reissued with the Pasteur Institute as a co-holder, and asked for recognition that Montagnier's group was the first to discover the virus and apply for a patent. The Pasteur officials also demanded that a test kit produced by Genetic Systems Corporation in Seattle, Washington, under license to the institute, be allowed on the U.S. market without infringing the government's patent.

Federal officials have argued that the Pasteur Institute's test would be useless without a method for growing the virus in quantity. They have also maintained that the institute's application was flawed because it states that there is no immune response to the virus's envelope protein. The envelope protein is now known to be the most immunogenic viral antigen.

Negotiations have been proceeding ever since. According to James Swire, an attorney with the New York law firm Townley and Updike, which filed the suit on the Pasteur Institute's behalf, the U.S. government had agreed to recognize the French group as coinventors and said the Genetic Systems kit would be allowed on the U.S. market without the payment of royalties to the federal government.

However, according to Swire, the government was not prepared to share royalties with the Pasteur Institute. Caroline Chaine, a spokesperson for the institute, also says that the government officials imposed other conditions on the settlement that were unacceptable to the Pasteur Institute. She declined to discuss these conditions, however.

Pasteur officials thus decided to press their case with the U.S. Patent Office by requesting an "interference." This would require the government's patent to be withdrawn pending resolution of the institute's claims. In addition, they authorized the filing of the suit charging that Gallo's group broke a contract with the Pasteur Institute.

The charges in the suit center on a sample of the Pasteur Institute's viral isolate, which was sent by Montagnier to Gallo in September 1983. The suit contends that Gallo gained information from this virus that was useful in developing his antibody test, although he accepted the virus on condition that it be used for research only. The suit, in fact, strongly implies that Gallo grew the French virus in the cell line he used to mass-produce virus for the antibody test. The legal complaint states, for example, that the virus described in the U.S. patent "is, or is substantially identical to," the Pasteur Institute's virus.

Gallo has vigorously contested these charges. In a recent interview with *Science*, he said that Montagnier sent a sample of supernatant from his cell culture that contained very little virus. At no time did he receive a virus-producing cell line. Gallo and Popovic both say they could not get the virus to grow, and froze the material.

Gallo also argues that he had several isolates of his own before Montagnier's was sent. The Pasteur Institute's suit contends, however, that "as of December 1983, the scientists at NCI had not successfully isolated such virus." Asked the basis for that charge, Swire would only say "no claim with a specificity of that sort would have been made without a basis for it."

According to published research papers, Gallo's antibody test was developed from virus produced by a cell line infected with supernatant pooled from ten different patients. He later determined the genetic sequence of this virus. However, Gallo's group also infected cell lines with isolates from single patients, and data on some of these were included in the patent application.

Gallo contends that this should be conclusive proof that he did not deliberately grow the French virus. If he already had lines infected with other viruses, why would he do the sequencing and other analyses on virus from the line he is alleged to have infected with the French isolate?

Could the culture have been contaminated accidentally with the French virus? Gallo points out that the genetic sequence of virus growing in the line established from pooled isolates is not identical to that of the French virus, as the suit contends. They differ by about 1.5 percent, a disparity that Gallo says cannot be explained by changes in culture. However, the fact that the line was infected with multiple isolates complicates analyses of the genetics of the virus.

The lawsuit and the patent infringement are unlikely to be resolved for months. In the meantime, unless a settlement is reached quickly, research on both sides will be sidetracked by a convoluted process of legal discovery. One unfortunate result of the suit and the bitter dispute that preceded it is that scientific collaboration in research that is remotely linked to commercial application may be discouraged. ■ COLIN NORMAN

Biotech Market Changing Rapidly

A shakeout looms as investment wanes and cash reserves dip; delays, competition affect all but the fittest biotech ventures

AMID glowing forecasts of miracle drugs, super cows, and hardy high-yielding crops, investment in the infant biotechnology industry in the early 1980's began to mushroom—reaching $2.54 billion by mid-1985. The drive to sculpt new diagnostic tools, drugs, and plants with gene-splicing and cell fusion techniques has been propelled by scores of small companies. These new ventures were seen leading new-product development and spurring upheaval in old-line industries.

In the past 3 years, however, the dynamics of the biotechnology marketplace have changed dramatically. Products are taking longer and costing more to develop, and as a result new venture capital is more difficult to attract. At the same time that biotechnology ventures are striving to become more business-like, they are being battered by mounting domestic and international competitive pressures. Pharmaceutical and chemical companies like Eli Lilly and Monsanto are moving aggressively to position themselves in the biotechnology field.

By setting groups of talented scientists to work on specific problems, these specialized "biotechnology" companies were expected to overtake larger pharmaceutical and chemical houses in the race to produce revolutionary new products for health care and agriculture. The soothsayers have been partly right. Entrepreneurs are creating a host of medical tools to diagnose diseases such as acquired immune deficiency syndrome (AIDS), to treat cancer, and to enable children missing vital growth hormones to attain normal height. Says Stanley T. Crooke, president of research and development at Smith Kline & French Laboratories, "It is impossible to exaggerate the value of biotechnology in the preparation of novel therapeutics."

But what has proved a bit optimistic are predictions for quick exploitation of biotechnology. To date, few of these products

have actually reached medical suppliers' shelves or appeared in farmers' fields. "Some of these entrepreneurs hadn't thought through the sequence of events: to get the science into a product," says Gregory Lawless, a program director in Du Pont's biomedical products department. "Not only does that require a lot of money, but it requires a different set of skills than many of these companies have."

The falloff in new investment in the industry from its 1983 peak of $849.5 million to a projected $200 million this year is typical of a business cycle for a new industry. "Most investors now recognize that it is nothing but a tool to dissect biology," says Crooke. "Anyone who knew anything about it as early as 1976 could have predicted all that has happened." Investor enthusiasm, industry specialists note, has cooled in part because near-term profits—and in many instances products—for venture companies have proved to be elusive. Says Linda I. Miller, an analyst with Paine Webber, "All the elements are in place for a restructuring."

The effects of a shakeout could take years to comprehend because of the fragmented nature of the industry, which breaks down into three areas: human diagnostic and therapeutic drugs, process engineering and instrumentation, and agriculture/animal health. The investment and product timetable varies in each of these areas. In the case of human pharmaceuticals, diagnostics based on monoclonal assays are near-term products, while therapeutic drugs tied to recombinant DNA have longer development times. In agriculture, where plant genetic systems are more complex and less understood, altered microorganisms and animal pharmaceuticals are seen as the first revenue producers for companies.

"How everyone fits in the industry is going to be different. How it will fall out is uncertain," observes Miller. Government and industry analysts believe that a stronger, healthier industry will emerge from the consolidation. Still, Commerce Department and National Science Foundation officials worry that widespread upheaval could provide European and Japanese competitors with broader opportunities in the American market. Numbers of small American companies already have tapped overseas sources for financial support and these linkages are expected to grow.

Indeed, it is not clear that the major pharmaceutical houses and chemical companies in the United States will continue to dominate the industry. "In 15 years, if you look at the top dozen companies in biotechnology," predicts Scott R. King of Montgomery Securities, "half of them will be companies you never have heard of today. . . . There are some very interesting things happening with smaller, lesser known companies. Let's just say 'buyer beware'."

Companies like South San Francisco–based Genentech, Inc., and Cetus Corp. have made no secret of their strategies for becoming major-league players. They have attracted $320 million and $210 million, respectively, in investment capital and they generate sufficient revenues from product licensing, research contracts, and other sources to weather today's hostile environment. More important, both have streams of products—tissue plasminogen activator, interleukin-2, alpha interferon, and human growth hormone—that promise to ensure their futures. They also have begun building marketing forces as part of their drives to become fully integrated companies. Still, they will have to compete with domestic and overseas rivals.

Cotton plants

Researchers at Agricetus are trying to develop high-yielding, pest-resistant cotton plants.

Chemical and industrial firms, seeking to diversify or expand a limited presence in the biotechnology field, also are moving to challenge established pharmaceutical companies' markets. Says Michael A. Wall, chairman of Centocor, a small Pennsylvania-based company specializing in cardiovascular and cancer therapeutic and diagnostic products, "The fact that companies like Monsanto and Du Pont are coming into it would indicate that they think the Smith Kline & Frenches of this world do not really have the will to run with it," says Wall.

Whether major pharmaceutical companies are headed for a fall remains to be seen, but the emergence of so many independent biotechnology companies "is a very negative statement about the way the pharmaceutical industry is run," concedes Crooke of Smith Kline & French. These small venture companies " . . . did stimulate a measure of change in the pharmaceutical industry," he adds. But Crooke is not convinced that they can survive in the long run.

Most of the 300 biotech companies operating in the United States lack the economic strength to become industry giants. In fact many are experiencing economic stress now. The slump in investment comes at a bad time for many companies that are in the midst of costly clinical trials, field tests, and management shuffles to move their business emphasis away from science research to product production. Of the 60 or so publicly traded companies only 27 have been able to raise $4 million or more at one time in the past 5 years, says Kathy M. Behrens, an analyst with Robertson, Colman & Stephens of San Francisco. Funds invested in these companies alone, she says, account for $1.4 billion of the industry's total $2.54-billion capitalization.

The weakness of many of the industry's players also is illustrated by declining capital reserves. Of the $2.5 billion raised, Commerce officials say half has been spent. Behrens estimates that the actual cash holdings of 27 prominent companies have fallen from approximately $1.5 billion to $630 million. Of the funds in corporate treasuries, $394 million is held by just six companies: Genentech, Genetic Systems (estimate preceded Bristol-Myers' takeover bid), Cetus, Biogen, and Applied Biosystems.

Improved cash flows from biotech product revenues in 1986 and 1987 are not expected to be sufficient to supply the investment needed by the industry, says Paine Webber's Miller. Products like alpha interferon have great market potential, but their economic benefit to companies like Genentech and Biogen may be diluted by licensing pacts with major drug companies and future competition. Most receipts are derived from research contracts conducted for large pharmaceutical houses, chemical companies, or the federal government. Product sales in 1985 are estimated to account for only 25 percent of income.

When products reach the market, financial success is not assured. Although Genentech of South San Francisco has the lead on developing a clot-dissolving agent, tissue plasminogen activator, ten other domestic and foreign companies are developing variations of the therapeutic drug. Similarly, in the area of diagnostic tests based on monoclonal antibodies, eight or more companies are producing or developing kits to detect antibodies to HTLV-III, the AIDS virus.

In agriculture, product competition is less

severe but the risks may be even higher than producing human pharmaceuticals. Development times are longer and the economic value less than for human health-care products. "We have some short-term products, but we are not looking at them to make a living," says Winston J. Brill, vice president of Agricetus of Middleton, Wisconsin. "We are after major targets—corn, cotton, and soybeans." With the wave of such genetically enhanced plants not expected until the early to mid-1990's, research tends to be centered in fewer and larger companies.

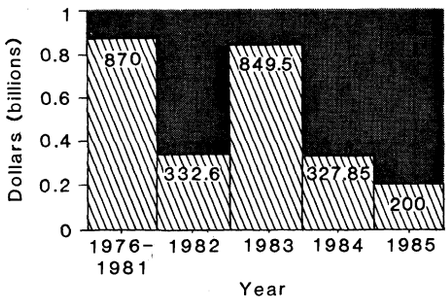
Few biotechnology companies can afford to develop a spectrum of diagnostic and therapeutic products, much less attempt to evolve into a full-fledged drug company. To stay "independent," they are either strengthening their alliances with major corporations, limiting the scope of their product activities, or serving increasingly as research boutiques. The alliance strategy, for example, has been adopted by Amgen, which is tying up with Johnson & Johnson, and by California Biotechnology, which is working with American Home Products and Eli Lilly. Behind these close relationships is the fact that corporate investments in public companies provided the bulk of new capital—an estimated $128 million—in the first 9 months of 1985, according to Behrens.

The danger of spreading oneself too thin also has been recognized by industry leaders. Genentech, which aims to become a major pharmaceutical house, has refrained from trying to produce and market its own diagnostic kits, industrial enzymes, and process instruments. Instead, it has opted to enter into joint ventures with Travenol Laboratories, Corning Glass, Hewlett-Packard, and other companies that carry out the manufacturing and marketing tasks. This has freed the company to concentrate on developing therapeutic drugs.

Similarly, Cetus has sold 51 percent of Agricetus, its agricultural research division, to W. R. Grace & Co. Weaker companies also are using such strategies to preserve cash, but long-term survival may require that even relatively strong biotech firms merge or deepen their financial ties with well-heeled drug and chemical giants.

"The big companies have something the little companies need: established marketing forces, experience with the FDA in getting things approved, and money," says analyst King. Even two relatively strong companies, Hybritech Inc. and Genetic Systems, Inc., weighing their long-term futures, have succumbed in the last 3 months to respective offers of more than $300 million from Eli Lilly and $294 million from Bristol-Myers, Inc. Not many biotech ventures have the scientific talent and pending products to command such prices. But for some trailing companies, the hefty cost of acquiring a Genetech or a Cetus could be a bargain.

Joseph Bouckaert, chairman of Advanced Genetic Sciences of Oakland, says that "For the industrial companies that have missed the train on the first stage . . . the only way to get hold of the technology for their own activities is to acquire them." Contract research agreements are only a stopgap measure and are not conducive to long-term strategies, pharmaceutical executives note. Hubert J. P. Schoemaker, president of Centocor, says time may have run out for building research teams within corporate structures. "The acquisition fever in these large companies will accelerate," he predicts.



Falling investment

The Commerce Department estimates that from 1976 through 1981 private investment in biotechnology totaled $870 million. The agency projects investment slipped to $200 million in calendar-year 1985.

To the extent that a takeover rush breaks out, American companies may find the bidding has an international flavor. "Growth in Japan and Europe is going to be very slow," says Crooke of Smith Kline. " . . . Access to the U.S. market is very important." Indeed, Commerce projects that domestic sales of biotechnology-based pharmaceutical and agricultural products could jump from $200 million in 1985 to $1.5 billion by 1990.

"The Europeans are scared to death they are going to be left behind in biotechnology, just as they were in computers," says Schoemaker. European investment in American biotechnology firms has been growing steadily and manifests itself in many ways. European companies like Ciba-Geigy have set up operating subsidiaries here; Boehringer Ingelheim International recently bought 5 percent of Genentech; and companies like West Germany's Hoechst are funding research foundations at prominent medical centers and universities. Similarly, some 28 Japanese companies, such as Mitsubishi, Green Cross, and Suntory own parts of small American biotechnology companies, or have joint-venture and licensing agreements with these companies.

But American companies also are a driving force in the internationalization of the industry. Observes Lawless of Du Pont, "You can fund research in Europe's university environments, its private institutions . . . The U.K. is a good example of where a lot of first-class work has gone on." Furthermore, access to European markets and operating subsidies also compel American companies to set up joint ventures, says Advanced Genetic Science's Bouckaert, whose company is building a production facility in the Netherlands. Other companies such as Molecular Genetics and Centocor are doing the same.

The influx of foreign money, however, bothers ranking officials at Commerce, the National Science Foundation, and the Office of Science and Technology Policy. They fear that years from now the United States could be left a giant research center for overseas manufacturers that capture the enhanced value of finished products. This concern is expected to be discussed soon before the White House domestic policy council, Commerce officials say.

Harvey Price, former director of the Industrial Biotechnology Association, says the government has reason to be concerned. "The U.S. has a lead, but it is a very fragile one. The fact is that there is a lot of scientific talent outside of the country." Price's view is shared by Centocor's Schoemaker, who sees the Japanese coming on strong. "I think the Americans are set up to lose. You have a one way flow of technology in that direction [Japan]." To protect themselves American companies need to strike up international alliances, "so if they succeed, you succeed," he says, noting that biotechnology will be a global industry.

Just how many merger opportunities really exist remains to be seen. "Most of the companies are vastly overpriced relative to their growth potential in the next couple of years," says Crooke. "I think it is possible to make radical changes in the pharmaceutical industry fairly rapidly and build a technical base [in-house]." Smith Kline's strategy has been to build from within, but he concedes "that situation may change tomorrow if we find a company that fits."

Takeovers of biotech firms, industry executives and analysts agree, will be done selectively based on acquisitions complementing corporate strategies. "Outright bankruptcy is not going to be that rare an event," says Montgomery Securities' King, noting that there may be as few as 20 attractive targets. Summing up the climate for takeovers, Du Pont's Lawless says, "Those that are shrewd, have good business judgment and put their bets down in the right place will win, whether they are Japanese, American, British, or whatever." ■ **MARK CRAWFORD**