Cloning Gold Rush Turns Basic Biology into Big Business

Cloning a gene can help raise $50 million for your company. Will the laboratory suffer?

The date on which molecular biology became big business was 16 January 1980. Reporters had been notified by telegram that a "major announcement" in molecular biology would be made by the company Biogen and two members of its scientific advisory board, Charles Weissman of the University of Zurich and Walter Gilbert of Harvard. The news delivered at the Boston Park Plaza Hotel was that Weissman had cloned and got expression of the human leucocyte interferon gene in biologically active form.

A major announcement in molecular biology this was not. For one thing, the cloning of human fibroblast interferon had already been achieved and published in a Japanese journal. Even the commercial significance of the news was far from clear. Biogen is only one of several competitors in the race to produce human interferon, a substance of possible though still unproven use in cancer therapy. As one Wall Street analyst, Scott King of F. Eberstadt and Co., advised his clients, Biogen's announcement "should not be interpreted to mean that it has any significant advantage in either technology or patent protection. Achieving expression of the [interferon] gene is only the first of many steps required to demonstrate a commercial process."

By all accounts, neither Weissman nor Gilbert exaggerated the significance of the news to the assembled reporters. Nonetheless, the mere context of the occasion, which linked the recombinant DNA technique with the possibility of manufacturing a promising anti-cancer drug, sufficed to produce a major impact on the public imagination and on Wall Street. The stock of Schering-Plough, which owns 16 percent of Biogen and rights to its interferon process, rose by 8 points, temporarily adding some $425 million to the paper value of the company's shares.

The purpose of the press conference, however, was not to help Schering-Plough but to help Biogen. Schering-Plough's purchase last year of 16 percent of Biogen for $8 million had set the company's paper value at $50 million. A few months before the January press conference, Biogen had decided to raise more capital on the basis of a self-assessed paper value of more than $100 million. Biogen president Robert Cawthorn says that the purpose of the press conference was not primarily to help raise more capital for the company. "The intent was to draw attention to Biogen. The day may come when we want to go public. So it is better that the public knows something about Biogen." But Cawthorn confirms that the company is looking for new investors, preferably those who are minded to stake at least $10 million apiece.

Molecular biology has come of age.

The sudden eagerness of investors to put money into genetic engineering has begun to reach the frenzy of a gold rush. "Every venture capitalist has looked at this—there are so many people out there it is like a bloody battlefield," notes one Wall Street analyst. The clearest manifestation of the cloning gold rush is that the paper value of the four most publicized gene splicing enterprises (Biogen, Cetus, Genentech, and Genex) has more than doubled in the last 6 months, to a total worth of over $500 million. Biogen is only following the general pattern. Yet none of the companies has so far brought any gene spliced product to market and it could be several years before any succeeds in doing so.

Every study of innovation upholds the transfer of knowledge from academy to industry as a socially laudable objective. The investment hoopla surrounding molecular biology is a sign of this process going with a swing. Nor is it immediately obvious why the transfer of this particular technology should present any special problems. But the possibility of certain growing pains in a basically healthy process is already evident.

One is the turbulence being caused in academe as large sums of money become available to a community of researchers that has not previously had to decide how to deal with the profit motive. Some welcome the development, others feel strongly that the business ethic is different from the scientific ethic and that basic research into molecular biology may be compromised by the subject's commercial exploitation. A danger of another sort lies in the possibly excessive expectations which now surround the field's commercial future. Even some of the gene splicing entrepreneurs agree that there has been a lot of hyperbole written about their activities, although all deny seeking publicity in order to raise money.

"There are millions of dollars floating around. If you claim you've done something fancy you can raise a lot of money," says a leading molecular biologist. "The question is, what will this do to the academic atmosphere?"

One fear is that it will reduce the ability of academics to provide independent

Biotechnology Survey

"Biotechnology is one of the biggest industrial opportunities of the late twentieth century," the London *Economist* opined last month. Corporate investors have become so enamored of recombinant DNA that the paper value of the four small enterprises that specialize in gene splicing has more than doubled in the last 6 months alone.

The commercialization of molecular biology is a fundamentally healthy process. But the recombinant DNA technique, promising as it is, seems on occasion in danger of being oversold. And some problems lie ahead for academic biologists as they work out the ground rules for assisting in the transfer of biotechnology to industry while preserving the university's role as a source of independent advice. The following articles consider the present stage in the evolution of the gene splicing industry, as well as the less publicized but probably more immediately significant technology of monoclonal antibodies.

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advice on controversial issues, a function of a university which may be no less important than its role in the transfer of knowledge. Stanley Cohen and Herbert Boyer, who hold the basic patent application on the recombinant DNA technique, have renounced all royalties they may receive if the patent is issued. One of his reasons, Cohen says, is that he was involved in the public debate about control of recombinant DNA research, and "the fact that I had already turned over all royalties to Stanford enabled me to speak out in ways which would not have been possible if my motives were being questioned."

Those within the community of molecular biologists are unlikely to question a colleague's position on an issue merely because he has some financial interest in it, but the wider public is more skeptical. In recent arguments before the Supreme Court on the patentability of genetically altered bacteria, Genentech cited a prominent molecular biologist in arguing that worries about the dangers of genetic engineering had all but disappeared. But the U.S. solicitor general in his reply brief contended that because of this researcher's involvement with a gene splicing company, "He is thus hardly an impartial observer in the debate over the biohazards associated with genetic engineering developments."

Another concern is that the direct involvement of academics in the commercialization of recombinant DNA will allow commercial interests to influence the goals and nature of academic research. "Just as war-related academic research compromised a generation of scientists, we must anticipate a similar demise in scientific integrity when corporate funds have an undue influence over academic research," Sheldon Krimsky of Tufts University has contended. Krimsky, a member of the NIH Recombinant DNA Advisory Committee, considers that for a researcher to be a principal in a company as well as an academic poses too great a conflict of interest in terms of dividing time and resources between university and company research.

Gilbert, who along with Herbert Boyer of the University of California, is one of the academic pioneers in the commercialization of gene splicing, sees in it an opportunity for rewriting the usual relationship between university and industry. In gene splicing, it is the academics who will be in control, if the Biogen model is successful. "Industry likes academics to be consultants. What we are seeing here is an attempt by academics to control the industrial development."

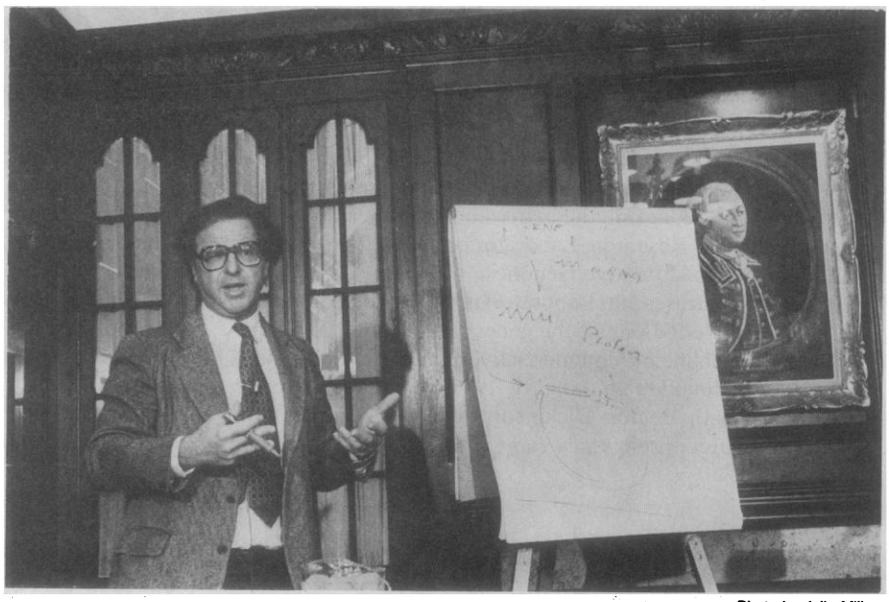

Photo by Julie Miller

Charles Weissman at Biogen's $50 million press conference.

Gilbert and the eight other members of Biogen's scientific advisory board, of which Gilbert is chairman, hold 15 percent of the company's stock with the option to increase their holding to 30 percent. The stock holding is worth only so much paper until the company goes public, unless a private market should develop, but the fact that the Biogen board members are presumably millionaires, even if only on paper, has excited an array of emotions, envy no doubt included, among those who feel equally well qualified. The issue is a matter of some sensitivity to Biogen's scientific principals. Gilbert, who was erroneously introduced to the NBC public by John Chancellor as a "recent millionaire," dismisses the paper value as a "crazy reflection of the way the company structure is controlled." The higher the paper value can be set, "the less control we have to give up to people buying into the company."

Biogen at present employs 16 scientists in an 8000-square foot laboratory in Geneva. Gilbert believes that the company's activities will eventually provide employment for hundreds, perhaps thousands, of scientists. The existence of the companies, the job market they create for postdoctorates, "is already changing people's attitudes," Gilbert observes. The friction being created in universities by the commercial exploitation of recombinant DNA is in his view a temporary phase: "In the short term there are stresses. We will go through these growing pains for 5 years or so, after which the pure and applied aspects of the field will be further apart."

Stanley Cohen is another who perceives a change in biological researchers' attitudes toward industry. "Five years ago, questions of patents and involvement in industry were often viewed in a negative light. But the whole view of the biological community towards industry has evolved over the past few years," Cohen says.

Whatever the reason for the new attitude, whether a conservative trend in the country at large, or biologists' sudden perception of the commercial opportunities opening up for their profession, the ground rules for researchers' involvement still remain to be defined in several areas. One is the release of information to the public. Both Genentech and Biogen have been criticized for announcing results at press conferences prior to their publication in the scientific literature. "Competition and the increasing involvement of academic scientists in the field of commercial application may be part of the problem. Free inquiry and the pressures of competition associated with the application of technology are not necessarily compatible," Stanford University science writer Spyros Andreopoulos complained in a recent article in the *New England Journal of Medicine*.

In practice, the traditional embargo on prepublication release is often honored in the breach. Genentech's cloning of somatostatin was announced before publication by the president of the National Academy of Sciences at a Senate committee hearing, perhaps to counter the committee's interest in an incident involving an infraction of the NIH gene splicing rules. Why shouldn't the companies also announce their results to serve their own purposes? Andreo-

Three New Entrants in Gene Splicing Derby

Three small companies which are already established in the biotechnology business have recently entered the gene splicing race alongside the better known contestants. They are Bethesda Research Laboratories, New England BioLabs, and Collaborative Genetics.

Bethesda Research Laboratories announced in March that it had cloned one of the genes involved in the biosynthesis of proline, a commercially significant amino acid. BRL was founded in January 1976 by Stephen Turner, formerly with Becton Dickinson, a medical supply firm. When restriction enzymes came into prominence, Turner wanted Becton Dickinson to produce them but, meeting with indifference, he decided to start his own company.

Photo by Witwicki

New England BioLabs with president Donald Comb (fourth from right, front row)

With $30,000 of his own money, Turner hired a technician, rented 1000 square feet in Rockville, Maryland, and went round the nearby campuses of NIH and Johns Hopkins selling restriction enzymes from an ice bucket.

By the end of 1976, he had sold $100,000 worth of restriction enzymes and had hired two more technicians. From that point the company has expanded with great rapidity. It now employs 150 people, including 35 Ph.D.'s, and has sales of more than $2.5 million.

Almost half of BRL's sales are still in restriction enzymes, but Turner is diversifying as fast as possible into other fields, chiefly the recombinant DNA and hybridoma technologies. Recombinant DNA projects include production of amino acids and cellulase. Peter Kretchmer, formerly of NIH, is joining BRL to head its new department of genetics. BRL has a scientific board that includes Jack G. Chirikjian of Georgetown University and others.

Turner's goal is to make his company the Sears Roebuck of molecular biology: "We are part of the flow of information and materials. Our mission is to supply the tools and techniques of molecular biology, wherever it may lead," he says. Turner considers that by making new techniques available as soon as they are developed, BRL can help shrink the lead time and break down the "feudalistic kind of structure" which makes it hard for those outside the elite institutions to get immediate access to what the front-runners are doing.

The current BRL catalog offers several hundred different products of relevance to molecular biology, including almost everything a cloner might desire, from restriction enzymes to plasmids and molecular linkers.

Almost 90 percent of BRL is owned by Turner and other principals of the company. The rest is owned by a small venture capital firm, New Enterprise Associates of Baltimore. Only recently has the company raised venture capital. "Having gone 4 years without outside capital means that you can bring it in on your own terms," Turner says.

New England BioLabs, of Beverly, Massachusetts, is also a producer of restriction enzymes. The company was founded in 1974 by Donald G. Comb, then at the Harvard Medical School, and is wholly owned by Comb and his wife. Sales last year were $3 million, Comb says.

New England BioLabs and Bethesda Research Laboratories dominate the restriction enzyme market. Each believes it has the larger share. On the basis of literature citations, New England BioLabs considers it commands 75 percent of the market, with BRL taking the rest. BRL, on the other hand, believes from questionnaires that it has 65 percent and its rival 25 percent. Whatever the exact shares, the two little companies seem to serve their market well enough to have kept bigger competitors out.

Comb says he is interested in keeping his company small—he has only 22 people, compared with BRL's 150—but has started to recruit cloners for a project to do with malaria.

New England BioLabs apparently has the distinction of being the first company to bring a recombinant DNA-made product to market, even if to a somewhat specialized group of consumers. Since 1975 the company has been selling DNA ligase from *Escherichia coli* produced from a gene cloned by Robert Lehman of Stanford. Three other recombinant DNA-made enzymes are featured in the company's catalog.

A third small company entering the gene splicing field is Collaborative Research of Waltham, Massachusetts. Founded in 1962, the company now employs 85 people and has sales of under $5 million, tissue culture being a major part of its business. In November last year, Collaborative Research president Orin Friedman set up a majority-owned subsidiary, Collaborative Genetics, which is focused on the manipulation of yeast, by gene splicing and other means, for energy transformation and industrial application.

Collaborative Genetic's advisory board includes David Baltimore and David Botstein of MIT, Ronald Davis of Stanford, and Gerald Fink of Cornell. "We have in fact cornered the market in yeast genetics," claims Friedman. Despite which, Friedman is highly guarded in his expectations of producing ethanol more efficiently from genetically engineered yeast. Much effort has been devoted to seeing how gene splicing might help to improve the venerable art of fermentation. But, says Friedman, "There are no obvious or simple ways in which the recombinant DNA technology can be applied to make major improvements in alcohol production by yeast."—NICHOLAS WADE

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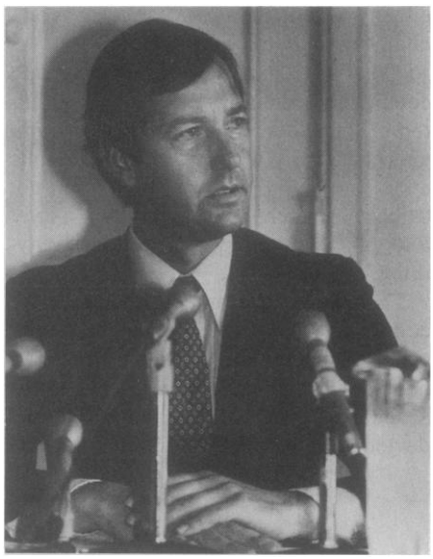
poulos's concern is that exaggerated claims made or implied at such press conferences cannot be checked out by reporters if the results are not generally available. Though this may be true, the press conferences given by the companies are only one among several ingredients that have contributed to the high expectations surrounding commercial gene splicing.

The business world was perhaps surprisingly late in awaking to the wonders of gene splicing, but has made up for its tardiness with enthusiasm. There are still remarkably few investment analysts who follow the field. Best known among them is Nelson Schneider of E. F. Hutton in Washington, D.C. A seminar arranged by Schneider in New York last September gave the financial world its first serious exposure to gene splicing. Investors' interest has been whetted by a series of articles in which Schneider's upbeat commentaries on the commercial future of gene splicing have been echoed, naturally enough, by the principals of the four best known gene splicing companies.

"Some people feel there has been a nationwide promotion campaign to benefit selected individuals and companies, that this is all a contrivance that will adulterate science. But this just isn't so," notes Fred Middleton, vice president of Genentech. Genuine public interest is the reason that so much has been written on the subject; as for Genentech, "We are trying to avoid overexposure at this point," Middleton states.

"I am the first one to say that the whole field has been subject to too much hype, particularly in relation to the business projects," observes Ronald Cape, chairman of Cetus. Yet the hyperbole, or enthusiasm, is part of the climate in which investment money is pouring into the four gene splicing companies. As one raises more capital, the others are forced to follow suit. "Now that everyone is spending money hand over fist, if we don't expand as fast as the other people, we will fall out of our position, and if we didn't have the big stockholders we have, we would have to say this is the end of the game," explains Cape.

Cetus, worth $100 million in November last year, is trying to raise another $55 million based on a paper value of $250 million. Its 1979 income, almost entirely from contract research, is said to be about $7 million. Genentech, worth $65 million 6 months ago, has not raised any capital since then, but claims its corporate worth now to exceed $100 million. Biogen has upped its valuation from $50 million to $100 million, and Genex has ascended from $9 million or so to a vaunted $75 million.



Stephen Turner, president of Bethesda Research Laboratories.

The first gene spliced products to reach the market are research enzymes, produced by New England BioLabs and Bethesda Research Laboratories (see p. 690). None of the four new companies yet has a marketable product and only Genentech has sought NIH permission to proceed to large-scale culture with a recombinant DNA project. Last month the NIH approved five such projects, concerning human growth hormone, somatostatin, the A and B chains of human insulin, human proinsulin, and thymosinalpha-1. By this criterion, Genentech is five necks ahead, but in a race that has a long way yet to go.

There is, of course, a solid basis for confidence in the commercial future of gene splicing, but some observers wonder if the present levels of expectation haven't gotten out of hand. The established pharmaceutical firm of Upjohn is worth about $1 billion yet Cetus is claiming to be worth $250 million, notes Charles Newhall of New Enterprise Associates in Baltimore: "That means Cetus is valued at one-quarter of Upjohn. What stream of products will come from Cetus that could justify that investment?" Newhall wonders.

Boosters of gene splicing often liken its golden future to that of the microelectronics industry. But in the world of bugs and chips there's many a slip twixt cup and lip. Analysts such as Schneider of E. F. Hutton and Daniel Adams, former head of the venture capital division of Inco, take the view that the corporations who are investing in the little gene splice companies are big enough to know what they are doing. "A company is worth whatever people are willing to pay for its stock, and more and more people are believing in the economic potential of the area," says Schneider. According to Adams, who had a major role in founding Biogen, "None of these companies is worth anything by conventional criteria because you can't put price/earning multiples on them, but a value of $50 million to $100 million is not excessive in that I think the value will ultimately be realized. The people who are paying these prices are not dumb. It is not a question of widows and orphans being taken to the cleaners."

Others are not so convinced that the corporations are that much less gullible than the widows. Says one Wall Street analyst, "People really don't understand anything at all about this field; all they want to know is how to invest in it." "These business people who come to my laboratory are not interested in the complications, they are interested only in the bottom line of what might happen. They want to be in on something that could be big, and it is worth it to them to risk $10 million," says a well-known molecular biologist.

Even the corporate players in the gene splicing game have doubts about some of the investments that other corporations are making. "Many corporations are looking into this area with some concern, because of fear that they are being passed by. There are some who are willing to pay almost anything to get into it and I think that is totally wrong," comments Donald Murfin, president of Lubrizol Enterprises, the venture capital division of Lubrizol. Lubrizol Enterprises now owns 25 percent of Genentech; it paid $10 million for 15 percent of the company last September, and recently bought out Inco's holding for $15 million.

Another interesting line of skepticism comes from the principals of several small companies which, with an established position in other areas of biotechnology, are now gearing up to join the gene splicing derby. Their criticism, though it is easy to see a motive behind it, is not without interest. The present funding levels of the four best publicized companies, says Orin Friedman, president of Collaborative Research of Boston, "have lost touch with reality." Friedman has recently set up a new company, Collaborative Genetics, to specialize in gene splicing applications, but in his view "The enormous publicity given to the commercial potential of recombinant DNA may be counterproductive because it is creating unreal expectations. I think

there are potentialities in the technology, but based on my experiences with other technologies, the gap between a laboratory process and reduction to commercial reality is going to take much longer than the impression created in the numerous articles about the subject," Friedman observes.

"Without the PR, there is no question that the high flying money perceives you as being of little value. But these paper valuations have a way of folding," notes Stephen Turner, president of Bethesda Research Laboratories. Turner raises the analogy of a chain letter, with the man in the street being the ultimate recipient when the gene splicing companies go public.

"That is 100 percent absolutely and completely ridiculous," says E. F. Hutton's Schneider. "None of these companies has any thought of going public and if they were we would tell them not to because there is no guarantee as yet that this technology will produce anything."

There is no guarantee either that the companies now developing particular gene splicing technologies will be able to hold onto their advantage. What if the academic research community should develop a general method for cloning and amply expressing the product of any known gene? With the basic technology available to all, the advantage might move away from the little companies, whose major asset is access to leading molecular biologists, and toward enterprises that either have large sales forces, as do the pharmaceutical companies, or possess advanced expertise in fermentation technology, as do the Japanese.

The cloning gold rush has entered an interesting but unpredictable phase. There is certainly gold to be found, but no one can be quite sure just how soon, or how easy it will be to protect whatever is struck.—NICHOLAS WADE

Hybridomas: A Potent New Biotechnology

A new biotechnology with far-reaching practical applications is about to make a major commercial impact.

Hybridoma technology was invented at about the same time as recombinant DNA but has grown up in its shadow. Yet the technique promises to revolutionize immunology and all the areas of research and medicine which immunology embraces.

Hybridomas are artificially created cells that produce pure or "monoclonal" antibodies. Having a constant and uniform source of pure antibody, instead of the usual mixture produced by the immune system, not only affords a powerful research tool but can be expected to provide quicker and more accurate diagnosis of viruses, bacteria, and cancer cells. The long-range promise of monoclonal anitbodies is that they will be therapeutically useful as vaccine replacements and in the treatment of cancers.

The hybridoma technique was invented in 1975 by Cesar Milstein and Georges Köhler working at the Medical Research Council's Laboratory of Molecular Biology in Cambridge, England. A mouse is injected with antigen and the antibody-making cells of its spleen are then fused in a test tube with a cancerous type of mouse cell known as a plasmacytoma. The hybrid cell so formed produces the single type of antibody molecule of its spleen cell parent and continually grows and divides, like its plasmacytoma cell parent. Once the clone of cells producing the desired antibody has been selected, it can be grown as a continuous cell line from which large amounts of the pure or monoclonal antibody can be harvested. The power of the method is that one or more specific antibodies can be developed against any organism or substance antigenic to the mouse. By contrast, the natural antibodies made against a given antigen are a mixed bag of molecules, with each type targeted against a different feature of the antigen. Monoclonally produced antibodies also have the virtue of consistency—each rabbit produces a different mix of antibodies against a given antigen—and their production costs are cheaper.

The vast promise of hybridoma technology has made it a field of active commercial interest. Industry investment in hybridoma research will amount to some $25 million in 1980 and the potential worldwide market for monoclonal antibodies will grow to more than $500 million by 1987, according to a recent estimate by Boston Biomedical Consultants.*

Pharmaceutical companies such as Eli Lilly and Hoffmann-La Roche have an active interest in hybridoma technology, and five small companies devoted exclusively to monoclonal antibodies have already been founded. Hybritech, of La Jolla, California, was founded in 1978, launched its first hybridoma product in December 1979 and now has three product lines on the market. With $2 million in venture capital, the company expects to expand its present staff of 52 people to 100 by the end of the year.

Another company, Centocor of Philadelphia, has a senior staff of 20, but doesn't expect to launch its first product until the end of next year. Centocor's interest is in applying the hybridoma and other technologies to four areas of diagnostics, those concerning tumors, liver, heart, and viruses. Set up in 1979 by Edwin Allen, formerly of Corning Medical and Instrumentation Laboratories, the company is funded by the Bank of Paris and Venroc, the Rockefeller family's venture capital firm. "We are part of the process of taking basic technology and converting it into useful products. But we are interested in stretching the technologies, so most of our projects are long term in nature," says Allen.

Centocor has ties with leading researchers in the field, particularly the Wistar Institute of Philadelphia. Institute director Hilary Koprowski is chairman of Centocor's board of scientific advisers. The company also has an exclusive license for two important hybridoma patents which were recently granted to the Wistar Institute.

Two other hybridoma ventures are Clonal Research of Newport Beach and Monoclonal Antibodies of Palo Alto, both founded in 1979. A European entry in the field is Sera Laboratories of Crawley Down, England.

Another small company that has entered the field is Bethesda Research Laboratories. Under Sudah Agarwald, ex-NIH, and Richard Farishian, formerly of the Wistar Institute, the company has developed several hybridoma product lines and some 30 more are planned.

Industrial activity in the field is so intense that many researchers have been drawn into it one way or another. According to Henry Weinert of Boston Biomedical Consultants, "Most experi-

*_Monoclonal Antibody Production_. February 1980. 298 p. Boston Biomedical Consultants, 55 William Street, Wellesley, Massachusetts 02181. $8,500.

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