider says. By selling a product more cheaply, a Johnny-come-lately taking advantage of the "technology margin" could leave the big companies with a white elephant of an operation, Schneider says.

Worry about competition from abroad, especially from Japan, is another element of the genetic engineering frenzy. Japan hasn't done much research on recombinant DNA, although Japanese investigators working in U.S. labs have contributed to key advances in the technique. However, a few months ago recombinant DNA research was added to Japan's list of national goals. And U.S. businessmen fear the worst. Although Japan may be well behind in experience in manipulating DNA, it is way ahead in the next industrial step — growing large volumes of productive microorganisms. Japanese industry uses large-scale fermentation in production of products ranging from soy sauce to vitamins. Schneider speculates, "Maybe the harder thing to do [in applying genetic engineering techniques] is to come up with production capability in fermentation."

In the midst of the frenzy, some skeptics still hold that the excitement is unfounded. Not a single product of recombinant DNA is on the market. Some large companies still hold back. But among those in the genetic engineering industry enthusiasm seems unbounded. The companies are expanding their laboratories, increasing their scientific staffs and taking on new projects. The results, Farley predicts, will "shake the pants off" the traditional chemical industry. □

Patent question moot?

Lawyers, as well as chemical manufacturers, are boning up on their biology as recombinant DNA patent applications stack up. Imagine a case in which the details of sophisticated laboratory procedures must be explained to a jury of postal clerks, nursery school teachers and housewives. That is just the situation the Young Lawyers Committee of the Bar Association of New York did imagine for its recent annual moot court competition. The committee jumped right into the biological entrepreneurial spirit by naming one company "En-Gen" (for Environmental Genetics), then got a bit carried away, naming the other company "MicroWonder" and a scientist Dr. Kevin Klone. Will En-Gen be allowed to cut into MicroWonder's market with an unpatented, three-plasmid bacterium that degrades oil and detergent? Or did MicroWonder sew up the market with its patent on bacteria having two or more plasmids for degrading oil? And can ordinary citizens, unschooled in clones and plasmids, make reasonable decisions on such technical cases?

So far in real life the judicial system lags behind the Young Lawyers Committee's imagination. The Supreme Court has not yet decided whether or not genetically engineered bacteria can be patented, let alone whether patenting a bacterium with two plasmids rules out marketing one with three. Although applications have been filed, no U.S. patents have yet been granted for recombinant DNA processes or products. Some of the decisions wait upon resolution of a case now before the Supreme Court that poses the question of whether a living organism can be patented at all (SN: 4/14/79, p. 248). If the Court decides that the answer is "no," however, the genetic engineering businesses will not be unduly disturbed.

One reason the patent decision may not be crucial to the fledgling industry is that many of the entrepreneurs favor the protective cloak of secrecy over patent protection. For instance, the bacteria that now are used to make antibiotics are not patented; they are kept under lock and key instead. Some industrial scientists working on recombinant DNA say they would never apply for a patent because in the process they would have to reveal too many trade secrets.

Another reason that the Supreme Court decision is not seriously worrying the genetic engineering entrepreneurs is that there is more to patent in that business than the living organisms. Nelson M. Schneider, investment analyst for E. F. Hutton, explains, "Processes and end products are patentable. There is no question of that." Peter J. Farley, president of Cetus, agrees: "There are process patents in the pharmaceutical industry with bugs [microorganisms] in them." Farley says that Cetus in its genetic engineering work that uses more traditional methods always tries to obtain a series of patents that "put a fence around an entire area." He expects the same strategy to work for recombinant DNA achievements.

In one situation, however, the Supreme Court decision will make a difference. That is where the product to be marketed is the "bug" itself. For example, if bacteria after a bit of genetic remodeling become able to leach valuable minerals from soil and rock, then the producers would want to sell those microorganisms to the mining concerns. "In that case the patent is probably very important," Schneider says. "Maybe a segment of the genetic engineering industry will ride or fall on the Court decision."