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**BIOTECHNOLOGY
IN EUROPE AND ISRAEL**

an assessment report
by Claire E. Zomzely-Neurath

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This publication is approved for official dissemination of technical and scientific information of interest to the Defense research community and the scientific community at large

Commanding Officer CDR John P. Simpson, USN
 Scientific Director James E. Andrews
 Editor C.J. Fox

This special issue of ESNIB, devoted to a survey and assessment of Biotechnology in Europe and Israel, was written by Claire E. Zomzely-Neurath. Dr. Zomzely-Neurath is the Liaison Scientist for Biochemistry, Neurosciences, and Molecular Biology in Europe and the Middle East for the Office of Naval Research European Office. She is on leave until July 1989 from her position as Director of Research, the Queen's Medical Center, Honolulu, Hawaii, and Professor of Biochemistry, University of Hawaii School of Medicine.

BIOTECHNOLOGY IN EUROPE AND ISRAEL CLAIRE E. ZOMZELY-NEURATH

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FOREWORD

This report, "Biotechnology in Europe and Israel," includes a presentation of government and industrial support of research on biotechnology in Western as well as Eastern European countries. Most important is the coverage on biotechnology research by scientists in governmental, academic and some industrial organizations. In addition, the names and addresses of more than 900 scientists, most of whose work is mentioned in this report, are listed in Appendix B.

The information contained herein was obtained during my tenure as liaison scientist with the Office of Naval Research European Office (ONREUR). As liaison scientist, I visited universities and research institutes, and in some instances, industrial organizations, and met with scientists for discussion of their research work. It was not possible for me to visit facilities in the USSR or the Eastern European countries. However, information on biotechnology research in these countries was obtained from presentations at scientific meetings held in Western and, in some instances, Eastern European countries. Some of the material on Western European research included in this report was also obtained from attendance at scientific conferences.

Since modern biotechnology is multidisciplinary, research work in many areas such as biochemistry, molecular biology (including genetic engineering), immunology, microbiology, chemical engineering), etc. is covered in this report. Basic research is necessary for potential practical application to biotechnology. Such research presented in this report is of potential and, in many cases, direct relevance to applied biotechnology.

A wide range of biotechnology and biotechnology-related research is covered. I must emphasize that the ex-

tent of coverage of research carried out in a particular country is not necessarily related directly to the full amount of its research activity, but is to some extent, a reflection of the information available to me. Furthermore, it is much easier to cover research in a small country such as the Netherlands in a couple of liaison visits than in much larger countries as, for example, France or Germany.

Undoubtedly, there may be some omissions of research projects and of the scientists involved, but this was unavoidable since it was impossible, in a finite time period, to cover more than is presented in this report.

Immediately following this foreword is my assessment summary based on the information contained in this report as well as on discussions with scientists and government agencies in the various countries; it includes an assessment of the status of biotechnology in Europe and Israel in relation to the US and Japan as well as of the areas of future emphasis in biotechnology. A list of my publications for ONREUR is given in Appendix A.

I would like to add that I was impressed by the level of biotechnology research in Europe, particularly when one realizes that at the end of World War II, Europe had to essentially start anew in research due to the devastating effects of the war on the civilian population as well as the cities of Europe. Fortunately, the US was instrumental in helping many universities get started again in their research activities. I found that most of the scientists were very appreciative of the help given by the US. Perhaps with the new policies of the USSR under Gorbachev, the USSR as well as the Eastern European countries will, hopefully, in the future, become partners in scientific exchange with Western Europe and the US.

ACKNOWLEDGEMENT

Sincere thank you to Mr. C.J. Fox, ONREUR Editor, and to Mrs. Bessie Thompson, ONREUR Editorial Assistant, for their assistance in preparing this document.

ASSESSMENT SUMMARY

The US is widely acknowledged to be the world leader in biotechnology, its superiority being founded upon a fast-moving intellectual base which has been able rapidly to translate its finding into the commercial market place. Its intellectual superiority probably stemmed from the catalysis provided by federal funding for basic medical and biological research, and above all for cancer research. The US leads the world in the fields of genetic engineering, immunology, and molecular biology. Where the US succeeds so well is in translating this intellectual base into commercial practice. This has created a new breed of intellectual entrepreneur who combines dynamism with drive and flexibility. However, pharmaceutical and agricultural applications are predominant with a relative lack of attention to the commodity chemicals and energy and food processing sectors. This is in contrast to Japan where the major emphasis comes from these two sectors.

The second ranking country worldwide in biotechnology is Japan. Unlike the US, Japan's strength in biotechnology lies in the fermentation industry, and it is the large corporations who are developing and exploiting these strengths rather than small companies. Even before World War II, Japan was producing various organic acids via fermentation. In the postwar period, these strengths led to Japan's becoming one of the world's major producers of antibiotics (Japan supplies 60 percent of the world's antibiotics today), to the bulk production via fermentation of glutamic acid and Japanese dominance of the amino acid market. Most important of all, perhaps, was the early application of immobilized enzyme techniques. Japan was the first country to make industrial use of the technique for the production of amino acids and high fructose corn syrup. Although by the end of the 1970's, Japan lagged some 5 to 6 years behind the US in recombinant DNA and cell fusion techniques, it has made a determined effort since then to catch up — a process involving a major government/industry research effort, link-ups between Japanese and American companies, and a substantial program of training doctoral and postdoctoral fellows abroad, mainly in the US. An extensive funding program of research and development was instituted by the government in 1981 in the following areas of interest: bioreactor development, recombinant DNA (particularly its application to industrial processes), and large-scale cell culture. Japan's real strength, however, lies in its company sector, both in the number of companies showing awareness of an involvement in biotech-

nological activities and the resources they are devoting to R&D in this area.

The pattern of biotechnology development in Europe is somewhat closer to the Japanese than the American experience. Although substantial differences exist between European countries, in general, it has been governments and large corporations who are providing the lead, the small "start-up" company playing a very small part. Like Japan, Europe also had traditional fermentation interests and, in West Germany at least, this led to early involvement in enzyme immobilization techniques and considerable interest in bioreactor development. Unlike Japan, Europe has also a very strong pharmaceutical industry, built initially upon the chemical expertise of Germany and Switzerland, but the postwar advent of penicillins shifted the focus of drug development and opened the door to US multinationals.

Looking at Europe as a whole, therefore, the intellectual base for biotechnology is strong and there are plenty of firms capable of developing the technology.

West Germany

The Federal Republic of Germany (West Germany) is considered to be the leading European country in biotechnology, followed by the UK and France. The German intellectual domination of chemistry and chemical engineering since the mid-nineteenth century gave it a natural entrée into biotechnology. Its strength and the excellence of its chemical and pharmaceutical industries has always lain not only in the pursuit of knowledge for its own sake, but in the practical application of that knowledge. A major feature of German industry is the presence on boards of directors of professors from the universities and Technische Hochschule (technical universities) with many of them holding joint appointments in the firm and university. Close linkage is also maintained with the countrywide network of research institutes.

One of Europe's largest spenders on biotechnology, West Germany has major public expenditures by both central (\$700 million over 5 years) and regional governments. Thus, with strong government support to stimulate research and start-up activities, a well-established global industrial infrastructure, and a world-class research base, West Germany has many of the key elements important to becoming a significant competitor in the commercialization of biotechnology.

Since 1981, nearly a dozen new biotechnology companies have sprung up in West Germany. Although this

number is small in comparison to the number of startups in the US and UK, it is nevertheless a significant achievement, since establishing a new high-technology venture in West Germany is not a simple matter.

In relative terms, the limited availability of venture capital, the high nominal corporate tax rates, the high cost of going public and the social stigma associated with failure have all tended to dampen the plans of would-be entrepreneurs. Although West Germany's 5-year-old venture capital industry is expanding, funding for most start-ups usually comes from a combination of other sources, including government grants, bank loans, and corporate investment.

A number of biotechnology companies are located in Heidelberg, where the proximity to prominent universities, research centers, and a technology park makes this city an ideal location for high-technology start-ups. Progen Biotechnik is an example. Located at the Heidelberg Technology Park, this company was started in late 1983 by four University of Heidelberg professors. The goal of the company was to commercialize new discoveries from Germany's scientific community. Products on the market include several types of monoclonal antibodies, recombinant Protein A, and a DNA test kit.

Not all new biotechnology companies are in Heidelberg. A promising set of recent start-ups which belong to the Bissendorf Biotechnology Group are located near Hannover. These include Bissendorf Peptide, Braunschweiger Biotechnologie, and Bissendorf Biosciences. Bissendorf Peptide was founded in 1983 and is currently developing a variety of human peptides for diagnostic and therapeutic uses. Braunschweiger Biotechnologie was founded in 1985 as a subsidiary of Bissendorf Peptide. The company is involved in a broad range of projects including the development of new bioreactor designs, separation/purification processes, and biochemicals for the pharmaceutical and food industries. Bissendorf Biosciences, founded 2 years ago, is a joint venture between Phillips 66 Biosciences, a subsidiary of Phillips Petroleum, and Bissendorf Peptide. The company's first product is expected to be a derivative of human growth hormone-releasing factor, which will be used for diagnosing human dwarfism.

Many of Germany's pharmaceutical and chemical giants have made a substantial commitment to biotechnology in recent years. Companies such as BSAF, Bayer, Boehringer-Ingelheim, Boehringer-Mannheim, Hoechst, E. Merck, and Schering have developed their internal biotechnology R&D capabilities as well as having coordinated their external affairs with US biotechnology companies. Many agreements have been made between the German corporate giants and US biotechnology companies.

West German government support for biotechnology development is evidenced by its 6-year \$400 million na-

tional program. Initiated in 1984, this extensive campaign is focused on funding institutional and industrial research projects, strengthening the link between academia and industry, and assisting the startup of new biotechnology companies. The 1988 federal budget for this program (\$80 million) is allocated approximately as follows:

- Nearly 45 percent will be used to fund key areas of research that the West Germans have identified as top priority, including microbial and plant genetics, cell culture technology, biochemical process engineering, and biological safety and risk management.
- About \$23 million will be used to support research at the Institute of Biotechnology, Braunschweig (GBF), the European Molecular Biology Laboratory (EMBL) located in Heidelberg, and other research organizations.
- \$11 million will go to support four gene centers at Cologne, Heidelberg, Munich, and Berlin. Gene centers are structured to bring together the resources of universities, industry, and research institutions. The gene center in Cologne, for example, involves the collaboration between the University of Cologne, the Max Planck Institute for Plant Breeding, and Bayer.
- Approximately \$12 million will be apportioned to support industrial R&D and human resource development in biotechnology.
- About \$1.3 million of the budget for this year will go for support of startups. Under the national program on biotechnology, the government will cover up to 75 percent of the product development costs and guarantee up to 80 percent of the commercial bank loans for product commercialization costs.

In addition to research conducted at a number of leading universities, several of West Germany's research institutes are involved in biotechnology-related activities. The Max Planck Society operates over 50 research institutes, at least seven of which are devoted to basic research in various aspects of the life sciences. Applied research is conducted mainly at the GBF and the Institute of Biotechnology at the Nuclear Research Center (IBT). Both the GBF and IBT are major government-supported biotechnology research institutions. To promote technology transfer, selected projects at these institutions involve extensive collaboration with industry.

Although the number of German biotechnology startups is relatively small, the talented transnational efforts of its chemical and pharmaceutical giants, combined with government support, will assure Germany's place among the leading countries commercializing this technology.

The United Kingdom

The British government and British public were, like the French, relative latecomers to developments in bio-

technology. The British government was prompted into action by the Spinks Report of 1980 and a series of Select Committee hearings in the House of Commons in 1982. The result has been a somewhat disjointed set of initiatives which nevertheless, in total, constitute a relatively coherent strategy. But if government and public were newcomers to biotechnology, industry and universities were not; indeed, Britain's relative strength in biotechnology stems from these two sectors.

Britain's intellectual achievements in the disciplines most closely allied to biotechnology are formidable. It is probably fair to say that in each of the major disciplines associated with biotechnology, there is at least one center in the UK that can claim considerable expertise. Unlike Germany and Japan, Britain was not caught short by the genetic engineering developments of the 1970's. Indeed with all the work on molecular biology at the University of Cambridge in the 1950's and 1960's and the subsequent discovery and development of monoclonal antibodies, Britain may be said to have contributed substantially to that revolution.

Of all European countries, the intellectual climate in Britain approaches most closely that of the US with the main emphasis of academic research being at the "high-tech" end of genetic engineering, and relatively less attention paid to fermentation technology. This is reflected in the bias of public R&D. Two features are striking; first, the bias towards medical and agricultural research – 37 percent and 55 percent of the total, respectively – with the biosciences and food receiving relatively short shrift; second, how much less Britain devotes to research support in these areas than its European neighbors: in absolute terms, Britain spent only 39 percent of German expenditures and 42 percent of French expenditures. It is also noteworthy that Britain spends more on agricultural research than medical research – a bias that has been increasing in recent years with the university and science budgets being cut back while the agriculture budget has increased with the expansion of agriculture.

As in Germany, there are a number of outstanding institutions in the UK that have attracted to them scientists of considerable distinction. However, the notion of "centers of excellence" as has been set up in West Germany is rejected by many British academics on the grounds that in a subject as broad and fast moving as biotechnology, there is a constant shifting of relative position across a very wide number of fields. There is, however, little complacency over British academic achievements in this area. Nobel prizes do not mean successful commercial exploitation. Too frequently, it has been the story, as in the case of monoclonal antibodies, of "discovered in Britain but exploited abroad." Recent government policy in biotechnology has been aimed at effective methods of bridging the academic/industry divide. It is noteworthy, for example, that although the bulk of public research

funding goes into the "high-tech" end of medical and agricultural research, much of the new funding in biotechnology has gone into fermentation technology and downstream processing, to chemical engineering departments rather than into biochemistry or molecular biology.

The main threat to Britain's research base, however, comes from cutbacks in government funding of universities since the mid-1970's, and particularly since the advent of the Conservative government of 1979. The effect of cutbacks on universities' staffing and equipment and the threat it posed to the basic research base has been a background issue since 1980. However, within the past few years, the UK government has taken a series of steps aimed at preventing general university cutbacks from damaging so-called growth areas like biotechnology. These have included the establishment of a special directorate in the Science and Engineering Research Council (SERC) to provide funds for biotechnology-related research with additional funds from the Department of Trade and Industry (DTI) for joint partnership programs linking universities and industry. In 1982, the DTI took over the main government responsibility for biotechnology (although university funding still comes through the research councils and is therefore subject to the Department of Education and Science). The DTI put together a series of measures which could be called a "biotechnology strategy." Unfortunately, the amount of funding available is much too low and in the long run may prove detrimental to the status of the UK in biotechnology.

One of Britain's strengths in biotechnology lies in the breadth and depth of industrial experience – experience that is not just the product of recent fashion but which goes back two decades or more into first and second generation biotechnology. In contrast to the US, but in common with Japan and Germany, the main interest stems not from small specialist firms but from large, well-established firms with substantial R&D departments. Like Germany, Britain has the advantage of a strong pharmaceuticals and chemical sector, but it also has a large number of companies in the agrifood sector that are large and well able – if so desired – to fund the necessary R&D and thus profit from developments in biotechnology. This oligopolistic environment means that, unlike the new biotechnology firms of the US, they have no need to broadcast their activities; indeed, that incentive is rather the reverse, to hide from rivals the specific direction of R&D interests and involvement. The danger, of course, is that the firms concerned will build up capabilities but do nothing, waiting to see what competitors do, and then find that they have acted too late. Britain has too long a history of risk aversion and failure to turn intellectual strengths into commercial advantage for there to be confidence that the company sector will seize the opportunities offered by biotechnology.

Of the main British-based pharmaceutical companies, those with substantial experience of fermentation drugs (i.e., antibiotics) – Beecham, Glaxo, and Wellcome – Beecham is by far the largest but its interests extend well beyond the ethical drug market and, to date, it probably has the smallest interest in biotechnology, with relatively modest in-house research capability and limited involvement with university research. Its stake in the semisynthetic antibiotics means, however, an obvious interest in using biotechnology to improve production efficiency. Glaxo has been building up its in-house resources and extending its capacity to produce fermentation-based drugs. Its interests range from protein engineering (i.e., the interferons, etc.) through enzymes to hybridomas. Wellcome, with its traditional expertise in vaccines is perhaps best placed of all three, and indeed has two genetically engineered products – lymphoblast interferon and a new foot-and-mouth disease vaccine. However, Britain's strength in pharmaceuticals derives as much from the subsidiaries of foreign multinationals as from its own pharmaceutical companies.

The British company that has probably explored most deeply the potential of biotechnology is ICI, the chemical giant whose pharmaceutical division has been growing strongly in recent years thanks partly to its discovery of beta-blocker heart drugs. ICI's effort in biotechnology is divided between its pharmaceuticals division, which has built up considerable expertise in genetic engineering and worked in conjunction with Searle to develop human urogastrone; its corporate bioscience department, which has the responsibility for building up ICI's capability in biotechnology; and its agricultural division, which has been responsible for the development of Pruteen – its SCP (single-cell protein) animal protein feedstuff based on methanol and PHB, a biological plastic (polyhydroxy butyrate) derived (like Pruteen) from a natural bacteria feeding off a methane substrate. PHB's biodegradability gives it advantage in some high-value-added markets (for example, medical sutures and bone repairs) and considerable market potential (for example, in the packaging, soft drinks market, etc.). Like other European companies, ICI is looking to biotechnology as a possible route into a wide range of specialty chemicals. Quite a number of Britain's major food manufacturers also have substantial interests in biotechnology.

Britain's major weakness is in the fine chemicals and enzymes field, where there is no firm to challenge the Danish company Novo or the French Roquette. This weakness is mirrored by the general lack of interest in the chemical engineering aspects of biotechnology. For example, although the major food manufacturers are engaged in the "high-tech" end of genetic engineering, few of them are putting research effort into the problems of scale-up and downstream processing – in marked con-

trast to their Japanese opposite numbers. This lack of interest is also seen in the relative weakness of the process plant industry. Nor, in spite of academic prowess, has Britain as yet established a program equivalent to the Japanese or German programs in "third generation bioreactors."

Until a few years ago, commercial biotechnology in Britain was dominated by the few large companies. However, in the past few years, due to changes in tax laws and to institutional developments in London, a fairly large development of small, specialist biotechnology firms has taken place. Thus, Britain now has a far more developed venture capital market than any other European country. About half of European venture funding in biotechnology is British, although as much as 70 percent is invested in the US. Celltech is now profitable as the world's largest producer of monoclonal antibodies. It was the first British start-up company to make the transition from small high-tech to tomorrow's new-style middle-size pharmaceutical firm. Although overall spending at the present time is limited, the UK actually has competence in a wider range of biotechnology activities than the US. Strong points include biosensors and protein engineering. The Inmos transputers are being assembled in parallel to give enormous real-time power for protein engineering applications in the hands of companies like British Biotechnology, which is perhaps the only British firm to offer routine gene synthesis.

France

France is considered at present to rank in third place in European biotechnology. Although France woke up late to the rapid development of biotechnology during the 1970's, a bold program of development was initiated in 1979-1980 aimed at making France the leading European country in biotechnology by the end of the century. The initiative is very much government-inspired and government-orchestrated. Whether it will succeed is yet to be seen. Since the French government recognizes that many commercial applications of biotechnology may be 10 to 20 years away, the emphasis is as much on education, training and long-term objectives as upon short-term goals.

As the home of Pasteur, father of modern microbiology, France has a strong tradition of academic research in the disciplines of microbiology, molecular biology, and cell culture. Two research institutes in particular are world-renowned – the Institut Pasteur in Paris whose interests include immunology, cell culture, and genetic engineering and INRA (National Institute for Agricultural Research) at Strasbourg, whose interests include soil microbiology, plant genetics, and nitrogen fixation. But there are a number of other substantial research institutes whose interests embrace biotechnology such as the Na-

tional Center for Scientific Research (CNRS), particularly its chemical laboratory at Strasbourg; the National Institute of Research in Health and Medicine (INSERM) in medical applications, and the French Institute for Petroleum Research (IPF) in biomass energy.

The French government's plans involve a linking of these research institutes with university research to build up a major research base. University science in the fields allied to microbiology has been generally weaker than that of the research institutes. Only three universities have faculties of world standing—Compiègne (enzyme technology and biochemistry), Toulouse (microbiology, biochemistry and chemical engineering), and Strasbourg (genetic engineering), although quite a number (for instance, Marseilles, Montpellier, Lyon, Paris Orsay) have specialist schools of distinction. But for all this academic expertise, France is weak in applied research. As in Britain, the elitist traditions of academic education led to a bias in favor of pure science. In addition, the French university system has tended to compartmentalize research, and neither research institute nor university has found it easy to bring together teams in the key disciplines of microbiology, biochemistry, genetics, and chemical engineering. Therefore, the government's recent strategy has been to use the main institutes and universities as centers of development. For example, the CNRS, INRA, Institut Pasteur, and INSERM were the core team on genetic engineering for pharmaceuticals; CNRS, the IFP, and Toulouse University on fermentation technology for chemicals. In an attempt to bridge the gap between academic and applied research, it has also established a number of industrial fellowships to encourage interchange between industry and university and has established four specialist technology transfer centers—at Compiègne, Toulouse, Institut Pasteur, and Paris-Grignon University. The aim of these technology transfer centers is both to act as receiving agents for industrial enquiries, and more importantly, to go out into industry and find developers for academic work of commercial value.

The French contribution to current world production of biologically derived products is estimated to be approximately 7.5 percent. France is probably weakest in pharmaceuticals where small capacity in antibiotics means it lacks experience. Indeed, much of its capacity in the antibiotic/steroid/cephalosporin field is possessed by the multinationals. France is, however, particularly strong on vaccines where the Institut Mérieux (an offshoot of Rhône Poulenc, the nationalized chemicals/pharmaceuticals giant) has a worldwide reputation, and the recent push also into diagnostics, bringing together the resources of Rhône Poulenc with those of the Institut Pasteur (with its semicommercial offshoots Hybridolab and Immunotech. The other major pharmaceutical company in France, Roussel-Uclaf, remains 60-percent-owned by Hoechst (German) and 40 percent

government-owned. Via this link, Roussel-Uclaf has access both to Hoechst research and to that of its American subsidiaries; but its mixed ownership also sets it somewhat apart from the government-sponsored efforts to develop the genetic engineering skills of the French pharmaceutical industry. The key firms in this area are therefore Sanofi, the Elf-Aquitaine pharmaceutical subsidiary; Transgène (Strasbourg) a start-up company in which Paribas, the merchant banking firm, has a majority holding (but where several other firms, including Elf-Aquitaine, have minority holdings); Genetica (an offshoot of Rhône Poulenc was set up by Institut Pasteur, INSERM, INRA and CNRS).

With food and wine such traditional industries, one might have expected to find France stronger than it actually is in the agrifoodstuffs area. But tradition also makes for conservatism, and the large French firms in this area have in the past spent little on research. The government is pushing some of the largest firms into taking an interest in the potential of biotechnology. France's real strength, however, lies in some of its medium-sized specialist firms. Orsan and Eurolysine produce the amino acids, glutamate and lysine, while Rhône Poulenc is also a major producer of methionine, used as an animal feed additive, making France the only European contender to Japanese domination of this market. Roquette is one of the world's leading producers of starch-based chemicals and the world's largest producer of sorbitol, the sugar substitute, while Lesaffre is a specialist producer of yeasts. Bel, the dairy products group, is exploring the development of lactic enzymes. As in Germany, however, the agrifood industry in France is relatively fragmented. The largest group by far is BSN-Gervais-Danone, but this is dwarfed by giants such as Unilever, Nestlé, or Allied Breweries/Lyon. However, the French government via the club system has set up a program to enhance agrobiotechnology. Limagrain has developed artificial seeds and Moët-Hennessy is looking at the micropropagation of woody plants. In countries such as the UK and France, an industrial "club" is a group of companies and government labs who pay a fee to share in the research and development of specific skills and technologies which are then made available only to industrial members of the club.

France does not have a developed venture capital market and although the government has been at pains to help the small-firm sector, much of this help consists in underwriting loans and credit facilities from the major banks. There are a number of small biotechnology companies in France, but most of them, as mentioned above, are not independent, but offshoots either of larger firms or research institutes. The largest independent firm is Transgène, based in Strasbourg, with links not just with Strasbourg and Paris but also with Heidelberg and Basel. It has three publicly announced genetic engineering

breakthroughs to its credit – gamma interferon, a rabies virus protein which could be the basis of a new vaccine, and a blood coagulating factor, IX, for treating Hemophilia. After Transgène is Genetica, an offshoot of Rhône Poulenc (although 10 percent of the stock is owned by the researchers themselves) and is concentrating on monoclonal antibodies. A number of other firms also support specialist biotechnology offshoots while many of the public research institutes have hived off their contract research into specialist companies (like Hybridolab and Immunotech from Institut Pasteur). Overall, therefore, although it would be wrong to say there was not a small-firm sector in France, much of it derives from decentralization of function on the part of larger groupings rather than from inherent growth as in the US.

With substantial cutbacks in public expenditure, the ambitious plans of the government have been trimmed to some extent, although priority is given to new technology programs. What the French government is trying to do is to force a marriage between a reluctant industry and a good, but not entrepreneurial research base. Whether they will succeed is a moot point. In their favor is the French ability to mobilize resources: the centralization of the education and university system, the tradition of administrative discretion wielded by French civil servants towards industry, and the now extensive nationalization of the large firms. Against France is the fact that the areas chosen for particular attention – agriculture, food manufacturing, and biomass conversion – are areas where the work is still centered on the research laboratory and commercial development is some years away. Such long-term risk targets with high payoff are, however, typical of French industrial planning. However, the French have considerable intellectual leeway to make up compared to their German or British counterparts, and while one may envy the boldness of their government's strategy, one must remain cautious about its outcome.

Comment on the Positions of the Three Leaders

Although basic research in biotechnology-related areas is necessary for the eventual development of a marketable product, unless the infrastructure for academic/industry collaboration is available, a country will never be a leader in biotechnology. The worldwide interest in biotechnology indicates the potential for profit from a particular biotechnology product. Therefore, because of its strong infrastructure, West Germany is the European leader in biotechnology today and will probably remain the leader. The UK, although having superb researchers, may lose its present position of second place in Europe in the long term if funds are not increased for industry/academic interaction and also for basic research. France is third mainly because of its large com-

panies, which are mostly government-owned and have extensive R&D departments. However, whether it will ever surpass Germany or even the UK is questionable. The West German government provides by far the greatest financial support for industry/academic collaboration and also for basic research compared with the other European countries. This factor is extremely important also for being a leader in biotechnology. Although there has been some decrease in funding recently in West Germany, it is relatively minor compared with the cutbacks in the UK and in France.

Other European Countries and Israel

Although the respective governments have extensive biotechnology support programs, countries such as Sweden, Denmark, Switzerland, and the Netherlands can never become leaders simply because their size (mainly in terms of population) limits the number of biotechnology-based companies. On the other hand, these countries do have important industries that produce biotechnology products. The large increase of investment for biotechnology by these countries also means that there will be more – and perhaps even more fruitful – biotechnology products in the future. Novo (Denmark) and Gist-Brocades (the Netherlands) are the leaders in the world enzymes market. Increased expertise is also developing in agrobiotechnology, biosensors, waste treatment, and specialty chemicals. The Netherlands is host to several multinationals. Dutch biotechnology revenue is of great importance, comprising 7 percent of the world's total. The government restructured biology research 6 years ago and most university work is now partly sponsored by industry. National skills include the developing of enzymes, yeast and dairy products, and protein engineering. Unilever (detergents and food chemicals), Phillips, and Shell (the oil giant) are investing in many biotechnology areas. Akao (pharmaceuticals including lymphokines and recombinant DNA technology) are also important in the biotechnology area. Many small companies are university- or institute-based and enjoy good relations with large companies. The Netherlands government encourages foreign biotechnology investment.

In Sweden, the leading role in biotechnology is occupied by two pharmaceutical firms, Pharmacia (a subsidiary of the larger pharmaceuticals/medical products group, A.B. Fortia) and KabiGen, a subsidiary of the state-owned pharmaceutical group, Kabivitrium. Pharmacia is closely connected with Uppsala University. It is a specialist producer of chemical reagents for isolation and purification, and has developed affinity chromatography techniques using antigen/antibody characteristics as a means of specific isolation. KabiGen is, more strictly speaking, a biotechnology firm, its main interest being

in research into drugs and vaccines which can be produced by recombinant DNA. Kabivitrium, its parent company, is the world's largest producer of human growth hormone. KabiGen is also carrying out research on interferon and plasminogen activators (substances that dissolve blood clots).

The three major Swiss pharmaceutical firms – Hoffmann LaRoche, Ciba-Geigy, and Sandoz are also engaged in biotechnology research in addition to the production of their pharmaceutical products.

In all these countries, the research carried out in the universities, research institutes, and industry is of top quality and their scientists are certainly equal to the best in West Germany, the UK, and France.

Israel is the the only player in biotechnology in the Middle East and has excellent scientists in all areas of biotechnology-related disciplines. There are several biotechnology companies in Israel, but the country probably can not become one of the leaders in the field because it is limited in terms of government support due to its precarious situation in the Middle East which necessitates an enormous military expenditure. In addition, there is only a small market for its products within the country and thus they must rely on export in competition with the European countries as well as the US and Japan.

Although also pushing biotechnology, the other European countries such as Italy, Spain, Portugal, Austria, and Belgium, are far behind such countries as West Germany, the UK, France, etc. in terms of coming very late into biotechnology and with limited government support.

Future Emphasis in Biotechnology

Microbial fermentation has played a role in domestic economy for a very long time and will continue to do so even more in the future. Microbiology represents an important proportion of biotechnological processes consisting of the use of bacteria, yeasts, molds, algae, and animal and plant cell cultures, of which the metabolism and the biosynthetic capacity are geared towards the production of specific substances.

Being a privileged area of research for microbiologists and enzymologists, biotechnologies have recently benefited from decisive progress made in virology, bacteriology, and molecular genetics and especially from the discovery of techniques to modify and transfer DNA between organisms. Biotechnologies, which include industrial and applied microbiology, make it possible, through the integrated application of the knowledge and techniques of biochemistry, genetics, and chemical engineering to derive benefit, at the technological level, from the properties and capacities of microorganisms and cell cultures.

The perfecting, intensifying, and automation of traditional biotechnologies such as microbial fermentation, as well as the development of new biotechnological processes contribute to the development of bioindustry. This includes, on the one hand, industrial activities in which biotechnologies can replace technologies currently in use (for example, production of flavorings, seasonings, plastics, and products for the textile industry; production of methanol, ethanol, biogas, and hydrogen; extraction of some metallic elements) and on the other hand, activities in which biotechnologies play an essential driving role. In the latter case, this concerns the following areas: (1) the food industry (mass production of yeasts, algae, and bacteria with a view to supplying proteins, amino and organic acids, vitamins, and enzymes); (2) the increase of agricultural productivity (cloning and selection of varieties from *in vitro* plant-tissue cultures, bio-insecticides); (3) the pharmaceutical industry (production of vaccines, biosynthesis of antibiotics, hormones, and interferons); and (4) the abatement of pollution (sewage treatment and transformation of wastes, and agricultural and industrial by-products).

In the area of human health care, the use of genetic engineering is likely to make research related to the development of new drugs less empirical and more rational than it has traditionally been. Greater understanding of the body's physiological processes, and, in particular, the functioning of the immune system is already having an impact on medical practice. In pharmacology, it is bringing a shift from block-busting therapies to drugs targeted far more precisely to specific problems. Genetic engineering is also enabling the production of new products, many of which were nonexistent or virtually unobtainable prior to the development of this technique. Production of vaccines is also being affected by recombinant DNA (rDNA) techniques. This is an expanding research area and constitutes a potentially important research area in terms of a profitable market. Recombinant DNA techniques are also being used in some diagnostic tests and this area will be expanding within the next few years. Ultimately, there may be application in the treatment of genetic diseases where the sufferer is missing an important gene.

The technical aspects of genetic engineering *per se* now pose few problems. The problems lie in scaleup with maintaining a continuous culture, with the stability of the manufactured gene in tissue culture (i.e., preventing it from reverting to its old form or developing into some unwanted form), and with all the problems of separation and purification of a highly sensitive, fairly thick culture. Overcoming these problems has proven far more costly and time-consuming than was originally estimated. Thus, research in scaleup and separation and purification technology (downstream processing) will receive even greater attention not only by industrial R&D laboratories but also by biotechnology-oriented institutes and university de-

partments. It is safe to assume that within a few years a major part of the health care industry will have been affected by genetic engineering. Perhaps a third of the present activity of pharmaceuticals and diagnostics sectors will have been replaced or greatly expanded as a result of the new genetics.

Research in protein engineering is expanding rapidly. It is now possible to alter the nucleotide sequence of a protein at will, and, therefore, the sequence of the encoded protein. This not only permits an analysis of the roles of individual residues in a protein but the construction of protein molecules with new properties. Designer proteins, built from first principles for a specific function, are the ultimate goal of protein engineering. Protein engineering research encompasses site-directed mutagenesis, computer-graphic modeling, x-ray crystallography, nuclear magnetic resonance, and other techniques. This field is in the early stages and much research is required for the future.

Monoclonal antibody (Mab) technology has advanced rapidly during the past few years. This technology now provides a new route for the identification and purification of molecules and cells of interest as well as for clinical diagnostics and may become important for therapy. Antibodies against tumor-specific antigens could be used for the targeting and destruction of tumor cells. The use of Mabs in diagnostic tests and for therapy represents an important and expanding research area since their specific combining power enables them to deliver drugs to specific target areas in the human body. The area of research in methods for site-specific drug delivery is also being emphasized and constitutes a rapidly expanding research area. Much work, however, is still required, but the importance of Mabs for diagnostics and therapy for medicine constitutes a valuable research sector with a very large potential market.

Research in the animal health care area is receiving increasing attention and will be pursued vigorously in the next few years. Important for the animal health care market is the production of animal health products, especially vaccines and fertility control agents by methods similar to those used for human health products. There is the potential for the development of both diagnostic and therapeutic drugs, new vaccines, and new hormone products. Production of single cell protein (SCP) for animal feed is another sector that is being addressed.

Research on transgenic animals is a relatively new area which is being pursued by several laboratories and may assume importance in biotechnology although it is still too early to predict the potential impact. The method of the transfer of foreign genes and their expression was first developed in the mouse but has recently been carried out using larger animals such as sheep and pigs. Goals for application of this methodology in domestic animals and birds include the stimulation of growth rates of cows

and pigs, and milk yields in cows by implanting growth hormone genes. Built-in resistance to pathogens can also be envisaged. Also, transgenic animals could be used for the production of human proteins by insertion of the appropriate genes.

In the sector of plant biotechnology, the areas of future influence of molecular genetics, whether direct or indirect, can be classified as follows: production of hybrid plants by fusion of modified cells, known as protoplasts, and the transfer of genetic information into and out of plant species using rDNA techniques. Applications of these techniques can result in:

- Production of a wider range of varieties from which genetic selection for yield and quantity can take place
- Introduction of characteristics, such as disease resistance or tolerance of unusual soil or climatic conditions
- Transfer of the ability to fix atmospheric nitrogen to plants not naturally capable of doing this
- Transfer into plants of synthetic capabilities so that crops become a source of various chemicals
- Transfer out of plants of synthetic capabilities into bacteria or other microorganisms
- Development of new types of pesticides and other agricultural chemicals by application of rDNA techniques to biochemical processes.

Plant biotechnology lags behind biotechnology in other areas such as pharmaceuticals and other products for the human health care sector. However, in recent years, much progress has taken place in plant biotechnology. This area is being emphasized increasingly by both academic and industrial organizations. In the long run the potential market could be much larger than in other areas of biotechnology.

Industrial microbiology (the production of useful substances by microorganisms) has been and will continue to be a prime area for biotechnology research and development. Microbial fermentation is being used to produce vitamins, amino acids, and organic acids used extensively, for example, in food preparation. The Japanese, who dominate the amino acid market, have used genetic engineering to raise the efficiency of production methods, and this is now being followed in other high-tech countries and will be emphasized even more in the future.

Research on finding novel bioactive secondary metabolites is being carried out at the present time and this area will probably receive increased attention within the next few years. In the past, the research has resulted in the isolation of metabolites possessing mainly antibiotic activity. However, it has now become possible to design screening procedures that turn up active molecules having entirely different properties. The availability of powerful tools for increasing genetic variability and ap-

preciation of the physiological characteristics of the producing organisms as well as advances in biochemical understanding have been of enormous importance in developing new microbial strains for industrial application and for basic research and in allowing microbial cells to be subverted for the purpose of making novel metabolites such as enzyme inhibitors and new types of antibiotics.

Microorganisms are very convenient enzyme sources because the enzyme concentration may be markedly increased by acting on environmental conditions and by genetic manipulation. Thus, microbial enzymes have increasingly replaced plant and animal enzymes and should continue to be emphasized in research and development programs.

Another area of research emphasis in the biotechnological utilization of microorganisms is that of technological processes. Although there has been extensive research in this sector, further work is required and will receive increasing attention in the future. Improvements of biotechnological processes may take place on several levels, the major ones being:

- Process intensification by increased catalyst density
- Extractive fermentations
- Integration of bioconversion and downstream processing
- Process control with the use of (a) conventional sensors and (b) biosensors
- Physiological control
- New environments for biocatalysts such as organic solvents and gas phase.

The use of microorganisms in pollution control will receive increasing attention in the future. Microbial strains could be isolated in order to control various forms of chemical pollution—for instance, to decompose biocides or the biodegradation of compounds difficult to achieve such as those for detergents, plastic materials, or hydrocarbons.

An expanding area of biotechnology, still in its infancy, that is likely to have major effects on medicine as well as industry involves the interaction between biological and electrical and electronic systems (i.e., bioelectronics and bioelectrochemistry). There have been significant advances in this area in recent years, both in

electronics engineering, leading, for example, to infusion pumps, and in effecting connections between biochemicals, especially enzymes and antibodies, and various types of electrodes. A range of specific sensing devices based on these principles has already been devised: nerve gas sensors for military use, for example, and glucose monitors, particularly for medical purposes. Most sensors developed to date are based upon detecting the results of enzymic activity by a conventional electrode upon which the biological system is immobilized. New approaches, however, which are leading to more sensitive and effective devices offering a wide range of possibilities, include direct electron transfer between electrodes and protein redox centers and the accommodation of proteins on the gate of semiconductor devices.

In the short term, quantitatively the most important enzyme-based medical sensor is the glucose sensor, of which there are a variety of configurations. There will be a range of products based upon this—in particular, cheap, accurate, reliable devices for *in vivo* sensing appear to be imminent. These are expected to have a major effect on improving the regulation of blood sugar levels in diabetics. The commercialization of other sensors for measuring blood chemicals (including bioelectronic immunosensors) and in some cases based upon field effect transistors, appears likely within the next decade. These could form the basis of relatively inexpensive systems capable of measuring and monitoring a wide range of substances in body fluids, which could revolutionize diagnosis. Rapid progress is also currently being made in the development of a range of sensors based on the interaction between immobilized, stabilized microorganisms and electrodes. The combination of chemical, biological, and electronics technology, although in its infancy, has tremendous potential and should lead to a whole range of specific sensing devices for process control in the chemical and food industries, medical diagnosis, monitoring and control, and environmental control. An especially exciting aspect of these developments is the possibility of devising semiconductor biosensors based on microchips. Once perfected, such devices could be manufactured cheaply and would offer the possibility of simultaneous monitoring of several parameters by a single, bioelectronic device.

INTRODUCTION

Biotechnology can be defined as the application of biological organisms, systems, and processes to manufacturing and service industries. This is a broad definition and has the advantage of emphasizing both the link (via biological organisms) with the long tradition of fermentation technology, and the fact that it is concerned with industrial and not just laboratory applications. Biotechnology can be represented as a multidisciplinary scientific effort to achieve industrial and environmental applications (Figure 1).

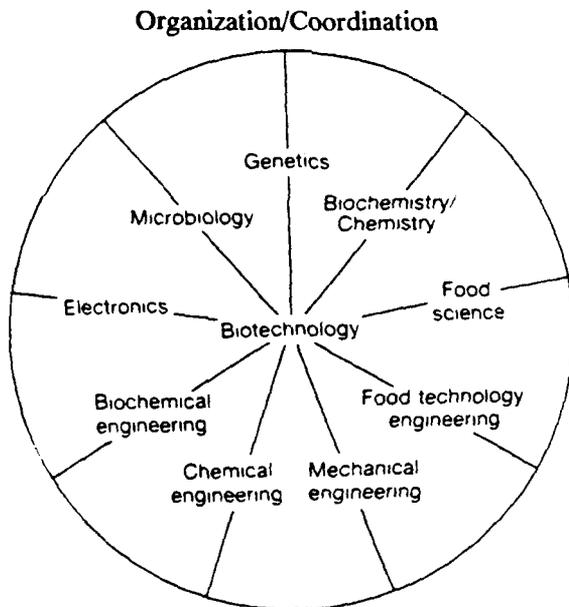


Figure 1. The interdisciplinary nature of biotechnology.

The history of biotechnology dates back to ancient Babylon and Egypt. Alcoholic beverages such as beer prepared from cereals and wine are among the oldest fermentation products. The making of cheese and bread also dates back to antiquity.

A glance at the history of biotechnology (Table 1) demonstrates the evolution and diversity of biotechnological products. The development of biotechnological products over the centuries follows the evolution of the underlying science and technology involved. In general, one can discern three phases in the evolution of natural science and technology, beginning with a phase of descriptive science and empirical technique, followed by a phase of greater insight as a result of improved understanding, ultimately leading to a final phase of more con-

trolled science and technology, which is the present status of biotechnology.

Table 1. Biotechnology-Calendar of Events.

PREPASTEUR ERA, before 1865

Alcoholic beverages (beers, wines)
Dairy products (cheeses, yoghurt)
Other fermented foods, yeasts, vinegar

PASTEUR ERA, 1865-1940

Ethanol, butanol, acetone, glycerol
Organic acids (citric acid)
Aerobic sewage treatment

ANTIBIOTIC ERA, 1940-1960

Penicillin: submerged fermentation technology
Large variety of antibiotics
Animal cell culture technology: virus vaccines
Microbial steroid transformations

POSTANTIBIOTIC ERA, 1960-1975

Amino acids
Single cell protein (SCP)
Enzymes (detergents)
Immobilized enzyme & cell technology (isomerase)
Anaerobic wastewater treatment (biogas)
Bacterial polysaccharides (xanthan)
Gasohol

ERA OF NEW BIOTECHNOLOGIES, 1975-19..

Hybridoma technology: monoclonal antibodies (1975)
Monoclonal diagnostic tests (1980)
Genetic Engineering (1974)
Animal diarrhoea vaccines (1982)
Human insulin (1982)

The Era of the New Biotechnologies

This period begins at about 1975 with the advent of controlled biological sciences and predictive technologies. The discovery of the genetic code of DNA as the basis of heredity and the enzymatic gene splicing techniques (*recombinant DNA technology*) are the highlights of long periods of fundamental research in genetics, biochemistry and molecular biology.

Altogether, the era of the new biotechnologies is characterized by three innovations. These are: genetic engineering, hybridoma technology, and bioprocess technology. These innovations will determine the biotechnology of the next decade. It is clear that the consequences, especially of genetic engineering, will reach beyond biotechnology in industry and environmental processes to broader applications such as for medicine and

agriculture. A brief description of the three innovations in biotechnology follows.

Genetic Engineering. Genetic engineering evolved and introduced the new aspect of *direct* intervention in the genetic material of microbial cells. By introduction of *foreign* genetic codes, sometimes made by chemical DNA synthesis in the laboratory, these cells could be transformed to make products they had never made before. Thus, for example, bacteria were modified to produce *human* insulin. Recently, this technology has been extended to plant and animal cells – a development which was possible because the genetic code has the same chemical basis in all living things. Genetic engineering of microorganisms to produce proteins of human and animal origin has become a new tool in research and has now led to the first commercial applications in the pharmaceutical industry.

Hybridoma Technology. This technique is based on the fusion of animal cells for the purpose of *in vitro* production of so-called monoclonal antibodies, or Mabs. Cells of the immune system, which cannot be grown *in vitro*, are fused with certain cancer cells which can. The hybrid cell lines so obtained combine the valuable property of producing *specific* antibodies with the ability to grow indefinitely *in vitro*; i.e., are *immortal*. In this way unlimited amounts of any desired antibody may be produced. These highly specific monoclonals are now being made to predetermined strategies which have led to a totally new field of immunology: *antibody engineering*. Mabs were first applied as specific reagents in commercial laboratory diagnostics (Table 1), and are now being used for purification of biological products such as interferons.

Both genetic engineering and hybridoma technology are major steps forward to the third phase in the development of biotechnology from "descriptive" and "understanding" to one which allows a large amount of control over biological processes.

Bioprocess Technologies. In the field of biotechnology, mathematical models of biological processes were developed by using the results of systems analysis. The insight into the parameters controlling the metabolic routes in living cells could be used to calculate optimal conditions for industrial biological processes. Experimental verification of these models gradually led to predictive *bioprocess technology* for controlled processes and optimal construction of bioreactors. This is the basis for computer-controlled automation.

Biological sciences and technologies have changed during this century from largely empirical activities to quantitative disciplines as increased understanding has led to increased levels of control. The breakthrough of the new biotechnologies has opened new perspectives in biotechnology in a broad sense. Thus, biotechnology as a recent phase in the long history of the practical use of

organisms is characterized by an increasing number of innovations.

While recombinant DNA technology has doubtless been the main cause of much of the recent publicity for biotechnology, it must be emphasized that there also have been important recent developments in other areas of activity which are essential for the development of the technology. The most important subjects in this regard are shown in Table 2.

Table 2. Subjects in which there have been recent advances of importance to biotechnology

| | |
|--|--|
| Genetic engineering (recombinant DNA technology) | |
| Biocatalysis | Enzymes (isolation, immobilization, stabilization) |
| | Intact microorganisms and cells from macro-organisms (immobilization, stabilization) |
| Immunology (especially monoclonal antibodies) | |
| Fermentation technology | Production |
| | Waste treatment |
| Bioelectrochemistry | |

Biotechnology will, in the future, make an important contribution to the quality of life via a range of goods and services, summarized in Table 3. In the short term, the

Table 3. Some recent important products and services based on biotechnology.

| Industry | Examples |
|-------------|---|
| Agriculture | Strain selection, plant and animal breeding techniques (including cloning) |
| Chemicals | Organic acids (e.g., citric, itaconic), use of enzymes in detergent formulations |
| Energy | Increasing use of biogas, large-scale production of ethanol as a liquid fuel |
| Environment | Improved test and monitoring procedures. Prediction of the fate of xenobiotic chemicals via increasing understanding of microbial biochemistry. Improvement in waste treatment techniques, especially for industrial wastes |
| Food | New methods of food treatment and preservation. Food additives (e.g., microbial polymers, microbiologically derived amino acids), use of enzymes in food processing. Single cell protein |
| Materials | Mineral extraction, improved knowledge and control of microbial biodeterioration |
| Medicine | Improved diagnosis using enzymes, enzyme sensors, use of microorganisms and enzymes in manufacture of complex drugs (e.g., steroids), new antibiotics, use of enzymes in therapy. |

most important contributions from biotechnology will, in general, be medical, but in the longer term (10 years plus) most informed commentators are of the view that applications in agriculture and the chemical industry will be more important in economic terms.

General Summary Survey

The products of biotechnology are expected to generate immense revenues. For example, pharmaceuticals and diagnostics made by recombinant DNA (rDNA) techniques are estimated to produce more than \$12 billion in annual revenue within the next 5 years or so. With other rDNA products involved in chemical synthesis, food production, biomass conversion, oil recovery, agriculture, animal health care, etc., a worldwide market of more than \$50 billion for recombinant products is expected by the year 2000. Thus, large corporations in many different industries have become involved in biotechnology. In addition to starting in-house research and development, large corporations have formed valuable relationships with academic laboratories and biotechnology companies in order to more quickly and efficiently get to the marketplace with products of biotechnology. This trend has taken place not only in the US but also in Europe. As in the US, the 1980's brought the formation of small companies in Europe to pursue the commercialization of biotechnology. Although the origin of many of these companies was the same; i.e., basic research laboratories, their original sources of funding were very different. In the US, venture capital played a large role in the support of new biotechnology companies. However, in Europe, where venture capital has been available to only a limited extent, many new European firms were funded with money from traditional industrial corporations and financial institutions, or by direct or indirect government support. In addition, many European companies initiated major programs in biotechnology.

European companies in biotechnology have interests ranging from food processing to chemicals to pharmaceuticals. However, the particular strengths are in the pharmaceutical industry and in the fermentation industry.

Individual European countries have resources and industrial efforts in biotechnology that are overshadowed by those in the US. However, as an aggregate, European biotechnology is almost as large in training, government funding, and the number of companies. Realizing that European biotechnology might lag seriously behind programs in the US and Japan, the Commission of the European Communities created programs to assist long-term research and development priorities in Europe. The Biomolecular Engineering Program, first proposed in 1976, was initiated in 1982 to support specific research projects. Another 5-year program, FAST (Forecasting and Assessment in Science and Technology), was initiated in 1978 to

determine futures in science and technology. Weaknesses in European biotechnology were noted, including lack of cohesiveness, emigration of scientists, and isolation of individual efforts, thus preventing the attainment of "critical mass." Steps had to be taken to allow the European Community to create a concerted effort in biotechnology. The Biotechnology Action Program (BAP) was established along with the Concertation Unit for Biotechnology in Europe (CUBE), to help monitor and coordinate the program. The six-point program was proposed in late 1983 and approved in March 1985. The program includes support of research and training, uniform regulatory policies and patent laws, and other special forms of support. Many research projects have received support, especially translation projects.

One program with funding from the European Commission is the European Biotechnology Information Project (EBIP), housed in the Science Reference Library in London, UK. The main purpose of EBIP is to act as a focus for biotechnology information within the European Community — a federation of countries with different customs and languages. Toward this end, EBIP conducts seminars in biotechnology information for a more cohesive approach to biotechnology information within the European Community.

Another group working on coordinating biotechnology in Europe is the European Federation of Biotechnology. Founded in 1978, this group now has 52 member societies from 17 European countries. Their goal is to promote the interdisciplinary nature of biotechnology and its development in Europe through working parties, conferences, and documentation. In addition, they organize a European Congress of Biotechnology every 3 years.

Biotechnology in Europe is also served by the European Molecular Biology Organization (EMBO), based in Heidelberg, West Germany. The primary functions of EMBO are to promote transfer of information about molecular biology and to promote basic research. The first function is accomplished by sponsoring workshops, courses, and other educational programs. The second important function is the basic research taking place in their centralized facilities, the European Molecular Biology Laboratory (EMBL) in Heidelberg. A third function is the funding of short-term and long-term fellowships for study in molecular biology. However, this indirectly affects biotechnology in that the biotechnology programs at universities and research institutes as well as biotechnology companies recruit from the academic molecular biologists who benefit from EMBO's activities.

Biotechnology today is a knowledge-dependent industry; an industry that is perhaps unique in its requirement for rapid and efficient information. A coordinated European program is now required to provide resources and services such as data banks and advanced computers

to make a full contribution to efforts undertaken internationally. Already there are signs that Europe is slipping behind the lead given by the US and the rapid progress made in Japan. The technological base for biotechnology information in Europe is now inadequate for the demands being made upon it and the shortage of manpower trained in the hybrid skills of biotechnology and information technology might soon limit the rate of further growth. In contrast, the US government is putting several hundred million dollars in this area, and the National Institutes of Health (NIH), for example, recently commissioned their own CRAY supercomputer to undertake exhaustive pattern-matching searches between sequences. Access to such machines in Europe, however, is relatively limited at the present time. At this time, Europe and the US have an unrestricted and open collaboration, the link between NIH's Genbank (Genetic Sequence Databank) and EMBL being one notable instance. However, this can only continue on the basis of an equal partnership. Although as an aggregate research community, Europe is almost as large as the US, in its fragmented state there is no single country that can contribute on anything like equal terms. The message being voiced by CUBE is that Europe is in danger of finding itself excluded from some critically important areas of research. Biotechnology information has, therefore, been targeted for support in the Bioinformatics Collaborative Programs and Strategy (BI-CEPS), which is budgeted to spend \$114 million on an automated laboratory, automated process plant, and computerized training. The need for a European center is now widely accepted and the natural choice would be EMBL at Heidelberg where the development of computer resources, the Nucleic Acid Data Library, and training program is well under way. The infrastructure for more distributed collaborative networks is being established and one basic requirement, a European Biotechnology Research Directory (BIOREP), see Table 4, is due to be started this year by the Organization for the Advancement of Pure Research (ZWO) in the Netherlands. Biotechnology information projects receiving funds from the European Commission are shown in Table 5.

Government Support of Biotechnology. Governments in most European countries have sponsored multifaceted programs to achieve success in biotechnology. Government strategies include support for new companies entering the industry, support for large corporation-based projects in biotechnology, and support for industry-industry or industry-academic interactions. European government programs are aimed at large targeted or commercial goals. The combined government support

Table 4. Sources of biotechnology information in Europe.

| Information Source | Location |
|--|--|
| Molecular Data | |
| Nucleic Acid Data Library | European Molecular Biology Laboratory, Meyerhoffstrasse-1, 6900 Heidelberg, FRG |
| SWISS-PROT (Protein Sequence Data Bank) | Departement de Biochimie Medicale, Université de Geneve, 1 rue Michel Servet, 1211 Geneve, Switzerland |
| PG-TRANS (Protein Sequence Data Bank) | Computer Science Unit, Institut Pasteur, 28 rue du Dr Roux 75724 Paris, Cedex 15, France |
| ENZIDEX (Enzyme Data) | Biocatalysts Ltd., Main Avenue, Treforest Industrial Estate Pontypridd CF37 5UT, UK |
| Cellular Data | |
| MINE (Microbial Information Network in Europe) | CAB International Mycological Institute (UK Node) Ferry Lane, Kew Surrey TW9 3AF, UK |
| MICIS (Microbial Information Service) | Laboratory of the Government Chemist, Cornwall House Waterloo Road London SE1 8XY, UK |
| CFISM (French Database of Microbial Strains) | INRA Institut National Agronomique, 16 rue Claude-Bernard, 75321 Paris Cedex 05, France |
| <i>In Vitro</i> Conservation Database (Plant cell culture techniques database) | International Board for Plant Genetic Resources, Via Delle Terme Di Caracalla 00100 Rome, Italy |
| Hybridoma Databank | University of Nice/CODATA Parc Valrose, 0604 Nice Cedex, France |
| MIRDAB (Microbiological Resources Databank) | Elsevier Science Publications P.O. Box 211, 1000 AE Amsterdam, The Netherlands |
| Bibliographic Databases | |
| Abstracts in BioCommerce (Commercial Abstracts) | BioCommerce Data Ltd. Old Crown Building, Windsor Road Slough, Berks SL1 2DY, UK |
| Biotechnology Abstracts (Scientific Abstracts) | Derwent Publications Ltd. 128 Theobalds Road London WC1X 8RP, UK |
| Biotechnologies (Scientific Abstracts) | Centre de Documentation Scientifique et Technique 26 rue Boyer, 75971 Paris Cedex 20, France |
| Current Biotechnology Abstracts (Scientific Abstracts) | Royal Society of Chemistry The University Nottingham NG7 2RD, UK |

in all European countries approaches the same level as the US government support, but the focus of support of the largest government programs is quite different, as shown in Table 6.

Table 5. Biotechnology information projects receiving funds from the European Commission.

| Project | (location) |
|--|--|
| Nucleic Acid Data Library (1983-84) | EMBL, Heidelberg |
| European Biotechnology Information Project (1984-86) | The British Library |
| Hybridoma Databank (1986-) | University of Nice |
| BIOREP — A database of ongoing research (1987-) | Organization for the Advancement of Pure Research, The Netherlands |
| BIOROM — 'Biotechnology Abstracts' On CD-ROM (1987-) | Derwent, London/Tele-systeme, Paris |
| ----- | |
| BAP — Biotechnology Action Programme (1985-89) | |
| Protein Electrophoresis — Data capture, analysis and databank construction | |
| Automated DNA sequencing | |
| MINE — Microbial Information Network in Europe | |
| Automated control and monitoring of biotechnological processing | |
| Protein engineering software | |
| Proposed projects | |
| BICEPs — Bioinformatics Collaborative European Programmes and Strategy. 1988 — . Part of the FRAMEWORK research programme. Projects involve molecular modeling, advanced computing, automated process engineering, and computer aided learning | |

Table 6. Government funding of biotechnology.

| Country | Government Branch or Institute | Goals and favored technologies | Annual funding (x10 ⁶) |
|----------------|--|--|------------------------------------|
| France | Institut de la Recherche et l'Industrie; other biomedical agencies | Academic-industry collaboration Commercial processes Bioprocess scaleup | \$100 |
| West Germany | Ministry for Research and Technology; Society for Biotechnological Research | Academic-industry collaboration Technology transfer Basic biotechnology Scaleup Pharmaceuticals New compounds | 120 |
| Netherlands | Ministry of Science Policy | Five-year plan to foster collaborations Scaleup | 30 |
| Switzerland | Federal Institute of Technology | University-industry collaboration Bioreactor designs | |
| United Kingdom | Department of Trade and Industry; Medical Research Council; Science and Engineering Research Council; British Technology Group | Fund industrial projects Technology transfer to industry Scaleup Fermentation Downstream processing | 80 |
| United States | National Institutes of Health; National Science Foundation; Departments of Agriculture, Energy, Defense | Basic research (95%) Applied generic research (<5%) | 750 |

COUNTRY-BY-COUNTRY SURVEY

The research in biotechnology in Europe and Israel is presented in some detail in the surveys of the individual countries. This includes research emphasized by scientists at universities and research institutes in their respective countries. The information on the various countries is derived from my visits to them in my capacity as liaison scientist as well as from information obtained during my attendance at various national and international biotechnology meetings. Where appropriate, I have made reference to articles I have written for *ESN*, *ESNIB*, and *ONRL Reports*. Obviously, not every university or

research institute engaged in biotechnology research is included in this survey since there are far too many to have visited in a finite time period. Equally obviously, the extent of coverage for any given country reflects the opportunities I had for visits there. In addition, I have focused on what I considered to be some of the most important research and the key scientists involved. In this regard, as stated in the Foreword, the names and addresses of the scientists whose research is presented in the country surveys are listed in alphabetic order in Appendix B.

West Germany (Federal Republic of Germany)

West Germany's intellectual strengths in chemistry and the countrywide interest in beer and wine in many ways makes it a natural for biotechnology. Indeed, one of the outstanding features of German experience in alcoholic beverage biotechnology was the early recognition of its potential importance, matched by government research funding from the early 1970's onwards.

Government

The most notable feature of biotechnology in West Germany was the early interest in the subject stimulated in part by DECHEMA (Deutsches Gesellschaft für Chemisches Apparatewesen – the Chemical Plant Association), and in part by the Bundesministerium für Forschung und Technologie (BMFT [Federal Ministry for Research and Technology]). As early as 1968, DECHEMA was pressing the BMFT to support research in the area of molecular biology and enzyme chemistry and simultaneously using the trade association networks to promote awareness in the chemical and pharmaceutical industries of developments in biological process techniques. This was, of course, prior to the main breakthroughs in genetic engineering; i.e., it was second-generation biotechnology. At the time, there were two main areas of interest: enzymes (both the dis-

covery/application of natural enzymes to chemical and pharmaceutical processes and techniques for immobilization) and fermentation technology (including continuous fermentation and bioreactors). The founding in 1968 of the Gesellschaft für Biotechnologische Forschung (GBF [Institute for Biotechnology Research]) with Volkswagen Foundation money reflected these interests. They were further reinforced by two political issues of importance – the environmental lobby that was looking to pollution control, including the replacement of pesticides and herbicides and the recycling of waste products; and the global food shortage lobby, which stimulated interest in new routes to protein foodstuffs. After 1973, there was also intense pressure to find alternative routes to energy, which stimulated interest in biomass energy. These priority areas were reflected in BMFT funding decisions. In its 1972 program for biotechnology, it identified six priority areas:

- Security of food and feed supplies
- Reducing environmental pollution
- Pharmaceutical production
- New routes to raw materials, chemical, and metal production
- Development of biotechnological processes
- Basic research in biotechnology.

However, by 1982, the BMFT had switched its priorities to three main areas:

- Bioprocess technology – particularly bioreactors and enzyme technology
- Cell culture and fusion techniques
- Genetic engineering.

BMFT funding is split roughly 3:1 between project research and institutional funding. The institutional funding refers only to the federally funded institutions, the GBF, Gesellschaft für Strahlen und Umweltforschung (GSF [Environmental Research]), and Kernforschungsanlage (KFA [Nuclear Cancer Research]). Project funding goes mainly to firms and universities and preferably to both, as the BMFT funds up to 50 percent of research costs when firms and universities put forward joint projects. Those firms that figure most prominently are the major chemical and pharmaceutical companies such as Hoechst, Bayer, and Schering. All of them are involved in more than one project. However, one modest firm – Natterman in Cologne, which specializes in pharmaceuticals extracted from plants – also receives funding from BMFT. In the process plant area, again it is the well-known names – Udhe (a Hoechst subsidiary), Lindt, Messersmitt, and Krupp – that have received most money.

As well as the four centers of excellence at Berlin, Munich, Cologne, and Heidelberg, the West German government supports the special Research Institute for Biotechnology (GBF) at Braunschweig, which has established an international reputation for its work in fermentation technology. The Federal Government also helps fund research at the Max Planck Institutes, the Fraunhofer Society institutes and – through the Deutsches Forschungsgemeinschaft (DFG) – the German Science Foundation that, like the Science and Engineering Research Council (SERC) in the UK, helps fund basic research.

Looking more broadly at the fields related to biotechnology, the Federal and Länder (State) governments give substantial support to the medical sciences.

Universities

The Institute of Technical Chemistry of the University of Hannover is recognized as one of the major centers in West Germany having active research programs in biotechnology. It is directed by Professor Karl Schügerl, who has been instrumental in developing biotechnology research at the basic and applied levels.

The Institute of Technical Chemistry carries out research that encompasses many topics and projects, which can be divided into the following sections:

- Biotechnology
- Measurement technology
- Noncatalytic gas/solid and solid/solid reaction separation processes
- Enzyme technology
- Homogeneous gas reactions
- Molecular spectroscopy techniques and process dynamics and catalysis.

The focal point of the activities (50 percent) is on the sections on biotechnology, separation processes, and enzyme technology. An example of the latter research is the application of liquid membrane systems in a bioreactor in which the reaction and extraction take place via just one such membrane. The influences of acidity level and temperature on the activity of the immobilized enzyme are also being investigated since these factors can differ from those for pure enzyme systems.

Other interesting projects at the Institute of Technical Chemistry being carried out in collaboration with GBF are the development of a "low-shear" reactor in which the gas intake (ventilation) occurs by means of a moving membrane system that at the same time provides a complete mixing of the reactor, and measurements of the speed of bubbles in a bubble column with ultrasound Doppler anemometry so that speeds can be measured even in fermenting liquids with a high degree of opacity.

Further information relating specifically to Schügerl's projects are available in ESN 40-2:44, ONRL Report 8-002-C13, and ONRL Report 8-003-C24.

The institute's laboratories are equipped with a computer-infrastructure that permits an efficient use of the apparatus for diverse application. To this end, a computer system has been set up with a pyramid-shaped hierarchy: VAX/11 and PDP/11 machines are linked by various microprocessors. One of the uses of these facilities is in an enzymatic catalysis in an airlift-loop reactor. The process in the reactor is described by a distributed parameter model in which a single parameter can be varied experimentally at any time while the remaining parameters stay constant. In this way, the specific influences of the separate parameters can be carefully investigated.

The Institute of Biochemistry and Molecular Biology of the Technical University of Berlin was established in 1971 as part of the Physical and Applied Chemistry Department. The Director of the institute is Professor Horst Kleinkauf. Since 1971, Kleinkauf and his colleagues have focused their research on peptide antibiotics. These compounds have attracted biochemists because of their unusual structure and properties. Initially, Kleinkauf's interest was in aspects of their biosynthesis. Integration of D-amino acids, hydroxy acids, and various types of cyclization reactions have been shown to involve a special kind of enzyme machinery; i.e., protein templates carrying in

sequence the thioester-activated amino acids, elongation being accomplished by a swinging pantetheine arm. The proteins consist of polyenzymes with covalently linked units with sizes up to 450 kilodaltons (kDa). Various such templates have been characterized from bacteria and fungi including those for gramicidin, tyrocidine, enniatins, and cyclosporin. In addition, studies are carried out on various aspects of the enzymology of peptide formation and modification including *in vivo* and *in vitro* production methods.

Additional groups at the Institute of Technical Chemistry work on:

- Cloning of antibiotic biosynthesis genes and their regulatory regions in *Bacillus subtilis* (M. Marahiel)
- Characterization of protein templates from bacteria (J. Vater and H. von Döhren)
- Fungi (H. Kleinkauf and R. Zocher)
- The enzymology of peptidolactones in *Streptomyces* and *Clavicipes* (U. Keller)
- Synthetic peptides (Z. Palacz).

In addition, fundamental studies are being carried out in:

- Protein sequencing (J. Salnikow)
- Chloroplast proteins (J. Vater and J. Salnikow)
- Hormone metabolism (K. Bauer)
- Lignin degradation; biology of fungi (G. Kraepelin)
- Differentiation in fungi (J. Woestemayer).

Additional information is available in ESN 40-7:223.

The Institute for Biochemistry in the Department of Chemistry of the Free University of Berlin is one of only four institutions in Germany at which students can obtain a degree in biochemistry at undergraduate and graduate levels. The Institute for Biochemistry, whose present director is Professor Volker Erdmann, is of recent origin, having been established only in 1976.

The research projects at the institute include:

- Gene expression, with emphasis on protein synthesis
 - Nucleic acids structure and function
 - Protein/nucleic acid interactions
 - Molecular evolution
 - Gene technology
- and more recently,
- The molecular biology of archaebacteria.

Research in these areas is under the direction of V. Erdmann.

F. Hucho's group is engaged in studies of the biochemical characterization of acetylcholine receptors. E. Riedel and colleagues are studying the biochemical mechanisms of drugs and natural substances, especially of centrally effective compounds. In addition, these investigators are also involved in studies of membrane functions and transport events in biological membranes.

R. Riemschneider and his group are engaged in studies of amino acids and peptides; structure and function of collagen; characterization of prostaglandin receptors; and development of methods for binding studies.

The research of the above groups is oriented toward an eventual application for medical biotechnology, although the research is, at present, at a very basic level.

The Institute for Molecular Biology and Biochemistry is one of the nine institutes of the Faculty for Basic Medicine of the Free University of Berlin. It has as its purpose, research and teaching in the field of medical biochemistry. Research is carried out by single groups concentrating on different themes. A few examples of some of the projects are:

(1) H. Tiedermann and his group are carrying out research on embryonic induction mechanisms and the mechanisms of tissue differentiation.

(2) The regulation of gene expression in amphibia is being studied by W. Knochel and coworkers.

(3) B. Wittig and his colleagues are interested in the organization of chromosomes. Their studies have shown that transcription of the small gene for transfer RNA depends on a specific arrangement of gene with respect to nucleosomes. These studies were expanded to messenger RNA (mRNA) coding genes. The group has also developed a new method for the cloning of complementary DNA (cDNA) and has constructed a multifunctional expression vector. With these tools, this group is trying to identify genes which regulate early development of mouse embryos.

(4) W. Grässmann and his coworkers analyze the regulation of gene expression during embryogenesis.

(5) H. Huang and coworkers are investigating membrane fusion using influenza virus, reconstituted viral membrane, and liposomes as models.

(6) W. Reuter and colleagues are engaged in projects on the biochemical and biological properties of glycoproteins and glycolipids on the cell surface of normal and diseased organs (liver, skin, brain). The three main topics of their research are: isolation of different membrane glycoproteins from liver and hepatomas; biochemical and biological characterization of those glycoproteins (turnover characteristics, their role in cellular adhesion, oligosaccharide structure); and their potency as tumor markers.

(7) F. Körber and his group are interested in the significance of carbonic anhydrase in the metabolism of calcium and its regulation by parathyroid hormone, calcitonin, and calcitriol and in the way it is influenced by modulators and inhibitors.

Although the above research projects are in the realm of basic research, the information obtained from such basic studies is a prerequisite for eventual application to medical technology.

At the University of Düsseldorf, the research is directed toward applied biotechnology and genetic engineering.

earing. Professor Cornelius Hollenberg is the Director of the **Institute of Microbiology**. One of his (and his group's) interests is the construction of xylose-fermenting yeast strains. They are also dealing with studies of the expression of foreign genes in yeast as well as the development of new substrates for the production of alcohol from yeast.

M. von Ciriacy-Wantrup and coworkers are concerned with the conversion of pentose by *Saccharomyces cerevisiae* and related yeasts. (See ONRL Report C-1-85:12.)

An exciting new project that was initiated in January 1988 by the West German government is "Information Processing in Neural Architecture." Nine groups are being funded for three to four new positions at the Universities of Düsseldorf and Bochum. Professor Rolf Eckmiller of the **Institute of Biophysics** is heading the program at the University of Düsseldorf. The goals of the project are twofold: (1) to transfer knowledge about how the brain functions to the design and programming of parallel computers and (2) to develop intelligent robots that will be able, using neural processing, to "see, hear, write, speak," and otherwise respond to their environment. Although the US is, at present, the leader, the German government is anxious not to be left behind in this area, which has tremendous commercial potential.

Other research areas covered at the Institute of Biophysics, University of Düsseldorf, are under the direction of Professor Detlev Riesner, who deals with gene technology, biochemical kinetics, maximization of protein expression, development of gene technology methods, biochemical thermodynamics, and isolation of prokaryotic genes by hybridization techniques.

The **Ludwig Maximilians University of Munich** specializes in educational programs covering the areas of organic chemistry, biochemistry, genetic engineering, and pharmaceutical technology associated with research on enzymology, gene technology, production of pharmaceuticals, plant cell culture technology, and anaerobic processes as well as brewing technology.

Genetic engineering centers were set up in 1984 at the University of Munich as well as the Universities of Heidelberg, Cologne, and Berlin. Scientists at the **Center for Gene Technology at the University of Munich** are involved in research on many aspects of genetic engineering. One area is concerned with immunological-biological questions at a molecular level. Another area is research on the genetic engineering production of proteins like insulin in bacteria and yeasts.

Professor August Böck who is affiliated both with the Institute for Genetics and Microbiology and the Center for Gene Technology is engaged in a project funded by the Biotechnology Action Program (BIP). The research is concerned with the folding, assembly, stability, and

genetic modification of penicillin acylase and its precursor.

The **Technical University of Munich** is engaged in many kinds of biotechnological projects such as:

- Biological, chemical, and technical basis of bioconversion
- Biosynthesis of polysaccharides in high-viscosity medium
- Liquid two-phase systems
- Mathematical modeling for simulation of stationary and dynamic techniques.

A. Mersmann and his group are involved in the first three projects and E. Blass in the fourth project.

K.H. Schleifer (Institute for Botany and Microbiology, Technical University of Munich) and coworkers have carried out some interesting studies involving the cloning of the lipase gene using a new host system, a strain of *Staphylococcus carnosus*. This strain is nonpathogenic and can secrete exoproteins like lipase. An expression/secretion system was constructed and two strain-secreting lipase were found. The gene was subcloned and sequenced.

The **University of Göttingen** is renowned for general microbiology with important research directed at anaerobic processes and reactions involving hydrogen. Pharmacology is also emphasized at the University of Göttingen as well as at the University of Darmstadt.

A main field of interest at the **University of Bochum** is the genetics of plant and fungi while the research emphasis at the **University of Tübingen** is in the area of secondary metabolites from plant cultures.

Several other universities such as those at Heidelberg, Aachen, Hohenheim, Darmstadt, and Stuttgart, to mention a few, are also involved to varying degrees in biotechnology-related research. However, I have not as yet had the opportunity to visit the pertinent laboratories at these universities.

Industry

The breweries have a strong position, delivering a variety of beer mainly for local consumption, which is among the highest in the world. Munich, the beer capital of West Germany, has a number of renowned breweries such as Lowenbrau, Paulaner, Hacker-Pschorr, and Hofbrau.

Wine production, located mainly in the Rhine, Main, Franken, and Mosel valleys has changed greatly in the last few years. The Wine Act of 1971 has resulted in changes in the cultivation of wines. The trend in the biotechnology of wine manufacturing is towards wines of uniform taste for mass consumption.

Of the dairy products produced by microorganisms, various new varieties of cheese, different types of yoghurt, and others have been developed to large-scale produc-

tion. At the same time, the reliability of maintenance of the starter cultures has reached a high standard as a result, in part, of intensive research at several dairy institutes.

Bakers' yeast is produced on a large scale by the Deutsche Hefewerke, Pleser by batch-fed processing for local use as well as for export.

The chemical and pharmaceutical industries of West Germany count three companies among the world top 20. Hoechst and Bayer rank as numbers one and two, respectively, and Boehringer-Ingelheim as number 15 in world sales.

Hoechst produces quite a number and quantity of biotechnological products, of which the antibiotics are the most important. Hoechst is the most active firm in pharmaceuticals and has been involved in genetic engineering of insulin for some time. Hoechst has subsidiaries in the US and France. It has also formed coventures in biotechnology with firms in the US, the UK, and Japan. Being able to work on all these fronts enables Hoechst to gain expertise and increase its chance of commercial success. In addition, a few years ago Hoechst donated a very large amount of money to Harvard University and Massachusetts General Hospital in Boston in order to gain access to basic research in molecular biology and to train its scientists.

Bayer has a range of biotechnological products, and has a fair stake in the antibiotics market. In the field of animal health products, both Hoechst and Bayer have a large international market coverage with special strengths in the world's two largest vaccine markets – vaccines for foot-and-mouth disease and rabies. Bayer has also been active in the enzyme area, and their interest in medical diagnostics has led them into work in monoclonal antibodies. Their US subsidiary, Cutter Labs, has a joint venture with Genetic Systems Corporation to develop monoclonal antibodies for diagnostics.

Boehringer Mannheim is another firm active in the enzyme/diagnostics area. It is also developing a lively trade in specialist supplies (chemicals, etc.) for biotechnology.

Hoechst and Bayer are the most active companies in West Germany in biotechnology. Hoechst, as already mentioned, is the most involved in the pharmaceutical field, but both Hoechst and Bayer have identified the field of specialty chemicals as one for development. In the US, Hoechst owns Calbiochem-Bering and half of Hoechst-Roussel Pharmaceuticals, both involved in enzyme production. Bayer has been actively developing biological pesticides, herbicides, and fertilizers and has, jointly with Hoechst, been funding work at the Max Planck Institute in Munich. Through its subsidiaries, Miles and Cutter, Bayer is kept informed of biotechnology developments in the US: Miles is important in the enzyme and organic acid field, and Cutter is expanding its activities in purifying

enzymes and proteins. Bayer also helps fund projects at the Max Planck Institute for Plant Genetics in Cologne and jointly with the BMFT at the Institute for Genetics.

Next to Hoechst with respect to pharmaceuticals, Schering is the most active company. It has shown its patriotism by putting substantial amounts of money into the two universities in Berlin to establish a new biotechnology institute – the Biotechnikum. Schering also has links with the US. It has a contract with Genex to develop a blood protein via genetic engineering under which Schering will receive worldwide exclusive licence. Schering is also a world leader in the production of steroid hormones.

BSAF remains the German chemical company most dependent on bulk chemicals. It did not begin research on biotechnology until relatively late – 1981. However, it now has an in-house biotechnology research group and has built a combined research laboratory/pilot plant. It also has close links with Heidelberg and helps fund genetic research there with a substantial amount of money.

An area where the German biotechnology effort is weak is in the food and drink industries. Given the German strengths in fermentation technology and the excellence of the Berlin Institute (for Alcohol Production and Fermentation Technology), it is surprising that this area should be so weak. It is also in contrast to the Japanese experience: in other respects, German and Japanese experience with their emphases on fermentation technology and enzymes is very close. It was the food industry – and particularly firms in the industry like Ajinomoto, involved in the production of food additives – that took the lead in pushing Japan into large-scale production of amino acids in fermentation. Although Degussa, the Frankfurt chemical firm has considerable interests in amino acids, no West German, or for that matter, European firm yet rivals the major Japanese producers.

As in Japan, the main thrust into biotechnology has come from large firms and the government, and the German scene is notable for the relative absence of the small biotechnology firm. This is partly explained by the traditional relationship between the large chemical and pharmaceutical firms and the universities and research institutes in Germany. Thus, the industrial companies usually turn to the universities for answers to research problems they cannot solve. Until 1980/81, the main emphasis of research had been in the enzyme/bioreactor area and it was essentially process-oriented. By the time the large German companies moved into genetic engineering the major uncertainties of the early years had been overcome. Biotechnology had been shown to be a significant new technology, and the German companies were merely following their major US rivals in committing substantial internal resources to it.

The other reason for the lack of small biotechnology firms would seem to be the stock market restrictions and

the lack of venture capital. Most industrial finance in Germany comes from the commercial banking sector, which is dominated by three very powerful groups. In 1983 the first private venture capital fund – Genes Venture Capital GmbH of Cologne – was established but such funds do not face an easy time. Generally the equity market in West Germany requires a record of 7 years' profitable trading before a flotation can be made. In spite of these difficulties a few small firms have gotten off the ground – Heidelberg's Organogen and Hamburg's Biosyntech are examples. But there are no more than a handful of them and they remain very much at the periphery of the industry.

By contrast the German government, which has long been anxious to promote small and medium-size businesses, has the most supportive regime towards this sector of any major European country. Although financial institutions undoubtedly play a part, the main barrier to development seems cultural rather than institutional. Academic links have been, and remain, with the large enterprises, and the rather rigid, hierarchial academic environment in Germany militates against the American-style academic entrepreneur.

The German intellectual domination of chemistry and chemical engineering since the mid-nineteenth century has given it a natural entrée into biotechnology. Its strength and the excellence of its chemical and pharmaceutical industries has always lain not only in the pursuit of knowledge for its own sake, but in the practical application of that knowledge. A major feature of German industry is the presence on boards of directors of professors from the universities and the Technische Hochschule (technological universities) with many of them holding joint appointments in the firm and the university. Close linkage is also maintained with the countrywide network of research institutes. In addition, the adjacency of a strong university faculty in chemistry and the medical sciences to a substantial research institute has tended to create a strong interest and competence in biotechnology.

Institutes

The *Gesellschaft für Biotechnologische Forschung* (GBF) or Institute for Biotechnological Research, located in Braunschweig, is one of the 13 German research institutes committed exclusively to research in biotechnology. GBF is considered to be the foremost institute in Europe devoted to biotechnological research. Professor J. Klein, the present director of GBF, has been instrumental in developing GBF to its present top status. Currently, the BMFT provides 90 percent of GBF's support – the Land (state) of Lower Saxony (where GBF is located) providing the remainder. GBF carries out a broad program of research and development in the field of biotechnology, using microorganisms, plant and animal

cell cultures, and isolated enzyme systems. Areas covered include:

- Isolation, separation, and purification of natural products
- Genetic engineering to produce microorganisms of biotechnological interest
- Methods for obtaining biochemicals for industrial use or metabolites for use as basic materials in the pharmaceutical and food industries
- Bioreactor design and process control for the mass culture of microorganisms and related fundamental studies.

Recently, GBF has also become involved in protein engineering as a means of identifying the relationship between a protein's structure and function as a way of developing new substances and functions. GBF in their Protein Design Project is working on computer-aided protein modeling and structural analysis and modification of the active sites of growth factors. The GBF recently acquired "hardware" that is being used to improve computer-aided protein analysis and modeling. The Protein Design project is divided into five subprojects:

- Structural analysis of proteins and computer modeling (G. Schomburg)
- Modification of the specificity of protease inhibitors vis-a-vis the substrate (J. Collins)
- Optimization of biocatalysts of industrial interest (H. Tsai)
- Post-translational modification of proteins and biological activity (K. Dittmar)
- Analysis and modification of active sites of growth factors (parathormone, interleukin-2, PDGF, etc.) (W. Sebald).

Another new area of research at GBF is that of biosensor technology. A biosensor is a device, probe, or electrode which, when it makes contact with an appropriate sample, converts the presence of the desired analyte into an electrical signal. The biosensor is normally constructed by immobilizing a biologically sensitive material in intimate contact with a suitable transducing system to convert the concentration of the analyte into a quantifiable and processible electrical signal.

Some additional specific research projects at GBF, including the names of key scientists, are:

- Enzymatic and microbial transformation. M.R. Kula is a recognized expert in this field and much of her research was carried out at GBF. She has recently relocated to the University of Düsseldorf in conjunction with KFA, Jülich, as Director of the Institute of Enzymology. Kula has also been concerned with the recovery of biologically active proteins and has developed an aqueous two-phase

system for the extractive recovery of intracellular enzymes and other biologically active proteins. Another relevant and important project is the work of Kula and her group on new enzymes for the synthesis of chiral compounds as well as several new amino acid dehydrogenases. For details see *ESN* 41-2:65 (1987), *ESNIB* 88-02:10 (1988), and ONRL Report 8-002-C.

- Automation of bioreactor scale-up systems; applications of microcomputers in bioreactor control (R. Luttmann).
- Research on DNA synthesis and protein design (H. Blöcker).
- Recombinant DNA Research. GBF's Division of Cell Biology and Genetics is involved in the development of new recombinant DNA (rDNA) methods and the application of these methods to biotechnological problems. The aim of this division is to reconstruct the genes of bacteria, fungi, or animal cells in such a way that specific products are produced in large quantities. The main areas of research are: (1) to produce substances not available in sufficient quantities for clinical tests (for example, human interferon, parathyroid hormone, and other hormone-like peptides); (2) to replace conventional chemical processes that are too nonspecific, too poisonous for the environment, or too expensive, by improved enzyme-catalyzed processes (for example, application of penicillin acylase for the production of semisynthetic penicillins); (3) the elucidation of the structure of dangerous pathogens (for example, cytomegalovirus, other herpes viruses, etc.) for the development of new vaccines against viral disease. One of the new rDNA methods developed at GBF (the cosmid cloning system) is one of the best methods for the isolation and cloning of large DNA pieces from chromosomes. The division's Genetics Department also incorporates special units for the production of monoclonal antibodies for application in the area of clinical diagnostics and for hormone purification. This department is also involved in the chemical synthesis of oligodesoxyribonucleotides. H. Hauser has played a major role in much of the rDNA research. (See *ESNIB* 88-02:12, and ONRL Report 8-002-C.)

It should also be noted that the GBF has special capabilities so that more complex biotechnological projects – starting with microbiological or cell biological studies up to process engineering development (GBF-Biotechnikum) can be performed on site. The application-oriented basic research is carried out to the extent that industry can use the results as a basis for the development of new biotechnological processes. A broad and active cooperation with industry ensures a fast transfer of new methods

and technologies. (For additional information about GBF, see *ESN* 39-11:536 and *ESN* 40-2:37.)

The Deutsche Sammlung von Mikroorganismen (DSM), or German Collection of Microorganisms, is the national service collection of microorganisms and is located at GBF. The DSM, a member of the World Federation for Culture Collections (WFCC), cooperates with other service collections. (For details, see *ESN* 40-2:39.)

BIKE (Biotechnology Information Knot for Europe) also located at GBF, is an information service in the field of biotechnology. Its function is to direct questions from all areas of biotechnology to the most suitable address. It is based on the BIKE database, which was developed and is maintained at GBF. This database offers answers to questions such as who is doing what at which place. The BIKE database includes biotechnological information from West Germany, Switzerland, Austria, and East Germany. The information in BIKE is derived from all fields of biotechnology – from process biotechnology to genetic engineering. The sources are industry questionnaires, researches in scientific and business information databases and so-called "grey literature"; i.e., lectures and posters at scientific meetings, catalogues, company handouts, annual balance sheets, etc. Only information that is available publicly is included in the BIKE database, which is upgraded regularly.

A prominent center for research on DNA synthesis and gene cloning in West Germany is the **European Molecular Biology Laboratory (EMBL)**, located in Heidelberg. EMBL has an international reputation in genetic engineering and molecular biology. Young scientists, not only from West Germany but also many other countries receive training at EMBL. In addition to groups studying biological structure, gene structure, and regulation, there are also sections on cell biology, neurobiology, etc. The Director of EMBL is Professor Lennart Phillipson. Cloning sequences to simplify chromosome walking, to clone the ends of large fragments of DNA, to clone sequences containing rare restriction fragment sites as well as approaches to identifying overlapping cosmids are being investigated by H. Lehrach and colleagues at EMBL. (See *ESN* 41-5:236 and ONRL Report 7-009-C:3.)

The regulation of the copy number of plasmids of the Col E1 family in *E. coli* using site-directed mutagenesis is being carried out by M. Kokkinidis and coworkers. Some of the mutants are designed by employing interactive molecular graphics. The database obtained from the mutation work is expected to enable the prediction of the effects of amino acid substitution and to design mutants exhibiting specific structural features such as artificial enzymatic sites.

Gene technology studies are also carried out at the *Institute of Cell and Tumor Biology*. A well-known researcher in this field is G. Schütz, who, with his group, is

studying the DNA sequences required for steroid-dependent expression of the chicken lysozyme and rat tyrosineaminotransferase (TAT) gene. (See *ESN* 41-2:60 and ONRL Report C-10-86:14.)

E.F. Wagner and his group are involved in research on gene regulation in mammalian development and differentiation

C. Sander (Biocomputing Division) is concerned with computer tools for protein design. (See *ESN* 41-2:61.)

The Institute for Biotechnology (IBT), established in 1977, is one of the fourteen institutes that together form the Jülich Nuclear Research Center (KFA, Jülich). The institute consists of three units. Directors of these units are Professors H. Sahm, C. Wandrey and C.J. Soeder. The units share the general tasks of developing biotechnological processes and contributing to the treatment of solid and liquid wastes. Current research and development activities are focused on microbial degradation of polymers, conversion of substrates with biocatalysts (biotransformation), and biological treatment of wastewater.

The studies at IBT on the utilization of plant residues consisting mainly of cellulose and hemicelluloses are directed toward the eventual production of metabolites of pharmacological or technical interest (for example, glucose, xylose, ethanol, amino acids, and methane). In order to develop and optimize adequate biotechnological processes, the regulation and localization of important enzymes is being investigated in microorganisms capable of metabolizing plant residues. Of special interest are the enzymes cellulase and hemicellulase, which cleave the polysaccharides, cellulose, and hemicellulose into oligosaccharides or monosaccharides. Attempts are being made to increase the enzyme yields by mutant selection and gene manipulation.

The second group on biotransformations uses processes known from chemical engineering which have been specifically improved for the proper handling of microbes or purified enzymes. Thus, enzyme reactors are operated continuously not only with individual enzymes but also with coenzyme-dependent multienzyme systems. Target products are, for example, optically active organic acids such as amino acids. In membrane reactors, the products of the reaction are retained within the system by ultrafiltration membranes. Thus, a continuing homogeneous catalysis is ensured. Also, whole cells can be used for the exploitation of metabolic routes which lead from substrate to the end product (for example, an amino acid) in more than one step. They are held back in the reactor by membranes with larger pores than those described above; i.e., microfiltration membrane. The feed solution contains precursors of the target product that are available via chemical synthesis. Product formation can always be uncoupled from microbial growth. For instance, in the case of ethanol production from glucose, the growing micro-

bial cells are partially retained in the bioreactor in order to maintain a high catalyst concentration. This results in an increased yield in time and space and reduces retention time.

In biological wastewater treatment, as an alternative to entirely bacterial processes, photosynthetic bacteria are being used at IBT for biogenic aeration of flat pond-like containers in which bacteria oxidize sewage compounds. At the IBT, the interaction between suspended algae and bacteria is being studied under continuous flow conditions, especially as it depends on solar radiation, temperature, substrate concentration, pH, and retention time. The cooperation between algae and bacteria is also under study at IBT. The tests are carried out in the laboratory as well as at the pilot-plant scale. Since the biological treatment of wastewater can also proceed without a supply of oxygen, strains of anaerobic bacteria which participate in the conversion of dissolved organics into methane are also being investigated. Besides the work on pure cultures, the conversion of various substrates by defined, mixed populations is also being tested.

H. Sahm and his colleagues are especially concerned with research on microbial amino acid production, ethanol fermentation with bacteria and anaerobic wastewater treatment.

C. Wandrey and his group deal with the biotechnological production of L-amino acids from chemically synthesized precursors, development of bioreactors, continuous production of extracellular enzymes, and microbial anaerobic wastewater treatment.

C.J. Soeder and coworkers are mainly concerned with aerobic wastewater treatment, elimination of nitrates from soil, and wastewater, and also biofiltration development for wastewater purification.

The Max Planck Society funds a variety of laboratories, which are responsible for much of the basic research advances in biotechnology. These laboratories are called **Max Planck Institutes** and are funded by the West German government. Leading institutes working in basic research related to biotechnology include those in biochemistry at Martinsried (Munich), in biology and virus research at Tübingen, in cell biology at Ladenberg, and in plant breeding and genetic engineering at Cologne.

R. Huber and his group at the Department of Biochemistry, Max Planck Institute in Martinsried, have been carrying out extensive research on the flexibility and rigidity requirements for functions of proteins and protein-pigment complexes. (See *ESN* 41-9:474.) In 1988, R. Huber shared the Nobel Prize in chemistry with J. Deisenhofer (US) and H. Michel (West Germany) for their work on unravelling the structure of a complex of proteins that serves as the engine for photosynthesis in some bacteria. In 1982, Michel did what many researchers considered impossible: he grew crystals of the membrane-bound proteins that act as the photosynthetic

engine of a group of bacteria called *rhodospseudomonads*. Over the next 3 years, Huber and Deisenhofer (who was then working with Huber at the Max Planck Institute in Martinsried) probed the crystal with x-rays. Eventually they pinpointed the position of all 10,000 or so atoms in the protein complex. This knowledge has already provided insights into how plants and algae as well as the *rhodospseudomonads* carry out photosynthesis. The work may also help investigators to understand the role that membrane-bound proteins play in diabetes, cancer, and other diseases.

H.J. Fritz and coworkers, also at the Max Planck Institute in Martinsried, have been doing interesting work in protein engineering starting from an immunoglobulin variable domain. (See *ESN* 41-9:474). Fritz and his group are also concerned with new developments in the areas of mutation construction and chemical gene synthesis. (See *ESN* 41-260).

K. Hahlbrock (Max Planck Institute for Plant Breeding Research, Biochemistry Division, Cologne, West Germany) and his group are engaged in research dealing with

plant-biochemistry/molecular-biology and phytopathology. H. Saedler at the same institute is also carrying out studies in plant molecular biology.

At the Max Planck Institute for Molecular Genetics in Berlin, H.G. Wittmann and colleagues are engaged in research on the structure, function, and biosynthesis of peptides and proteins. At the same location, R. Kahmann and coworkers are studying gene regulatory mechanisms in prokaryotes and eukaryotes.

Among the specialized research institutes worthy of mention are the Institute of Industrial Fermentation and Biotechnology in Berlin (promoting new fermentation techniques), the Dairy Institute of Kiel and Weihenstephan (southern Germany) working, for example, on various aspects of starter cultures, and, in Geisenheim, the Institute for Wine Culture, Horticulture, Beverage Technology, and Agricultural Development.

Also of importance are the Fraunhofer Society Institutes dedicated to more practical research for industry.

United Kingdom

Like the French, the UK government and the public were relative latecomers to developments in biotechnology. The UK government was prompted into action by the Spinks Report of 1980 and a series of Select Committee hearings in the House of Commons in 1982. But if government and public were newcomers to biotechnology, industry and universities were not; indeed the UK's relative strength in biotechnology stems from these two sectors. The UK's intellectual achievements in the disciplines most closely allied to biotechnology are formidable.

Unlike Germany and Japan, the UK was not caught short by the genetic engineering developments in the 1970's. Of all the European countries, the intellectual climate in the UK approaches most closely that of the US, with the main emphasis of academic research being at the high-tech end of genetic engineering. In the past, relatively less attention was paid to fermentation technology, bioreactors, and chemical engineering. However, these important areas of biotechnology research have recently been given priority status by new government directives.

Government

Following the explosion of interest in biotechnology, the UK government has emphasized biotechnology research during the past few years. Funding for biotechnol-

ogy research in universities is mainly by allocation from the UK Research Council. The major expenditure is from the Medical Research Council (MRC). The Science and Engineering Research Council (SERC) has its own Biotechnology Directorate which has a separate budget. The SERC Biotechnology Directorate was set up in 1981 to develop and implement a policy for the support of research and training in biotechnology in UK universities and polytechnics. The Directorate maintains close association with those of the Biotechnology Unit of the Department of Trade and Industry (DTI). The DTI uses its funds for biotechnology mainly, but not exclusively, to pump-prime specific projects within industry itself to the point where revenues can be generated and the process becomes self-financing. Some funding from this source, however, has gone into universities. The DTI has a significant program of R&D support for public sector laboratories including Warren Spring Laboratory, Harwell, and the Center for Applied Microbiology and Research at Porton Down (CAMR). The aim is to encourage precompetitive research in collaboration with companies particularly in the area of fermenter design and the development of downstream processing plants. These laboratories also have pilot-plant facilities that can produce limited quantities of specific products for the evaluation of their departmental program to encourage

all parts of the biotechnology process, from genetic engineering through to product purification.

SERC also encourages collaboration between academic institutions and industry in both research and post-graduate education.

Additional funding into industry and to a lesser extent universities comes from the British Biotechnology Group, which has the specific directorate to act as pump-primer for promising projects in any scientific and engineering areas.

The Agriculture and Food Research Council (AFRC) is also a major supporter of biotechnology with inputs into universities and its own special interests.

University-Industry Relationships. Many universities are now working in close collaboration with industry on joint projects of various magnitudes. Specific and financial encouragement comes from the DTI and SERC. In some cases, this has gone as far as establishing specific research centers—as at the University of Leicester and Cranfield Institute of Technology. These institutions have established a major biocenter to carry out industrial biotechnology projects with industrial partners. The Liverpool government has taken steps to strengthen the region's biotechnology industry base, including the construction of a science park in the city. The park is linked to Liverpool University and Liverpool Polytechnic. The former's collaborations with local chemical companies has already led to the formation of two companies that supply materials and services to the nuclear biology industry.

Although the British are among the front-runners in molecular biology research, they have not been taking full advantage of its industrial spinoffs. Thus, in 1987, SERC created another mixed industry-research program that will promote rapid transfer of basic knowledge to commercial production. This project brings together several manufacturers in an extensive research program and, in exchange for their financing, allows them to take immediate advantage of significant results. The group includes Celltech, Glaxo, ICI, and RZT Chemicals, on the one hand, and the laboratories of the Universities of Bristol, Leeds, Oxford, and Sheffield, as well as two London colleges, Birbeck and Imperial, on the other.

Some universities have established their own biotechnology companies specifically to develop their own expertise and projects in conjunction with any industrial company which wishes to participate. Such universities include those of Cambridge, Sheffield, Imperial College (London), Manchester, Edinburgh, and the University of Wales. A major consortium has arisen at the Institute for Biotechnological Studies (operated jointly by the University of Kent, University College (London), and Polytechnic of Central London) which has created, with the aid of funding from the DTI, a biocatalysis group specifically to

develop the industrial applications of this emerging technology.

The North of England boasts biotechnological research activities at the Universities of Durham and Newcastle on Tyne, Newcastle Polytechnic, Sunderland Polytechnic, and Teeside Polytechnic. The five institutions have joined to create a program, "Higher Educational Support for Industry in the North."

The North East Biotechnology Center, a consortium of Teeside and Sunderland Polytechnics was developed to promote biotechnology. Designated as a national Center for Development, the organization oversees biotechnology activity at the two schools and biotechnology education in the region.

The Yorkshire and Humberside Development Association is actively promoting the health care and biotechnology industries. The region is home to about 120 companies that emphasize pharmaceuticals, hospital and medical supplies, dental equipment, and biotechnology.

Last year, four British pharmaceutical companies joined 11 UK universities and polytechnics to fund a \$2.5 million genetic manipulation program over a 3-year period. Their purpose is to boost and diversify antibiotic production. Coordinated by the Biotechnology Directorate of SERC and the Biotechnology Unit of DTT, this UK-government-sponsored program is centered on the creation of novel strains of *Penicillium*, *Aspergillus*, *Streptomyces*, and other producers of valuable secondary metabolites. It will exploit techniques such as those evolved by David Hopwood and his colleagues at the John Innes Institute (Norwich) as the basis for engineering "hybrid antibiotics." The program manager is Iain Hunter of the University of Glasgow. Among other campuses involved are the University of Manchester, Institute of Science and Technology, where researchers are studying the genetic switches mediating between antibiotic and biomass production; and University College, London, where there is particular interest in methods of increasing plasmid stability. Participating companies in this program of precompetitive research are Apcel (Slough), Beecham (Surrey), Glaxo (Middlesex), and Imperial Chemical Industries (ICI). University College, London, is expected to pair with the University of Birmingham in a quite separate biotech initiative. The two campuses are slated as joint headquarters for a new UK Biochemical Engineering Center focused on product recovery, advanced bioreactor control techniques, and other aspects of bioprocessing. Still evolving, the plan is for SERC to provide core funding for work financed in part by contracts with industrial companies.

Additional information about UK funding of biotechnology is available in: ESN 39-10:492 and 494; ESN 39-11:538 and ESN 40-3:110.

Institutes. The UK government through its various departments has about 30 research institutes involved to

a greater or lesser extent with biotechnology which may be funded directly from a department (for example, the Department of Health and Social Security is responsible for the Center for Applied Microbiology and Research [CAMR] at Porton Down) or from a Research Board (for example, the Agriculture and Food Research Council [AFRC] funds several institutes and groups with specific biotechnology interests). The larger institutions that may be cited include CAMR, Porton Down; National Institute for Medical Research, London; Food Research Institute, Norwich; John Innes Institute, Norwich; MRC Laboratory for Molecular Biology, Cambridge; Rowett Research Institute, Aberdeen; Warren Springs Laboratory, and the Biotechnology Group of the Atomic Energy Research Establishment at Harwell.

Specific research projects at some of these institutes as well as the scientists involved are presented in the following paragraphs.

Center for Applied Microbiology and Research (CAMR). P.M. Hammond and M.D. Scawen, in the Division of Biotechnology, are concerned with studies to improve existing methods and to develop new procedures for the scaleup of the purification of proteins for production. A. Maule and coworkers in the Microbial Technology Laboratory deal with research on the microbial production of commercially important hydroxylated compounds from haloaromatics. In the same laboratory, N.P. Minton is the project leader for studies of the development of host/vector systems in *Clostridia* of industrial and agricultural importance. T.A. Collinge and his group in the Microbial Technology Laboratory are involved in downstream process monitoring and the development of new separation techniques (see ONRL Report 8-003-C for details). In the same laboratory, D.J. Clarke and coworkers deal with studies concerned with the monitoring of reactor biomass.

The National Collection of Animal Cell Cultures (NCACC) at CAMR was opened in July 1984 under the auspices of the DTI's program to support biotechnology in the UK.

John Innes Institute (Norwich). D.A. Hopwood and his group at the Department of Genetics are using genetic engineering to develop new antibiotics. They have shown that "hybrid" antibiotic molecules can be synthesized by genetically hybrid strains. (See *ESN* 41-2:64 and ONRL Report C-10-86 for further information). K. Roberts and coworkers in the Department of Cell Biology are engaged in studies of the control of the differentiation of plant cells and of their regeneration into entire plants with special emphasis on cell membrane. D.R. Davies and his group are also involved in studies of relevance to agriculture. One project is the isolation, analysis, and expression of specific pea storage protein genes. Also in the plant field in the area of symbiotic relationships between plants and

Rhizobium, A.W.B. Johnston and coworkers are investigating the genetic basis of host range in *Rhizobium*.

Warren Spring Laboratory (Stevenage). The Warren Spring Laboratory (WSL), created in 1959, is an industrial research establishment of the DTI. The Biotechnology Division offers a range of technical and technicoeconomic expertise to the biotechnology and manufacturing industries. The group undertakes contract research and development (R&D), consultancy, and multicustomer club ventures. The division has expertise in bioprocess development and innovation and aids companies in maximizing their share of benefits from biotechnology. The Biotechnology Division possesses comprehensive laboratory and pilot-plant facilities and also combines its expertise with that of other divisions within WSL. (See *ESNIB* 87-02:13 for details.)

P.N. Whittington (Biotechnology and Separations Division, WSL) and coworkers are engaged in studies of the recovery of cells from fermentation broths. They are investigating several new separation processes as part of a collaborative project on downstream processing funded by industry and the DTI. Details are available in ONRL Report 8-003-C. Biosurface properties and their significance for primary separation are being studied by S.R. Warne and his group (Biotechnology and Separations Division). (See also ONRL Report 8-003-C.)

Agriculture and Food Research Council (AFRC). At AFRC's Institute of Animal Physiology and Genetics Research, Edinburgh Research Station, J.P. Simons and coworkers have been investigating gene transfer into sheep. The basis for this work is that gene transfer into animals has considerable potential for livestock improvement. If this potential is to be realized, the ease of generation of transgenic livestock will be of major importance. In a collaborative study with J.O. Bishop (Department of Genetics, University of Edinburgh), these researchers have been able to demonstrate that gene transfer into the germ-lines of sheep may be reliably accomplished by microinjection of DNA into pronuclei of fertilized eggs. The genes transferred were designed to direct the production of human proteins. Therefore, it is possible that transgenic animals carrying such genes may ultimately provide a new source of these and other therapeutic proteins.

D.J. Garwes and coworkers at AFRC's Institute for Research on Diseases are working on the identification and expression of epitopes of porcine transmissible gastroenteritis virus and these studies are being extended to the other viral genes and to their expression in other cells, including yeasts. At the Institute of Food Research in Norwich, M.J. Gasson and coworkers are engaged in studies of the genetic manipulation of lactic acid bacteria for improved dairy production.

Universities and Polytechnics

Most of the 50 British universities along with 30 or so polytechnics can now claim to be making an input into biotechnology through some part of their teaching in their departments of biochemistry, microbiology, genetics, or chemical engineering as well as research projects.

The following section deals with specific research projects and the scientists and universities and polytechnics involved. The listing is, of course, incomplete as it has not been possible for me to cover every institution, but at least the reader will be able to obtain a view of the excellent research related to biotechnology that is being carried out in the UK.

University of Birmingham. The University of Birmingham (UB) was selected in 1986 as one of two centers for Biochemical Engineering with a major new grant provision that started in 1987. (The other center is at University College, London.)

J.F. Kennedy and V.M. Cabalda (UB's Research Laboratory for the Chemistry of Bioreactive Carbohydrates and Proteins, Department of Chemistry) are using genetic engineering to allow optimization of starch conversion technologies both by creating novel enzymes and novel microorganisms of the desired efficiency, stability and activity to fit any process and to ensure they are produced in commercial quantities. These studies are carried out in collaboration with C.A. White (Chembiotech Ltd., Institute of Research and Development, University of Birmingham Research Park).

In the area of process engineering in biotechnology and, specifically, fermentation technology, A.N. Emery and A.W. Nienow (Department of Chemical Engineering) are developing a fermentation pilot plant for the support of mixing and scale-up studies. In conjunction with N. Thomas and J. Callow of the same department, they are also studying novel bioreactors for delicate materials.

A. Lydiatt also of the Department of Chemical Engineering and Emery are investigating controlled fabrication and operation of immunoaffinity adsorbents in biochemical downstream processing. Emery is also involved in a study of gel entrapment of cells and its effects on material transfer and bioconversion processes.

In the area of enzyme biocatalysis, Kennedy is investigating enzyme production, immobilization, and kinetics. In collaboration with R. Jefferis (Department of Immunology), Emery and Nienow are investigating the optimization of monoclonal antibody production in membrane-retained systems of hybridoma culture.

Plant biotechnologies – specifically, basic studies for plant fatty acid synthetase biotechnology – is being investigated by R.G.O. Kekwick (Department of Biochemistry). D.A.J. Wase (Department of Chemical Engineering) and C.E. Forster (Department of Civil En-

gineering) are studying microbial surface interactions in anaerobic reactors.

L.J. Kricka (Department of Clinical Chemistry) and G.H.G. Thorpe (Department of Clinical Chemistry, Wolfson Research Laboratories, Queen Elizabeth Medical Center) are engaged in studies of the application of immobilized enzymes in clinical analysis with particular emphasis on bioluminescent and chemiluminescent assays and test devices intended for use outside the main clinical laboratory.

University of Leicester. The university has been designated as a center of excellence in biotechnology by the UK government. In response to an identified and growing need for cooperation between the industrial and academic sectors, the university, with support from its industrial partners and the Biotechnology Directorate of SERC, established the Leicester Biocenter in 1982. The Biocenter seeks a rapid transfer of ideas and high-technology developments in biology from the university to industry. In addition, it aims to guide academic research into those areas that are of commercial significance. The Biocenter also offers facilities for contract research. In 1984, Professor I.J. Higgins, Leverhulme Professor of Biotechnology at the Cranfield Institute of Biotechnology was appointed as Director of both the Leicester Biocenter and the Cranfield Biotechnology Center.

Undoubtedly, the most dramatic research that has come from the University of Leicester recently is the discovery of "human genetic fingerprints" by Professor Alec Jeffreys (Department of Genetics) in collaboration with Dr. Swee Lay Thein, an MRC Training Fellow at the MRC Molecular Hematology Unit in Oxford. The study was supported by an MRC project grant.

I.B. Holland (Department of Genetics), in collaboration with W.J. Brammar (Department of Biochemistry) and H. Smith (Department of Botany), is studying plasmid replication, protein synthesis, and secretion in yeast as well as control of plant gene expression.

W.V. Shaw and W.J. Brammar (Department of Biochemistry) and coworkers are engaged in studies of synthetic nucleotides for *in vitro* genetic studies.

At the university's Biocenter P.S. Meacock and A. Boyd are carrying out studies on the yeast cell cycle and secretion of proteins from yeast.

G.D.D. Jones, P.M. Cullis, M.C.R. Symons, and J.S. Lea (Department of Chemistry) are studying the structure and mobility of electron gains and loss centers in proteins with respect to the fundamental processes involved in protein damage such as, for example, damage caused by radiation.

In the Department of Microbiology, W.D. Grant is carrying out studies on the ecology and taxonomy of archaeobacterial halophiles.

Imperial College of Science and Technology, London. D.W. Ribbons (Center for Biotechnology) has a

large group working on biotransformations for synthetic organic compounds. Their main objective is to produce new fine chemicals using microorganisms – principally bacteria and yeasts. (See *ESN* 41-7:358.) At the Department of Chemical Engineering, M.C.G. del Cerro and D.C. Stuckey are engaged in studies of liquid membrane extraction applied to fermentation processes.

K.W. Buck and H.A. Coutts (Department of Pure and Applied Biology) are developing plasmid vectors based on geminivirus replicons for monocotyledonous protoplasts. B.S. Hartley and coworkers (Center for Biotechnology) are engaged in studies of the pyruvate carboxylase gene. W.J. Albery, J.A. Barrie, and A.E.G. Case (Center for Biotechnology) are concerned with the development of biosensors. The overall aim of their research is to develop new types of enzyme electrode systems using flow systems based on the wall-jet principle and specially designed membranes to give optimum performance. Particular attention is being paid to low-level detectors based on the principle of accumulation on an enzyme bed.

In the protein engineering program, D.M. Blow and coworkers (Department of Physics) are carrying out research to expedite the most time-consuming aspect of protein crystallography, namely, the growth of crystals of adequate size and degree of order. H.R. Morris and coworkers (Department of Biochemistry) are involved in research on mass spectrometry of natural and recombinant proteins and glycoproteins.

D.J. Leak and his group (Center for Biotechnology) are engaged in studies of achieving specificity with alkane mono-oxygenases. Regio- and stereo-specific biological oxygen insertion reductions offer significant opportunities for the production of chiral alcohols and epoxides.

A. R Fersht (Department of Chemistry) and his coworkers are carrying out research in protein engineering. This area is one of the most promising scientific disciplines for the future. Fersht is one of the top investigators in the UK working in this area, which is supported by the MRC and SERC. Fersht and G. Winter (University of Cambridge) have developed molecular graphics and computational methods for application to protein engineering. (See ONRL Reports 7-009-C and 7-019-C and *ESN* 41-2:60.)

University College of London University. M. Hoare and coworkers (Department of Chemical and Biochemical Engineering) are engaged in biochemical engineering studies to improve protein processing i.e., protein enrichment and purification. One program is concerned with protein precipitation and precipitate recovery – a procedure developed by this group – and another on the action of shear on membrane-associated protein. (See ONRL Report C-13-85). The latter project is carried out in collaboration with P. Dunhill.

M.D. Lilly and coworkers are involved in studies of the kinetics of biological reactions involving a reactant-

containing organic phase. In conjunction with N.M. Fish and M. Hoare, Lilly is also investigating the influence of fermentation culture conditions on the production of nonmicrobial polypeptides or proteins by bacterial sources.

P. Dunhill and Fish are carrying out studies of scale-down in fermentation and recovery of enzymes and proteins. The overall aim is to use scaled-down pilot plant fermentation and downstream processing systems and to examine the potential of such systems to model large-scale performance. Fish is concerned with polypeptide aggregation in the processing of recombinant DNA products. C.R. Thomas is engaged in studies to develop image analysis as a tool for process control of fermentation of filamentous microorganisms. Software is being developed to permit a totally automated determination of the morphological parameters of interest. The investigators mentioned above are all members of the Department of Chemical and Biochemical Engineering.

R.E. Drew (Department of Biochemistry) is investigating the expression of cloned amidase genes. E. Keshavarz (Department of Chemical and Biochemical Engineering) is engaged in extensive studies of the biochemical aspects of cell disruption. (See ONRL Report 8-003-C.)

In a relatively new and rapidly progressing area related to biotechnology, namely, neural computing, M. Reece (Departments of Computer Science and Anatomy) is engaged in studies of neural systems and models. P. Treleven (Department of Computer Science) is also well-known for his work on programming languages for neurocomputers. The Neural Network Implementation Language (NIL) was developed at University College. Treleven, Reece, and coworkers have designed and are currently implementing in CMOS a primitive processing element for building a parallel MIMD neurocomputer. The goal of the neurocomputer is to support a range of connectionist algorithms spanning both neural network models and semantic network languages. (See *ESNIB* 88-04:6 and ONRL Report 8-010-C.)

Cranfield Biotechnology Center, Cranfield Institute of Technology. Cranfield Biotechnology Center is an integral part of the Cranfield Institute of Technology, which specializes in postgraduate training and applied research. The Biotechnology Center, which was created in 1981 with I.J. Higgins as Director, is involved in a wide range of research activities in the area of biotechnology; a detailed account is available in *ESNIB* 88-01:13. The Cranfield Biotechnology Center is especially noted for its research on biosensors and, in fact, has some biosensors already on the market or available for marketing in the near future. For additional information about the biosensor research. (See *ESN* 41-8:415.)

P.J. Warner (Biotechnology Center) and his group are working on studies concerned with the optical and

electrochemical detection of immobilized DNA. (See ONRL Report 7-032-C.) A.F. Turner is a leader in the research and development of amperometric biosensors at the Biotechnology Center. In the course of the last 4 years, a bioelectrochemical method for the assessment of microbial activity has been developed at Cranfield under the sponsorship of Paul de la Pena Ltd. and the DTI. This work, which has resulted in the production of a prototype instrument "The Biocheck," was carried out by Turner in conjunction with M.F. Cardosi and A. Swain.

I.J. Higgins has also been involved in research on the role of internal membranes, catabolic regulation, and location of enzymes in obligate methanotrophs. Turner and Higgins are carrying out research on quinoprotein-based immunosensors in addition to their other projects.

University of Surrey. This university is one of Britain's newest universities, having been granted its charter in 1966. The teaching and research emphasis is towards science, engineering, and technology.

Within a mile of the university is a recently opened 70-acre international science park (The Surrey Research Park). The university facilities are available to the companies located in the science park and collaboration between researchers at the university and those at the science park will be promoted. The following paragraphs deal with some of the research projects carried out by various scientists at the university.

R.J. Litchfield and coworkers (Department of Chemical and Process Engineering) are engaged in a project to tailor adsorbents for the efficient recovery of high-purity biological products from dilute aqueous mixtures. Another project by these investigators deals with the detection and isolation of antibiotic producers in soils.

R. Spier and coworkers (Department of Microbiology) have been engaged for the past few years on studies of animal cells in culture. One project dealt with growth factors from animal cells in culture. Spier and his group are also examining the productivity of animal cells in culture. These researchers also are working on an equipment design which will not only enable reliable operation free from exogenous contamination but which can also be readily scaled up. In a project, Spier, in collaboration with R.C. Chivers (Department of Physics), is studying the ultrasonic estimation of biomass for biotechnology. (See ONRL Report C-13-85.)

A.D. Murdin, J.S. Thorpe (Department of Microbiology), N. Kirkby (Department of Chemical and Process Engineering), and D.J. Groves (Department of Biochemistry) are collaborating on studies of the immobilization and growth of hybridoma cells in packed beds.

Animal cell biotechnology, one of the most rapidly developing fields of biotechnology, is being emphasized at the University of Surrey. The Animal Cell Research Group in the Department of Microbiology is headed by R.E. Spier. It was formed only about 3 years ago and has

become one of the leading research groups in the field. Murdin and Thorpe, mentioned above, are members of this group as well as P.G. Sanders. The group has attracted substantial funding from the DTI, SERC, MRC, and the Wolfson Foundation in addition to industrial funding for contract research. In addition to excellent research facilities for laboratory-scale culture, the group has a pilot plant for scale-up studies, and a purpose-built cytotechnology laboratory is under construction. (See *ESN* 41-7:358.)

University of Cambridge. The university founded its Biotechnology Center in 1984 to foster closer links with industry to achieve technology transfer and to train high-quality graduates. C.R. Lowe is the Director. The center is involved in a program of fundamental and applied research in several interlocking areas that fall into three categories: (1) downstream processing, (2) biosensors and bioelectronics, and (3) immobilized biocatalysts.

C.R. Lowe is well-known for the research carried out by him and his coworkers on development of biosensors for application in biotechnology. These investigators are developing novel solid-state biosensor devices for biotechnology with particular emphasis on new transducers, field-effect transistors (FET's), and amperometric devices. The program covers the development of immunologically sensitized field-effect transistors, optical fibers, waveguides and other optoelectronic configurations, surface conductance and thermal devices, and "electron transfer" amperometric sensors. (See *ESN* 40-9:301, *ESNIB* 88-01:16 and ONRL Report 7-032-C.)

E. Hall (Biotechnology Center) and coworkers have developed one of the simplest solid-phase constructions via an indicator dye around existing colorimetric determinations. Ideally suited to fiber optic technology, and using low-cost light-emitting-diode (LED) light sources and silicon photodiode detectors, these systems have a very low-power consumption and allow the benefits of battery-operated instrumentation to be exploited, according to Hall. She and her group are also working on immunosensors. (See *ESN* 41-8:415.)

Lowe's team at the Biotechnology Center is also involved in research on downstream processing. These investigators are mainly interested in developing affinity chromatography systems for purifying high-value proteins, using textile dyes and immobilized monoclonal antibodies. The major push is on anthroquinone dyes that are very cheap. Lowe says that these would replace more extensive purifying "ligands," such as the biological cofactors NADP or NAD, of very high cost.

J. Davidson (Department of Chemical Engineering) is involved in studying the dynamics of ICI's well-known airlift fermenter, the basis of its Pruteen process, which Davidson originally helped design. H. Chase, in the same department, is tackling the scaleup of adsorbent methods for purifying high-value pharmaceuticals. Chase and his

group are also comparing the performance of standard packing in affinity chromatography columns such as silica, or standard gels with immobilized monoclonal antibodies. Celltech, the British genetic engineering company, is interested in the development of such systems for protein purification. (See *ESN* 41-5:230.)

The antibiotics industry wants to redesign the traditional ways of purifying products to make them more energy efficient. N. Slater (Department of Chemical Engineering) and his colleagues are working with Glaxo to improve the performance of Glaxo's traditional amberlite resins to purify cephalosporins. N. Kenney, in the same department, is also working with ICI to see how other adsorption systems could be scaled up, using lysozyme and bovine serum albumin as models.

G. Winter (Medical Research Council [MRC], Laboratory of Molecular Biology, University of Cambridge) is well-known for his research in the area of protein engineering and is one of the top scientists in the UK working in this field. He is using the application of recombinant DNA technology for the purpose of engineering of enzymes and other proteins, such as antibodies. This technology may also permit the tailoring of enzymes for industrial or medical uses. (See ONRL Report C-13-85.) The laboratory's M.J. Gait is involved in the use of synthetic oligonucleotides in methods of site-directed mutagenesis, particularly with regard to the needs of protein engineering. C. Chothia and coworkers, also of the laboratory, are also engaged in studies of protein engineering. (See ONRL Report 7-019-C.)

G.T. Williams and M.S. Neuberger (MRC, Laboratory of Molecular Biology, University Postgraduate Medical School) are engaged in research on novel antibody reagents.

S. Brenner (MRC Molecular Genetics Unit, University of Cambridge), who is world-renowned for his many and varied research projects in the area of molecular biology, is presently involved in studies of the molecular evolution of genes and proteins.

M. Bennett and J. Heslop-Harrison (Plant Breeding Institute, University of Cambridge) have recently found that chromosomes in plants are arranged in patterns rather than at random as deduced from previous research. This finding has major implications for the genetic engineering of plants and animals. These researchers are now extending their studies to animals and even humans.

R.B. Flavell and coworkers, also at the Plant Breeding Institute, are carrying out studies on the cloning and characterization of grain protein genes and related genomic regulatory sequences. Gene transfer is by introduction of chromosomal segments into the Ti-plasmid.

University of Oxford. The University's Department of Biochemistry is one of the largest in Europe and its research programs cover a wide range of topics. Some of

the scientists involved in research having relevance to biotechnology are listed below:

- A.J. Kingsman and coworkers are concerned with studies of foreign gene expression in yeast. (See ONRL Report C-10-86.)
- M. Lee and P. Nurse (Microbiology Unit, Department of Biochemistry) are studying the cell cycle control genes in fission yeast and mammalian cells.
- R.A. Dwek (Oxford Glycobiology Unit, Department of Biochemistry) and his group are engaged in studies of the structure-function relationships of carbohydrates in glycoconjugates. For the past 5 years Dwek, who is director of the unit, and coworkers have been developing high-tech systems for analyzing N-linked oligosaccharides with the financial backing of Monsanto Co., St. Louis, Missouri. Oxford Glycosystems Ltd. is ready to commercialize some of these systems.
- A. Watts and coworkers are engaged in studies of structure-function relationships of proteins and lipids in membranes.
- S.M. Kingsman and his group are concerned with research on the molecular genetics of viruses.
- D.B. Roberts and coworkers are carrying out research on the control of gene expression in *Drosophila*.
- P.C. Newell and his group are studying cell signalling and chemotaxis in the amoebae *Dictyostelium*.

Relevant work is proceeding in other departments. Following are those I know of.

- B.S. Cox (Department of Botany) and coworkers are carrying out research on the cloning of yeast heat shock genes.
- H.A.O. Hill (Department of Inorganic Chemistry) and coworkers are engaged in research on the development of novel biosensors including microbiologically based amperometric sensors.
- A.R. Rees, B.J. Sutton and D. Phillips (Department of Molecular Biophysics) are carrying out research on antibody engineering. The aim is to investigate the structural and genetic determinants of antibody recognition of protein antigens with the eventual objectives of altering antibody affinity or specificity.
- B.J. Bellhouse (Medical Engineering Unit) is working on a novel membrane module for use in biotechnology that has high transmembrane flux rates and low fouling. This project is a collaborative effort with J.M. Wyatt of the Biological Laboratory, University of Kent and C.J. Knowles of BMP Ltd., Abingdon, Oxfordshire.

- D.H.L. Bishop (Natural Environment Research Council [NERC], Institute of Virology) and coworkers are engaged in studies of baculovirus expression vectors for animal virus vaccines.

U. Strange (Department of Geology and Physical Sciences, Oxford Polytechnic) is concerned with the analysis of immunological reactions on biochemically sensitized surfaces by optical biosensing techniques. This research is a joint project with N. Groome (Department of Biology) and L. Tarrassenko (Department of Engineering), both at Oxford Polytechnic. (See ONRL Report 7-032-C.)

K.W. Fuller and coworkers (Department of Plant Sciences) are carrying out research on the use of naturally immobilized cells systems (NICS) for biotransformation and biosynthesis in plant cells. (See *ESN* 41-7:358.)

I.D. Campbell and coworkers (Department of Biochemistry) are studying protein structure determination by nuclear magnetic resonance (NMR).

E. Rolls (Department of Experimental Psychology) and coworkers are carrying out studies related to the exciting new area of neurocomputers. He and his group are carrying out innovative and important experimental work involving memory in the primate hippocampus and back-projections from the neocortex. These investigators combine experimental studies, theory, and computer simulation of neural networks in a research program with unique capabilities.

University of Manchester. A center for the exploitation of science and technology, paid for mainly by industry, is being established in the science park attached to the University of Manchester. Its aim will be to identify for universities and industry, areas of research most likely to lead to commercial success. Thus far, 18 companies are involved, with the UK government contributing about \$2 million.

Scientists at the University of Manchester Institute of Science and Technology (UMIST) have developed a working prototype of an automated DNA sequencer. Their equipment specifically automates Sanger reactions, which take advantage of chain-terminating dideoxynucleotides. The apparatus is capable of sequencing 36 templates in 50 minutes. The British Technology Group (BTG) owns the rights to UMIST's work and is seeking to license it with a price tag of about \$35,000. The technique of DNA sequencing is of central importance in molecular biology and biotechnology particularly now that the US and other countries have decided to sequence the human genome. This work was a collaborative effort between two departments at UMIST. The scientists involved are: W.J. Martin, B.R. Galinski, M.S. Beck, and M. Gallagher (Department of Instrumentation and Analytical Science); and J.R. Waddington, R.W. Davies, and

S.G. Oliver (Department of Biochemistry and Applied Molecular Biology).

T.K. Sundaram and coworkers (Department of Biochemistry and Applied Molecular Biology, UMIST) are engaged in studies of thermostable enzymes for biotechnology. (See *ESNIB* 88-03:12.) In the same department, S.G. Oliver and his group are carrying out studies of enzyme export in *Aspergillus niger*. Also, J.A. Cullum and his group are studying the molecular basis of DNA amplification and gene instability in *Streptomyces*.

B. Robson (Department of Biochemistry, University of Manchester) and coworkers are carrying out research on computer-aided and protein engineering software development.

F. Mavituna, A.K. Wilkinson, and P.D. Williams (Department of Chemical Engineering, UMIST) are carrying out studies on the production of secondary metabolites by immobilized plant cells in novel bioreactors. Two types of bioreactors have been developed for the *in situ* immobilization of plant cell aggregates in reticulate polyurethane foam matrices.

Also in the Department of Chemical Engineering, G.A. Dervakos and C. Webb are investigating the building of a data base system to take a critical look at immobilized cell fermentation technology. These investigators have created a specialist data base which they are prepared to offer as a service to other researchers.

D.E. Brown (Department of Chemical Engineering) and coworkers are investigating downstream processing with respect, in particular, to cell separation techniques.

P.A. Payne is head of UMIST's Department of Instrumentation and Analytical Science (DIAS), and also director of the Medical Engineering Unit. His research interests cover several major areas: transducers and transducer materials, especially piezoelectric materials; applications of ultrasound in medicine and industry; medical instrumentation; dynamic analysis instrumentation; and applications.

M.S. Beck in the same department leads several research groups concerned with process instrumentation, including dynamic analysis systems, automation of instrument systems, fluid flow measurements in cases where measurement is difficult, flow imaging, and digital/optical signal processing for image reconstruction.

F.K. Kvasnik (DIAS) is studying optical instrumentation and techniques for remote sensing and measurement of physical or chemical parameters. He and his group are also actively engaged in the development and application of coherent image processors.

M.L. Waller (DIAS) and coworkers are carrying out research concerned with making quantitatively accurate measurements by improvements in transducer design and the development of new signal processing techniques. The work is carried out with ultrasound transducers,

high-resolution NMR imaging, and quantitative diffraction tomography for ultrasound.

M.A. Browne (DIAS) has research interests in image analysis for industrial, medical, and on-line applications, and in the application of microprocessor-based systems for the development of new generation "smart sensors."

R.J. Dewhurst (DIAS) has a wide range of instrumentation interests related to the development of laser-based sensing and control systems with applications in the field of nondestructive testing.

P.R. Fieldon (DIAS) and his group are working on multielectrode arrays for chemical analysis, novel solid-state electrochemical sensors for gas analysis, and liquid chromatography systems.

R. Narayanaswamy (DIAS) is manager of the Optical Sensors Research Unit, which is devoted to the development of chemically sensitive optical fiber sensors. This work has led to the development of a number of chemical sensors for species in both gas phase and solution.

R.D. Snook (DIAS) and his group are carrying out studies in atomic absorption and emission spectrometry, plasma spectrochemistry, ultraviolet-Fourier transform spectrometry, chemical sensors, electrochemical preconcentration techniques, and thermal wave imaging in photoacoustic spectrometry. Snook is also affiliated with Chelsea Instruments Ltd.

M. Butler (Department of Biological Sciences and coworkers are investigating growth parameters of anchorage-dependent mammalian cells in microcarrier culture. (See *ESN* 41-5:230.)

University of Warwick. Recently, the University of Warwick, located in Coventry, has acquired a new biotechnology building. The companies in Coventry's Science Park will be involved in collaborative projects with scientists in the university's biotechnology groups. Some of the current research and the scientists involved is presented in the following paragraphs.

In the Department of Biological Sciences, P. Norris and coworkers are involved in studies of high-temperature reactor mineral leaching. They are developing the uses of thermophilic, acidophilic bacteria in the treatment of mineral sulphide concentrates. Included in this project is the study of bacterial oxidation of sulphide minerals. R. Whittenbury and J.C. Murell are studying gram negative C2-C4 alkane utilizers, their isolation, properties, and potential biotechnological value.

In the same department, N.H. Mann and coworkers are engaged in studies of the instability of recombinant plasmids in *Bacillus subtilis*. J.M. Lord and L.M. Roberts are studying modified ricin for immunotoxin construction. Their aim is to identify and eliminate the galactose binding sites of ricin for the production of a modified protein to be used in the construction of improved immunotoxins. G.P.C. Salmond and coworkers are involved in the analysis of the pathogenicity genes and mechanism of ex-

tracellular enzyme export in *Erwiniae* as well as the molecular biology of phytopathogenic *Erwiniae*.

Finally, H. Dalton and his group carry out research centered principally on the exploitation of oxygenases to effect the production of a variety of oxychemicals from simple aromatic and aliphatic substrates. M.A. McCrae and coworkers are engaged in studies of non-group A rotaviruses: their characterization, contribution to disease, and vaccine construction. McCrae's group is exploiting recombinant DNA techniques to provide both reagents for diagnosis of these infections and starting materials for the development of virus vaccines.

In the Department of Chemistry, biotransformations are being studied using: (1) esterases and lipases; (2) decarboxylases; (3) dehydrogenases; and (4) oxygenases. These enzymes are being investigated for their ability to catalyze chemo- and enantio-selective transformations of meso or racemic substrates. The objective is to produce chiral building blocks of value in the synthesis of fine chemicals in optically pure form. The products of biotransformations are being included with chemical transformations in the development of procedures for the synthesis of biologically active compounds. In parallel with the synthetic program, studies are being made of the fundamental properties of enzymes with applications in biotransformations. In a recent project, D.H.G. Crout and M. Christen have been studying the enzymatic reduction of beta-ketoesters using immobilized yeasts. (See *ESN* 41-7:358.)

University of Kent. The Biological Laboratory of the University of Kent is one the UK's major academic centers for research in Biotechnology. It has been recognized by the DTI as a center of expertise for research in microbial biochemistry and physiology. Research in the laboratory covers a number of overlapping areas in biotechnology as well as extensive basic work in several fields of biochemistry and microbiology. Major areas include:

- Secondary metabolites
- Biodegradation
- Genetic engineering
- Continuous culture systems
- Enzyme studies and biocatalysis.

The following section deals with some of the research being carried out at the University of Kent and the scientists involved.

C.J. Knowles and A.W. Bunch (Biological Laboratory) are engaged in research on the biological potential of microbial hollow-fiber bioreactors. The aim of this project is to investigate hollow-fiber bioreactors containing intact microorganisms to establish their potential as novel reactors of high productivity and stability. (See *ESN* 41-6:296.) Knowles and coworkers are also involved in studies of cyanide as a nitrogen source for bacterial growth.

D.J. Hardman and A.T. Hull (Biological Laboratory) are carrying out research on the stability of recombinant plasmids in thermophilic and mesophilic bacteria. The overall aim is to study and develop a thermophilic/mesophilic recombinant plasmid. Hardman, in conjunction with M.F. Tuite, is also carrying out research on the development of plasmid vectors for the genetic manipulation of commercially important microorganisms. (See *ESN* 41-7:358.)

R.B. Freedman (Biological Laboratory) and coworkers are studying animal gene products synthesized in microorganisms. A.T. Bull is engaged in a study of microbial halogenation investigating the substrate specificities and properties of chloride peroxidase and other halogenating enzymes. This is a collaborative project with G. Holt (School of Engineering and Science, Central London Polytechnic) and M.D. Lilly (Department of Chemical and Biochemical Engineering, University College, London University). The source of the chloride peroxidase is *Caldariomyces fumago*. Freedman, in collaboration with K.A. Stacey and B.H. Robinson (Chemical Laboratory) is carrying out studies on the kinetics of enzyme reaction in water-oil microemulsions with the aim of investigating the thermodynamics, kinetics and mechanisms associated with reversed enzyme synthesis leading to compounds of interest.

A. Williams (Chemical Laboratory) and coworkers are engaged in studies of enzyme immobilization using soluble polymers. They are investigating microgels as colloidal enzyme immobilization matrices in the degradation of solid phase substrates.

Birbeck College, University of London. I will refer here only to the superb research in protein engineering being carried out under the primary scientists, T. Blundell, M.J.E. Sternberg, and J.M. Thornton, who have achieved an international reputation in this exciting area of research. These researchers are in the Laboratory of Molecular Biology, Department of Crystallography. Their research has made a major impact in the area of protein engineering. For full coverage, see *ESN* 41-4:181; *ESN* 41-9:474; *ESNIB* 88-03:12; and ONRL Report 7-019-C.

University of Bath. A project for Britain's largest science park, planned by a consortium of commercial and university partners has recently been launched. The park is being developed by the universities of Bristol and Bath with the backing of Chesterfield Properties, Hambro Lissandro, and Emerson's Green Development Company.

The University of Bath has a strong interest in biotransformations. According to J.A. Howell (School of Chemical Engineering and Director of the Membrane Applications Center), this interest has resulted from the close association between the university and the pharmaceutical industry and has consequently focused on the ap-

plication of microbial and mammalian transformations to the synthesis of pharmaceuticals and fine chemicals.

Howell and coworkers are carrying out research on modeling and fouling in ultrafiltration membrane fouling. In the same department, J. Hubble and S. Joyce are engaged in studies of biomass recycling on the performance of biotransformation fermentations using mutant organisms. Also, P. Heinemann and her group are engaged in studies of on-line monitoring of flux and rejection during microfiltration of protein solutions. (See ONRL Report 8-003-C.)

B.J. Brisdon (School of Chemistry) and R. England (School of Chemical Engineering) are carrying out studies on the separation of dealkylated drug intermediates and other fine chemicals from fermenter liquors. S. Mann and coworkers (School of Chemistry) are engaged in research on organisms that deposit bioinorganic solids (biominerals) which may have important future potential in biotechnology and materials science.

C. Soper and his group (School of Pharmacy and Pharmacology) are also involved in biotransformation projects with emphasis on the application of microbial and mammalian transformations to the synthesis of pharmaceuticals and fine chemicals. (See *ESN* 41-7:358.)

University of Bristol. N.L. Brown (Unit of Molecular Genetics, Department of Biochemistry) and coworkers are engaged in molecular and genetics studies of the regulation of the *gyl* operon of *Streptomyces coelicolor*. The *gyl* is a model system for studying the regulation of "housekeeping" genes in *Streptomyces* and may be useful in the efficient industrial exploitation of *Streptomyces*.

H.C. Watson and L. Hall (Department of Biochemistry) are engaged in studies on phosphoglycerate kinase. Their aim is to obtain the information necessary to convert a mesophilic enzyme into one which has the properties of its thermophilic counterpart.

I.A. Silver (Department of Pathology) is working on the use of microelectrodes as biosensors in medicine. In this type of usage, the electrodes are placed within certain areas in the patient; i.e., *in vivo*.

University of Nottingham. The university has strong research groups in plant manipulation and plant genetics. D. Grierson and coworkers (Department of Physiology and Environmental Sciences) are carrying out molecular studies on the control of gene expression during tomato fruit ripening.

J.F. Peberdy (Department of Botany) and coworkers are studying the biochemical genetics of cephalosporin C production.

E.C. Cocking, D.M. Gilmour, and M.R. Davey (Plant Genetic Manipulation Group, Department of Botany) are carrying out studies on protoplast fusion and regeneration, with emphasis on fusion technology. The studies deal with somatic hybridization in forage legumes. In conjunction with R. Sotak and J.B. Power, Cocking has

carried out an assessment of chemical and electrofusion for somatic hybridization.

S.S. Davis and his group (Department of Pharmacy) are studying methods of formulating polymeric microspheres and their potential as vehicles for drug delivery as well as the role of surface properties in the fate of the carriers. (See *ESNIB* 88-01:16, *ESNIB* 88-04:6, and ONRL Report 8-007-C.) In the same department, M.A. Khan and coworkers are studying bacterial adhesion to a modified polystyrene surface. Bacterial adhesion is considered to be an important step in the pathogenesis of infections associated with prosthetic implants and medical devices. (See ONRL Report 7-032-C.)

University of Glasgow. There are three universities located in or near Glasgow with a strong emphasis on research in the various aspects of biotechnology. Besides the University of Glasgow are the University of Strathclyde and Heriot-Watt University. All three institutions are involved in the active promotion of the transfer of technology from the academic research laboratory into the commercial sphere.

C.A. Fewson and coworkers in the Glasgow's Department of Biochemistry are engaged in studies of biodegradation of xenobiotic and other persistent compounds and the causes of recalcitrance. In the same department, R.L.P. Adams and coworkers are studying DNA methylation in eukaryotes. A.M. Campbell is carrying out studies on the identification of nuclear antigens in systemic rheumatic disease by cloning techniques; J.R. Coggins is involved in the cloning of the *E. coli* genes coding for the enzymes of the early common pathway of aromatic amino acid synthesis; and R. Eason is studying DNA-protein interactions and protein-protein interactions by analytical ultracentrifugation using computer-linked analysis and simulation. Eason's group is also concerned with the application and development of computer analysis of nucleic acid sequences and structure. Further work in the Department of Biochemistry includes that of B.E.H. Maden and coworkers, who are involved in the isolation and characterization of genomic clones for the visual receptor protein (opsin), and E.J. Milner-White, who is working on the development of methods for clinical use for determining the concentrations of isozymes of creatine kinase in serum. In addition, Milner-White and coworkers are carrying out research on the chromatographic visualization of intersubunit and ligand binding sites in proteins. Finally, W.S. Stevely and his group are concerned with the regulation of gene expression in herpesvirus-infected cells.

D.N.J. White (Department of Chemistry) and coworkers are engaged in studies of the use of molecular graphics in drug design. These investigators have recently developed a procedure which allows real-time, on-the-fly calculation of the intermolecular potential energy as a

function of all of the interactions concerned to optimize the docking method. (See *ESN* 40-3:79.)

H. Marsden (Institute of Virology) and his group are engaged in research on antivirals. Recent work on a novel way of inhibiting virally encoded enzymes has led to the collaboration of the university, the Medical Research Council, and Glaxo Group Research Ltd. Essentially, Marsden and coworkers obtained evidence of specific inhibition of herpesvirus ribonucleotide reductase by synthetic peptides. The potential therapeutic implications of specific inhibition of the subunit interaction are currently being investigated.

J.C. Swaffield (Biotechnology Unit, Department of Genetics) and coworkers are studying the topic of messenger RNA (mRNA) translation and protein folding.

University of Strathclyde, Glasgow. The Department of Bioscience and Biotechnology is one of the largest in the Faculty of Science of Scotland's University of Strathclyde. It was formed in 1982 from four smaller departments to facilitate the integration of research and teaching in the rapidly developing area of biotechnology.

The department's P. Halling and coworkers are involved in studies of enzyme technology, with particular emphasis on enzymes in biphasic systems. An area of special interest is the use of biocatalysts in low water, predominantly organic reaction mixtures (for example, mixtures containing 99 percent of an organic solvent). According to Halling, these offer considerable industrial advantages, notably higher solubilities for many reactants of interest as well as the use of readily available hydrolytic enzymes to catalyze the reverse, synthetic reactions. Halling and his group are now extending their investigations to cover redox catalysts. Halling thinks that the application of biocatalysts in these reaction mixtures must offer commercial opportunities. Other areas of research on bioconversions include fermentation process improvement, isolation of microbes with novel transformation activities, and reaction of redox enzymes with electrodes.

W.H. Stimson and coworkers are carrying out studies of lymphokine production of T-cell hybrids and recombinant DNA. E. Senior and his group are carrying out studies of the metabolism of xenobiotic and semirecalcitrant molecules by interacting microbial associations under anoxic conditions. Their overall aims are to investigate methods of tailoring effluent treatment for industrial/domestic users with particular attention paid to the generation of methane and the production of high-value products. D. Berry and his group are concerned with the control of fungal growth and differentiation. Much of the research has been concerned with industrial fermentation and the use of continuous culture to study the physiological control of fermentation processes. Berry is also carrying out research into the growth of genetically engineered yeast. This work is being done in the biotech-

nology unit in collaboration with V.F. Larsen (Department of Chemical and Process Engineering). The research is aimed at studying the effect of plasmid copy number and levels of expression of heterologous genes on the growth characteristics of yeast, and optimizing the growth conditions to obtain maximum product yields in large-scale fermentations.

In the area of enzyme technology, A. Paterson and coworkers are carrying out research on the use of cellulases to degrade crystalline cellulose as well as the development of new enzymes for the Food Industry. Projects on biocontrol and biostimulants include:

- Development of fungal pathogens as biological control agents against bracken (M.N. Burge)
- Scale-up technology for mycorrhizal fungi of commercial forest trees (J.E. Smith)
- Mycorrhiza (I.C. Gardner and E. Senior)
- Microbial breakdown of oil on railway tracks (B.J.B. Wood and British Rail).

Downstream Processing projects include:

- Protein and glycoprotein purification and affinity chromatography; possible application to processing culture fluids from mammalian tissues (A. Robb and J. Patterson)
- Food processing (J. Scholefield)
- Food quality improvement and product development (J.E. Smith)
- Monoclonal antibody recovery from tissue culture media (C.M. MacDonald).

Rapid enumeration of microorganisms is being investigated by: (1) fluorescence microscopy using Auto-trak (J. Scholefield) and (2) by impedance monitoring as well as by endotoxin assay (J.G. Anderson).

Research projects in the area of animal cell technology include:

- Culturing of mammalian cell lines for product formulation and immortalization of differentiated primary liver and lymphocyte cells, cell fusion (C.M. MacDonald)
- Production of neuron-derived cell lines by cell hybridization (A.B. McCrudden)
- Production of human lymphokines by T-lymphocyte hybrid cells (G. Gallagher)
- Production of human, rodent, and ovine monoclonal antibodies (C.M. MacDonald and W.H. Stimson)
- Direct immortalization of human/animal cells using oncogene insertion and large-scale culture (C.M. MacDonald and W.H. Stimson)
- Physiology of cultured animal cells (C.M. MacDonald and P.J. Halling).

Research projects on gene cloning technology include:

- Animal cells – expression of cloned genes for therapeutic use (C.M. MacDonald), regulatory sequences and eukaryotic gene expression (R.H. Burdon), cloning of the gene for the human enzyme L-asparaginase (H. Brzeski)
- Plant cells – herbicide resistance and its genetic manipulation (R.C. Kirkwood and R.H. Burdon)
- Microorganisms – cloning of surface antigens of *Toxoplasma gondii* (W.M. Hutchinson and R.H. Burdon), cloning of genes for various enzymes into *Saccharomyces cerevisiae* and other yeasts (J.R. Johnston and D.R. Berry), cloning of fungal genes into yeast for production of commercial enzymes (A. Patterson), cloning of flocculation genes in *Saccharomyces* and *Pseudomonas* (J.R. Johnston).

In the areas of immunodiagnosis and immunotherapy, Strathclyde has many projects on monoclonal antibody technology and vaccines. Projects in monoclonal antibody technology include:

- Production of murine, human, and cross-species monoclonal antibodies for use in enzyme and radio-labeled immunoassays for detection of food/agricultural contaminants as well as cancer/pregnancy monitoring (W.H. Stimson)
- Bacterial/parasite detection and typing (W.H. Stimson and J. Alexander)
- Blood group typing and anti-rhesus therapy (C.M. MacDonald and W.H. Stimson)
- Detection of rhesus disease of the newborn and *in vivo* imaging and cytotoxic drug targeting of ovarian and lung cancers (W.H. Stimson)
- Identification of neurotransmitter substances (A.B. McCrudden).

Projects in vaccines include:

- Vaccine potential of selected *Leishmania* antigens (J. Alexander)
- Electronic sensing and fluorescence modification in antigen-antibody interactions for use in novel immunodiagnostic assays (W.H. Stimson).

The following projects are being carried out in the area of microbial physiology:

- Regulation of organic acid biosynthesis (M. Matthey)
- Control of fungal morphology and product formation (J.G. Anderson and J.E. Smith)
- Control of yeast growth and metabolism (D.R. Berry)
- Mycotoxin biosynthesis (J.E. Smith)
- Relationship between yeast plasmids and growth physiology (D.R. Berry)
- Study and strain manipulation of fungal secondary metabolic activities (A. Patterson)
- Modeling (E. Senior)

- Genetic and environmental control of flocculation in yeast and *Pseudomonas* (J.R. Johnston)
- Identification and monitoring of genetic stability of industrial yeasts by electrophoretic karyotyping (J.R. Johnston).

Research in hydrogel technology includes (1) growth of microorganisms in water-retaining polymers (J.B. Wood) and (2) soil-applied herbicides in slow-release polymers (R.C. Kirkwood).

In biomass and its utilization, lignin, cellulose, hemicellulose, and lignans are being investigated by A. Patterson, E. Senior, J.G. Anderson, and J.E. Smith.

In the area of cereal technology, W.R. Morrison and coworkers are applying genetics of glycolipids in wheat and evaluating eventual bread quality.

B. McNeill (Applied Microbiology Group, Department of Biosciences and Biotechnology) and coworkers are engaged in studies of fermentation processes. Using a test microorganism, *Aureobasidium pullulans*, the effect of controlling dissolved oxygen levels upon fermentation has been studied in stirred tanks and in the novel loop bioreactor. These investigators have recently designed a tubular loop reactor for scaleup and scaledown of fermentation processes.

D.C. Sherrington (Department of Pure and Applied Chemistry) and coworkers are carrying out studies to develop polymeric sorbents and membranes for the separation of simple organic molecules from aqueous solutions. In the same department, N. Graham and his group have been involved in research on hydrogels as carriers of drugs during the past few years. (See ESNIB 88-01:16.)

C. Brown and coworkers (Biotechnology Unit, Department of Chemical and Process Engineering) are carrying out studies of an improved enzymatic analysis of low-level glucose concentrations in batch and continuous fermentations. (See ONRL Report 8-001-C.)

D. Lewis and T.L. Whately (Department of Pharmacy, School of Pharmacy and Pharmacology) are studying the absorption of proteins and enzymes at the solid/liquid interface which has implications for drug delivery and blood handling procedures. (See ESNIB 88-01:16.) In the same department, A.T. Florence and coworkers are concerned with studies of different types of hydrogels and their use in drug delivery. (See ESNIB 88-04:6 and ONRL Report 8-007-C.)

Heriot-Watt University, Glasgow. L.R. Weatherly (Department of Chemical and Process Engineering) is carrying out studies on the electrically enhanced solvent extraction of biochemical products. This is a collaborative project with C.J. Slaughter and I. Campbell (Department of Brewing and Biological Sciences). The overall aims are to explore the application of electrically enhanced solvent extraction to the recovery and purification

of selected biochemical products. The initial experiments are concentrated on the extraction of penicillin into a range of nonconducting solvents.

University of Edinburgh. M.M. Yeoman (Department of Botany) and coworkers are engaged in research on the production of fine chemicals by immobilized plant cells. This is a collaborative project with F. Mavituna (Department of Chemical Engineering, University of Manchester Institute of Science and Technology). In the same department, S.M. Smith and coworkers are studying DNA transposition events during plant cell culture.

B.M. Lowe (Department of Chemistry) and his group are involved in studies of biochemical product separation by inorganic molecular sieves.

I.W. Sutherland (Department of Microbiology) and coworkers are studying adhesive polysaccharides. They are investigating polysaccharides synthesized by microorganisms involved in fouling of submerged films, and development of rapid methods for structural determination using fragmentation procedures and liquid chromatography. In the same department, I.W. Dawes and coworkers are involved in research on the genetic manipulation of phenylalanine production in yeast.

K. Murray (Department of Molecular Biology) and his group are studying the expression of viral genes in transformed cells. These investigators are also carrying out research on the functional elements of plant mitochondrial plasmids.

An area of research of great potential for commercialization is that of putting foreign genes into domestic animals. The Edinburgh Research Station of the Institute of Animal Physiology and Genetics Research, Agriculture and Food Research Council (IAPGR), is very involved in the use of domestic animals for the production of large quantities of human clotting factors and other hitherto scarce proteins of medical value (A.J. Clark). Although many human proteins can be made in bacteria, producing them instead in animals might be advantageous.

G. Bulfield of the Roslyn laboratory of the Edinburgh branch of IAPGR and his group are using transgenic engineering in chickens to improve the muscle growth, egg production, and disease resistance of the birds. Both the sheep and the chicken work have attracted the attention of venture capitalists. Pharmaceutical Proteins (in Cambridge) is a start-up company that funds and hopes to commercialize the Edinburgh transgenic sheep research. It is backed by Prudential Venture Managers, Transatlantic Capital Bio-Sciences Fund, and the Scottish Development Agency.

D. Willshaw (Center for Cognitive Science, University of Edinburgh) and coworkers are engaged in studies of neural systems and models; i.e., neural networks or neurocomputing. This area is considered to have a potential for commercial exploitation. Research on neurocom-

puting is being actively pursued not only in Europe but also in the US and Japan. The latter countries are, at this time, at the top in research and development. (See *ESNIB 88-01:6* and *ONRL Report 8-010-C*.)

Central Polytechnic of London. M.W. Adlard and D. Perry (School of Biotechnology) are carrying out research on enzymes and intermediates in the beta-lactam biosynthetic pathways of *Penicillium chrysogenum*. In the same institute, R.I. Scott and D. Perry are carrying out studies on beta-lactam biosynthesis in free and immobilized *Streptomyces*.

J.R. Leigh and J. Tampion (Department of Engineering) are developing and applying the Kalman filter to fermentation processes to obtain on-line estimates of biomass and secondary product fermentation with the ultimate objective of improved fermenter control.

G. Holt and M. Adlard (School of Engineering and Science) are engaged in research on gene transfer, cloning, and expression of beta-lactam genes. They are constructing suitable vectors and strains to allow studies on the regulation and expression of biosynthetic genes for the beta-lactam antibiotic pathway with the long-term aim of developing novel antibiotics.

C. Bucke (School of Biotechnology) and coworkers are carrying out studies on a medium for the entrapment of microbial cells.

Industry

There are currently more than 300 companies within the UK which can be described as biotechnology product producers. Some, though not many, are subsidiaries of multinational companies. These companies include not only the large pharmaceutical companies (Beecham, Glaxo, Pfizer, Searle, Wellcome) and the large oil and chemical companies (British Petroleum [BP], Imperial Chemical Industries [ICI], Monsanto, Shell, and Unilever) but also some of the newer companies such as Celltech, Boots-Celltech, Biomass International, and Seward Laboratory. There are also additional companies with smaller budgets. These include various engineering companies (such as APV, John Brown, and Matthew Hall) as well as very specialized ones such as Amersham International. There are, in addition, a further 30 or so companies with a strong, if not total, commitment to biotechnology. These cover the whole spectrum of biotechnological activities.

A new biotechnology company recently formed in the UK will focus on the separation and purification of high-value-added proteins. Protein Separations Ltd. signed a technology transfer agreement with the University of Surrey and then acquired Bioprocessing Ltd. The merged company will continue trading as Bioprocessing Ltd. Dr. Frank Roberts, managing director, said that the new company will develop process systems for the production of

diagnostic and therapeutic proteins, including monoclonal antibodies and Factor VII, for human and veterinary health care. Bioprocessing Ltd. has also expanded its range of purified specialty growth factors. In addition, recognizing that traditional soft gel matrices, such as agarose, are inherently fragile and present major difficulties when applied to large-scale processes, Bioprocessing Ltd. has devised a method to overcome these obstacles. The company, which has developed a rigid matrix using controlled pore glass, has also developed special chemical methods to bind proteins and other ligands to the glass in such a way as to eliminate the traditional problems of unstable and nonspecific binding. The product is being sold under the trade name of Prosep.

Fermentech, the Scotland-based (Edinburgh) biotechnology process development company is providing funding for genetics research at Queen Mary College, University of London, by D. Mitchell in the School of Biological Sciences to work on the molecular biology of Fermentech production systems. The group is studying the genetics of the microorganisms used in Fermentech's long-term continuous fermentation processes. One of the products currently manufactured by the company is hyaluronic acid for use in eye surgery.

Cymbus Bioscience Ltd. (Southampton, Hampshire, UK) has recently been formed to market a range of monoclonal antibodies for clinical diagnosis and research and to provide R&D service utilizing hybridoma technology. Cymbus Bioscience also operates a "help-line" technical advisory service for its customers, giving access to scientists experienced in monoclonal antibody applications.

APV Chemical Machinery Ltd. (Stoke-on-Trent) and ICI Biological products Ltd. have agreed to collaborate on a new range of microbial fermentation systems. Primarily intended for use in biotechnology, the fermenters will also have application in the manufacture of antibiotics and vaccines and the production of amino acid and other organic acids as well as animal feeds.

Chembiotech Ltd., a newly-formed company, has opened its new premises in the University of Birmingham Research Park. The company markets analytical and laboratory equipment and services for understanding the structure and interactions of industrial and pharmaceutical biopolymers such as polysaccharides, proteins, glycoproteins, enzymes, and antibodies.

British Biotechnology Ltd. in the UK has announced a series of major international distribution agreements to market the company's range of synthetic genes. British Biotechnology Ltd. (BBL) was started only in 1986. In this short period, BBL has become one of Europe's fastest growing biotechnology companies with capitalization totaling \$17.9 million and stocks in trade including a potential AIDS cure and a world-leading line of laboratory products it calls "Designer Genes." BBL's long-term strategy is to merge the disciplines of synthetic organic

chemistry, computer modeling of molecular structures and genetic engineering for the purpose of designing and synthesizing drugs for the treatment of coronary heart disease, rheumatoid arthritis, cancer, and viral diseases. K. McCullagh, one of the founders of the company was formerly at the University of Bristol and a researcher at G.D. Searle (now owned by Monsanto Chemical Co., US).

Celltech Ltd. (Slough) founded in 1980 has become Europe's leading specialist biotechnology company and has an international reputation based on its expertise in recombinant DNA and cell hybridization and its world lead in monoclonal antibody production. In 1986, Cell-

tech was the first company to be awarded an FDA license for bulk production of monoclonal antibodies by cell culture. Celltech is currently undertaking research and development in several key areas, including targeted antitumor drugs, tissue inhibitor of metalloproteinases (thought to have potential for arthritis treatment), and several other human-derived recombinant DNA products.

Cambridge Biotechnology Laboratories, formed in 1980, was the first British company to manufacture restriction endonucleases and other enzymes for genetic engineering research. The company now manufactures an extensive range of enzymes.

France

Biotechnology in France originated with Louis Pasteur (1863) and the Pasteur tradition is still reflected in the prominent French position in the field of sera, vaccines, and diagnostics as well as in the classical fermentation industries. Wine, cheese, and ethanol production all have a long history in France.

France woke up late to the rapid developments in the new biotechnology during the 1970's, but made up for this by publishing three reports within the span of 2 years (Gros, Jacob, and Royer, 1979; de Rosnay, 1979; Pelissolo, 1980) and by initiating a bold program of development aimed at making France the leading European country in biotechnology by the end of the century. The initiative is very much government-inspired and government-orchestrated. Whether it will succeed has yet to be seen. Since the French government recognizes that many commercial applications of biotechnology are still 10 to 20 years away, the emphasis is as much on education, training, and long-term objectives as upon short-term goals.

Government

Both the de Rosnay and Pelissolo reports outlined what was in effect a "biotechnology strategy" for France, with the government taking a firm lead in expanding university (and school-based) competence, in encouraging and facilitating technology transfer, and in promoting awareness in French industry of these developments. These included areas like monoclonal antibodies, where they admitted that France lagged behind other countries but where they argued there was considerable potential for development in the diagnostic field. They were also anxious for France to establish strengths in the agricultural and foodstuffs area, and wanted more work on seeds and plant propagation techniques (genetic engineering,

nitrogen fixation, plant cell fusion, etc.), on cellulose and sugar conversion into alcohol, and on the production of fine chemicals via immobilization and cell culture techniques. The subsequent Mobilization Plan, published in the summer of 1982, drew substantially on these ideas. This plan provided for government spending on biotechnology of \$92 million over a period of 3 years and matched by industrial financing of up to \$180 million per year – the aim being to increase France's share of world markets in biologically derived products from 7 to 10 percent. In addition, under the Committee for Strategic Industrial Development (CODIS) arrangements (targeting money to specific firms), the French government was putting a further \$80 million into 10 biotechnology projects over a 3-year period. Again, under CODIS financing, government funds had to be matched by industry financing. Also of importance is financing through the Agence Nationale de Valorization de la Recherche (ANVAR), which can meet up to 50 percent of the cost of introducing new products or processes. ANVAR also acts as an intermediary between the small/medium-size firms and government laboratories. (See *ESN* 39-11:399.)

With the substantial cutbacks in public expenditure in France in the past months, these ambitious plans have been trimmed even though, as in Germany, priority has been given to new technology programs. Also, French industry, hit by recession, has been unable to meet anything like the levels of expenditure projected. Nevertheless, while funding and timetable may slip, the essence of the strategy remains. What the French government has been trying to do is to force a marriage between a somewhat reluctant industry and a good, but not entrepreneurial research base. Whether they will succeed is still not certain. In their favor is the French ability to mobilize resources:

the centralization of the education and university system, the tradition of administrative discretion wielded by French civil servants towards industry, and the now extensive nationalization of the large firms. Against them is the fact that the areas chosen for particular attention – agriculture, food manufacturing, and biomass conversion – are areas where the work is still centered on the research laboratory, and commercial development is some years away. Such long-term high-risk targets with high payoff are, however, typical of French industrial planning. Nevertheless, the French have considerable intellectual leeway to make up compared to their German or British counterparts.

The government's strategy has been to use the main institutes and universities as centers of development, establishing research groupings in all the major areas of biotechnology. For example, the Centre Nationale de la Recherche Scientifique (CNRS) [or National Center for Scientific Research], the Institut National de la Recherche Agronomique (INRA) [National Center for Agricultural Research], the Institut Pasteur, and the Institut National de la Santé et de la Recherche Medicale (INSERM) [National Institute for Health and Medical Research] were the core team on genetic engineering for pharmaceuticals; CNRS and the Institut Francais du Petrole (IFP) [French Institute for Petroleum Research and Toulouse University for chemicals]. In an attempt to bridge the gap between applied and academic research, the government has also established a number of industrial fellowships to encourage interchange between industry and university, and has created four technology transfer centers at Compiègne, Toulouse, Institut Pasteur, and Paris-Grignon University. The aim of these technology centers is both to act as receiving agents for industrial enquiries and, more importantly, to go out into industry and find developers for academic work of commercial value.

One example of the close collaboration between the public and private sectors is the Intergene Program. Several organizations are working jointly in this program: the Ministry of Research and Technology; INSERM; CNRS; Bio-Mérieux; Immunotech; and Transgène. The Intergene Program involves research in immunoenzymology, bacterial immunology, parasitic and viral immunology, monoclonal antibodies, and enzyme purification.

Public funding in the medical and biological sciences is considerably lower than comparable figures for Germany, but its support for agricultural research is substantially higher.

In spite of extensive academic expertise, France is weak in applied research. As in the UK, the elitist traditions of academic education led to a bias in favor of pure science. In addition, the French university system has tended to compartmentalize research, and neither re-

search institute nor university has found it easy to bring together teams in the key disciplines of microbiology, biochemistry, genetics, and chemical engineering.

Institutes

The field of biotechnology is covered by a number of institutes of which the CNRS is the largest. It conducts basic research related to biotechnology in three divisions.

The National Institute for Public Health and Medical Research (INSERM) covers the health part of biotechnology, with clear priorities in genetic engineering and applied immunology.

The Commission of Atomic Energy (CEA) has at its disposal a number of biotechnological developments devoted to photosynthesis, and radioisotopic metabolism studies as well as radiation of food and wastewater treatment.

The National Institute for Agricultural Research (INRA) is highly diversified in various sectors such as agriculture, agro-food, and renewable energy sources, including basic research in soil microbiology, plant genetics, nitrogen fixation, plant cell culture, and biomethanation.

The French Petroleum Institute (IPP), specialized in energy applications, has focused on ethanol as fuel and on cellulose degradation.

The Pasteur Institute is a private foundation 50-percent financed by the French government. Its activities are mainly in biology, oriented toward the new biotechnologies such as: genetic engineering (in collaboration with CNRS, INSERM and INRA); hybridoma technology; virology (vaccines, animal cell cultures, oncogenes), and immunology.

At the CNRS unit in Toulouse, Laboratory of Chemical Genetics, M.R. Durand and his group are engaged in research on enzyme electrodes, convection electrophoresis, and fluidized reactors. M.G. Durand (CNRS Institute of Applied Natural Science) and coworkers are carrying out research on biological reactors, catalysis, production and purification of enzymes, immobilized enzymes, and optimization of operating conditions of fermentation.

M.R. Poilblanc (CNRS Laboratory of Chemical Coordination) and his group are concerned with the study of ions-peptides, modeling of the active site of enzymes, transport of cations, and pharmacological studies.

In plant biochemistry, a large number of Toulouse laboratories are concentrating on the improvement of plant productivity, including the Plant Physiology Center of the Paul Sabatier University (UPS) and joint molecular biology laboratories of CNRS and INRA. M. Gillois (INRA Toulouse, Laboratory of Cellular Genetics) is concerned with research on the modeling of biological functions and genetic manipulation of animal cells.

As for pharmacology, Toulouse is home to a CNRS pharmacology and toxicology laboratory and to a research group in biology and digestive pathology, both attached to INSERM. There are also pharmacological companies in this region, such as Sanofi in Toulouse and Pierre Fabré at Castres, in Tarn. Today, Toulouse hopes to gain the greatest possible benefit from the industrial spinoffs of the Toulouse research potential. In this respect, a biotechnology and microbiology transfer center (CTBM) was created in Toulouse in 1985. This center is financed by the contract plan for national funding to regions and has administrative links to INSA (National Institute for Applied Science). This center has a triple purpose: to conduct basic research on systems of industrial interest; to promote research in technological concepts and their implementation; and to collaborate with the economic sector (training, information, accessibility of the center's expertise, etc.). Thus, six teams work on enzyme and microbial engineering, cytocultures, and data processing (factory automation and instrumentation). A technology unit run by Phillipe Blanc coordinates the industrial development activities.

With an impressive concentration of scientists, research centers, and companies, Toulouse and the surrounding region are fast becoming one of the strongholds of French biotechnology. Thus, the Elf-Aquitaine and Sanofi biotech research center was established at Labège, in the Toulouse suburbs. A scientific group has also been established in the field of microbiology: the Research Center for Biochemistry and Cellular Genetics, directed by Professor Jean-Paul Zalta. Some of the research activities at this center concerns fermentation, immobilized cells, nitrogen fixation, cell culture, enzyme catalysis, and the production and purification of enzymes. This center unites the laboratories of the Paul Sabatier University and the CNRS, teams from INRA, and the Department of Biochemical and Food Engineering of INSA.

The enzymology laboratory of the Toulouse National Institute for Applied Science is involved in the development of reagents for agrifood industries (enzymatic hydrolysis of saccharose, enzyme fixation on corn cobs, etc.).

At the National Institute for Applied Chemical Research, the work has been oriented since 1982 toward:

- Bioreactors – production of new membranes for fermentation application
- Production of synthetic peptide intermediate compounds (amino acids, oligopeptides, phosphorylated derivatives)
- Industrial contracts for the development of processes to produce organic acids through bioconversion.

In December 1983, the Grenoble Polytechnic Institute (INPG) created the Intelligent-Machine Research

Institute. The majority of the laboratories at the INPG are associated with CNRS. There are five laboratories or research teams:

- LIFA (Basic Data-Processing and Artificial Intelligence Laboratory)
- LCP (Voice Communication Laboratory)
- Research team on computer architecture and VLSI design
- LITRF (Image-Processing and Shape-Recognition Laboratory)
- Robotics Center.

At the National Polytechnic Institute of Grenoble, A. Cheruy and his group are engaged in a project to develop and provide "bioinformatics" tools (algorithms, software, and hardware) for monitoring and computer control of bioreactors and biotechnological processes with the aim of yielding optimization and product quality improvements. These tools are being rationalized so as to accommodate a broad class of biological models and industrial processes. They will be validated by simulation and on the pilot-plant scale.

In Nancy, J.M. Engasser and coworkers at the National Polytechnic Institute of Lorraine are studying the control and organization of animal cells in culture. Their aim is to design more efficient bioreactors and operational models for the mass culture of different kinds of animal cells by a better control of the limiting physical, chemical, and biochemical parameters. This group is also working on improved scale-up technologies especially with respect to aeration, automatic control and feeding strategies.

C. Ropars and colleagues (Laboratory of Biopharmacology-CNRS, Tours) are studying the development of circulating bioreactors by encapsulation of enzymes in lysed and resealed red blood cells (RBC).

At INRA (Tours), G.L. Dubray and his group are studying the gene cloning of *Brucella* antigens which, as vaccines, do not interfere with a specific diagnosis. Thus, this group is working on a new *Brucella* vaccine and a new serological test that will not be subject to interference of cross-reacting antibodies nor interference of vaccinal antibodies since the vaccine does not contain the antigen used for diagnosis.

J. Huppert and his group at the Eduard Hériot Hospital in Lyon, INSERM Unit 51, are engaged in fundamental and applied studies of viruses, hybridomas, and cell lines for the isolation and identification of viruses.

M.H. Pacheco and coworkers, INSERM Unit 205 (Lyon), are studying the chemical and biochemical pharmacology of novel antimetabolites as well as the synthesis of analogous structures of natural nucleosides and nucleotides.

At the Center of Biochemistry and Molecular Biology of the CNRS (Marseille), the research activities in-

clude studies of the chemistry and physical chemistry of protein structure and mechanisms, molecular biology of plant development, biochemistry of photosynthesis, biological membranes and model membranes, and molecular biology of protein export in prokaryotic and eukaryotic cells. The director of the center is Jacques Ricard. The project leaders in the various sections are:

- Plant biochemistry/molecular biology (G. Moat, J.C. Meunier and R. Miassod)
- Lipase structure (M. Rovey)
- Model membranes (R. Verger)
- Protein export (C. Lazdunski)
- Protein nutrition (A. Puigserver)
- Biological membranes (S. Maroux).

The Immunology Center of Marseille-Luminy was opened in 1976 and was the first Institute of Immunology built in France. The funding is by INSERM and the CNRS. Most scientific projects at the center aim at explaining molecular mechanisms of the immune response with a close collaboration between biochemists, molecular biologists, and cell biologists. The major scientific interests are in cellular receptors for antigens (membrane immunoglobulins and T-cell receptors). More specifically, the various disciplines and their project leaders are:

- Immunoglobulin structure/genetics (M. Fougereau)
- H-2 immunogenetics (F. Kourilsky)
- Analytical immunology (A. Cailla)
- Membrane structure (C. Goridis)
- Molecular biology (B. Jorda)
- HLA immunogenetics (C. Mawas)
- Membrane function (M. Pierres)
- T-lymphocyte receptors (B. Rubin)
- Cellular immunity (A.M. Schmitt-Verhulst)
- Liposomes (L. Leserman)
- T-cell immunology (P. Golstein)
- Cell-sorting (Z. Mishall).

Pierre Golstein is the present director of the immunology center. (See also *ESN* 40-6:197.)

A. Flamand and coworkers at the CNRS Laboratory of Viral Genetics located in Gif-sur-Yvette (Paris) are investigating expression vectors for animal virus vaccines.

At the Laboratory of Biochemistry, École Polytechnique, located in Paliseau (Paris), A. Parmeggiani and his group are studying the construction and biological function of altered proteins defined by their spatial structures.

M.F. Roquebert, Laboratory of Cryptogamy, Museum of Natural History (Paris), is concerned with the development of improved techniques for the preservation of fungal strains of biotechnological importance.

Universities

Universities, including Compiègne, Strasbourg, and Toulouse, are playing an important role in biotechnology.

The Technological University of Compiègne has close ties with industries, especially in the agro-food sector. Enzymology and bioprocess technology are internationally recognized fields of research. M.D. LeGoy at the Laboratory of Enzyme Technology carries out research on the bioconversion of hydrophobic compounds by enzyme systems.

University science in the fields allied to microbiology has been generally weaker than that of the research institutes. Although quite a number of universities (for instance, Marseilles, Montpellier, Lyons, and Paris Orsay) have specialist schools of distinction, only three have faculties of world standing. These are: Compiègne (enzyme technology and engineering); Toulouse (microbiology, biochemistry and chemical engineering); and Strasbourg (genetic engineering).

At the University of Lyon, V.M. Nigon and colleagues are investigating the development of transgenic animals (including fish) with novel characteristics.

The École Supérieure de Chimie de Marseille (ECSM) [College of Chemistry] is under the direction of M. Cerbesy, concerned with bioconversions of fine chemicals, immobilization of enzymes, and microorganisms.

At the University of Nancy, R. Nabet and colleagues are studying the control and organization of animal cells in culture with emphasis on enzymatic and metabolic markers.

At the Jacques Monod Institute, University of Paris VII, S.D. Ehrlich and coworkers are carrying out studies of segregational and structural plasmid stability in *Bacillus subtilis*.

J. Garnier and colleagues (Laboratory of Biochemical Physics, University of Paris-Sud) are engaged in the development of computer-aided peptide and protein engineering software. At the same university, J. Janin and his group are carrying out studies on the engineering of an extracellular ribonuclease by gene modification.

Industries

French biotechnology in fine chemicals and pharmaceuticals is based on less than 50 companies, half of which are multinational, such as Rhône-Poulenc, Roussel-Uclaf, Sanofi, Sandoz, CM Industrie, Synthelabo, l'Oréal, Behring, Merck, Sharp & Dohme, Roche, Ciba-Geigy, Shering-Plough and Solvay. The main biotechnology research in these fields is concentrated in three large pharmaceutical groups: Rhône-Poulenc, Roussel-Uclaf, and Sanofi.

Rhône-Poulenc produces antibiotics and is a world leader in the production of vitamin B12. Most of its research in immunology is carried out by Institut Mérieux, a large producer of vaccines. Research in genetic engineering is carried out by the subsidiary company, Geneti-

ca. In the field of diagnostics, the leading firm in France is Bio-Mérieux which is very active in research on monoclonal antibodies. Diagnostic reagents are commercialized by Rhône-Poulenc through a subsidiary of Pharmuka, IBF.

Rhône-Poulenc has invested several million dollars in the creation of a new biotechnology research laboratory in its Health Division Research Center at Vitry. This new center, bringing together about 200 researchers, is expected to become operational in 1989. The techniques being brought together include the following: those related to cellular biology, biochemistry of macromolecules, the biochemistry of metabolic by-products, genetic engineering, and research on biochemical processes. There will also be a pilot plant and the resources necessary to study extraction procedures.

Roussel-Uclaf is 60-percent owned by the giant West German company, Hoechst, and 40-percent government-owned. Via this link, Roussel-Uclaf has access both to Hoechst research and to that of its American subsidiaries. Roussel-Uclaf has major biotechnology interests in antibiotics (third generation of cephalosporin), steroids, and vitamin B12. The company is involved in the immunomodulator market through its subsidiary, Casenne, and has a genetic engineering group which collaborates with Cetus (US) and Transgène (Strasbourg, France). Roussel-Uclaf has also created a biotechnology and development company (Bio-Europe) in conjunction with Sucre Union (which controls 30 percent of the French sugar production). Bio-Europe's goal is to work on biocatalysis and on purification and extraction techniques (i.e., on enzymes and fermentation).

Elf-Aquitaine has committed a large effort to biotechnology. In the field of human biologicals it has acquired a number of subsidiaries such as Sanofi, Choay, and Pasteur Institute Production. Elf Bioindustries and Elf Bioresearch are developing technology in the food and agricultural sectors, respectively.

Two newly created companies in the pharmacological domain are Transgène (genetic engineering) and Immunotech (immunodiagnostic methods). Immunotech

was established in 1982 on the campus of the University of Marseille (Luminy) as a privately owned company with a large and dynamic research department. Many of Immunotech's antibodies have been developed within the company's research laboratory. Others have come from a collaborative agreement with INSERM, the main French agency for national medical research. Immunotech now has a US subsidiary, AMAC (Applied Monoclonal Antibodies Corporation). Other new companies are: Cloatec (monoclonal antibodies); Biosystems (immuno-enzymatic methods); Oris (*in vitro/in vivo* diagnostic procedures); and in biosensors, Setric in Toulouse, Solea Tacussel in Lyon, and Seres in Aix-en-Provence.

France does not have a developed venture capital market, and although the government has been trying to help the small firm sector, much of this help consists of underwriting loans and credit facilities from the major banks. There are a number of small biotechnology companies in France, some of which have been mentioned above. However, most of them are not independent companies, but offshoots of either large firms or research institutes. The largest independent firm is Transgène, founded by the Paris-based investment bank Paribas, with four other partners—Assurances Générale de France, BSN-Gervais-Danone, Moët Hennessy, and Elf-Aquitaine. Based in Strasbourg, Transgène has links not just with Strasbourg and Paris but also with Heidelberg and Basle.

After Transgène, the largest group is Genetica, an offshoot of Rhône Poulenc (although 10 percent of the stock is owned by the researchers themselves). A number of other firms also support biotechnology offshoots while many of the public research institutes have hived off their contract research into specialist companies (like Hybridolab and Immunotech from Institut Pasteur). Overall, therefore, although it would be wrong to say there is not a small-firm sector in France, much of that sector derives from decentralization of function on the part of larger groupings rather than from inherent growth as in the US.

Republic of Ireland

Ireland is a country which the reader may not immediately associate with biotechnology. However, for a small country, with a total population of only 3.6 million, it has a growing number of biotechnology companies, a wide range of university-based expertise, and a strong commitment from government to develop this technology. In

common with most countries, Ireland's biotechnology industry is a blend of long-established companies and of new biotechnology firms formed by a combination of venture capital and new technology. The older companies are mainly in brewing, distilling, dairy, and other agrobusiness industries. Many of these companies have

become involved in biotechnology, encouraged by state incentives for research for licensing of technology and for employment of technical graduates.

Government

One of the limitations of national biotechnology policy in any country is that the sector is becoming dominated by multinational companies. Investment in manufacturing by these companies can be made in almost any country. As a result, an important aspect of government policy—in Ireland as well as in the UK and on the continent—has been to create an environment that is attractive to multinational biotechnology companies.

The critical elements in this environment are the technical skills, the regulatory environment, and the grants and tax packages available. These factors are also very relevant to the development of indigenous industry. Additional factors for the latter include new enterprise development assistance, availability of risk capital, and technical assistance to start-up companies.

Industrial policy. All Irish governments since the 1960's have supported a specific policy of grant assistance and tax relief for new manufacturing industry. In the 1960's, Ireland was still a predominantly agricultural country with a low level of indigenous industry. A new agency—the Industrial Development Agency (IDA)—was set up in 1970 to implement a policy of attracting foreign manufacturing industry to Ireland, and has pursued it successfully since then. The result has been a significant change in the Irish industrial economy to its current position as a high-technology industrial center. Among the industry sectors targeted by the IDA for development were chemicals, pharmaceuticals, and health-care. This attracted several international companies including many who are now very clearly involved in biotechnology. They have been attracted to Ireland by a combination of grants and tax incentives, and a technical educational infrastructure which can supply graduates with the required skills. The grant package includes up to 60-percent capital grants, 100-percent training, and 50-percent R&D grants.

Attraction of biotechnology companies also requires strong national technological infrastructure. This is achieved through technical education and training and by the development of research and technical facilities. The range of biotechnology research facilities was increased during 1987 by the creation of the National Biotechnology Program.

Biotechnology research policy. Total government spending on science and technology in 1985 was about \$600 million. The R&D expenditure is mainly on agricultural research (24 percent) and on grant aid to manufacturing industry (28 percent). A significant proportion (27 percent) is also spent in supporting university-based re-

searchers, almost half of whom are in bio-related fields. The current government gives a high priority to science and technology and has increased the expenditure in certain areas of science and technology which are related to economic growth. In 1987, the major science policy and research funding agency, the National Board of Science and Technology (NBST) was merged with the Institute for Industrial Research and Standards (IIRS) to form EOLAS (the Irish Science and Technology Agency).

Biotechnology has been a priority area for funding by NBST since 1983. This agency maintained an active program to develop Irish biotechnology research facilities and expertise including grants for research, travel and equipment, seminars, and publications as well as publication of a bimonthly newsletter *Irish Biotech News*. The NBST also dealt with Irish participation in EEC research programs in which Irish scientists have been very successful. In the most recent EEC biotechnology program, 13 contracts to a value of \$2 million were obtained. All of these activities will now be administered through BioResearch Ireland in association with the new agency EOLAS.

The IDA policy on industrial R&D has been to provide R&D facilities, and also 50-percent funding to industry for product and process development. Grants for 50 percent of the cost of licensing technology are also available. More recently, in recognition of the need to get more firms to start performing R&D, capital grants have been provided for R&D laboratories and for the initial year of employment of an R&D manager. Grants are also available for employment of young graduates in these facilities under the Scientists and Technologists Employment Program (STEP) and a Teaching Companies scheme.

Education and training. Uniquely in Europe, almost half of the Irish population is under 25 and almost a million young people are now in full-time education. About half the graduates from second-level education enter university or technical college. Consequently, education and training forms a high proportion (34 percent) of the overall government spending on science and technology.

Irish higher education colleges have long-established strengths in the biomedical and agricultural sciences. Government policy has been to further develop those aspects of the educational infrastructure that are relevant to industrial growth. This has resulted in a large growth in technical education, including the establishment of Regional Technical Colleges and refurbishment and expansion of technology-related facilities in existing colleges. Over half of the 38 degree- and certificate-awarding institutions in Ireland were established in the last 20 years. The emphasis on technical education has resulted in 30 percent and 63 percent increases in the number of science and engineering undergraduates, respectively, in the last 10 years. Apart from courses in the biotechnology-re-

lated disciplines, there are currently eight courses specifically on biotechnology in Irish colleges.

Regulation of biotechnology. The major regulatory considerations are those relating to the use of recombinant organisms and to authorization of biological products for medical or veterinary use. Government policy on recombinant DNA (rDNA) regulation has been to ensure reasonable safeguards without unnecessarily hindering either research progress, or industrial use of genetically engineered organisms. Regulation of rDNA research was the responsibility of the Medical Research Council from 1974 until 1981 when a National Recombinant DNA Committee was established. Approval for medical preparations is administered by the National Drugs Advisory Board (NDAB), while veterinary preparations are the responsibility of the Department of Agriculture.

BioResearch Ireland. This is a contract research organization set up under the National Biotechnology Program (NBT) to commercialize biotechnology research in Irish universities and research institutes. The NBT was announced by the Minister for Science and Technology, Dr. Sean McCarthy, in June 1987 as part of the Government's efforts to develop science and technology in economically important sectors. Its objectives are:

- To encourage research activity in Ireland by both home-based and overseas companies
- To establish a significant reputation for Irish biotechnology research and thus help attract overseas companies to locate in Ireland
- To engage in the transfer of biotechnology from Irish third-level colleges to industry.

The program objectives are to be achieved by establishing, equipping, and staffing centers of biotechnology research expertise dealing with research topics in which there is existing Irish expertise, and which are of relevance to industry. In 1987, three research centers were established: (1) National Diagnostics Center, University College, Galway; (2) the National Cell and Tissue Culture Center, National Institute for Higher Education (Dublin); and (3) the National Food Biotechnology Center, University College, Cork. These centers will be maintained, managed, and marketed by BioResearch Ireland. Client biotechnology companies are being offered an opportunity to either become involved in on-going research at the centers or contract their own research to the centers.

Because these three centers do not cover all of the relevant biotechnologies, further centers were being established in 1988 in other colleges. With this expansion, BioResearch Ireland will be able to provide a comprehensive range of commercial research services. Apart from the centers, BioResearch Ireland also has a networking arrangement that will allow researchers not within a specific center to become involved in contract

research. It is planned to form BioResearch Ireland into a limited company in 1990 by offering the majority of its shares for purchase. The detailed arrangements for this development, including the relationship of the universities and the state to the company, are currently being worked out.

Universities

Apart from in-house company research, most Irish biotechnology research is performed in universities and the Agricultural Institute. The main colleges involved are:

- University College Galway (UCG)
- University College Dublin (UCD)
- University College Cork (UCC)
- Trinity College Dublin (TCD)
- The National Institute for Higher Education, Dublin (NIHE-D).

Additional research is carried out in some of the smaller institutions such as St. Patrick's College, Maynooth, and the Dublin Institute of Technology, Kevin Street, Dublin. The state-funded Agricultural Institute concentrates on application of biotechnology to agriculture and food. A considerable amount of applied research in association with companies is carried out by all of these institutions in addition to their basic research.

Trinity College, Dublin. Trinity College, Ireland's oldest university, has a long tradition in the biological sciences. Industrial biotechnology expertise is mainly in the departments of Genetics, Microbiology, Biochemistry, and Pharmacy.

The Genetics Department is involved in recombinant DNA research on industrial enzymes, pharmaceuticals, and biosynthetic pathways, and is one of the leading European laboratories in recombinant *Bacillus subtilis* research. The group has cloned the genes for a number of industrial enzymes and has a contract from the Beijing Agricultural University to develop recombinant porcine growth hormone. The group has recently shown that the Chymosin gene has a high degree of polymorphism which is partly explained by the discovery that Chymosin genome clones seem to be members of a multigene family. In a project for A. Guinness & Co., the team has transferred the *B. subtilis* beta gluconase gene to brewing yeast. They were also the first to clone the alpha-amylase gene from *B. licheniformis* into *B. subtilis*. The scientists involved in these projects are: D.J. McConnell, P. Humphries, K.M. Devine, G.J. Farrar,; P.M. Sharp, and M.T. Geraghty.

Another project in this department is to locate the genes causing the inherited disease, Retinitis Pigmentosa (RP). A \$1 million grant from the RP societies in the US, UK, and Ireland has been obtained to pursue this research. The scientists involved in this

study are D.J. McConnell, G.J. Farrar, M.T. Geraghty, and P. Humphries from the Department of Genetics and J.M.B. Moloney from the Research Foundation, The Royal Victoria Eye and Ear Hospital, Dublin.

In the Microbiology Department, cellulolytic enzyme systems are being studied. Monoclonal antibodies have been produced to differentiate between the various cellulases produced by *T. emersonii*. In addition, beta-glucosidase genes from *T. emersonii* have been inserted into *E. coli* and expression achieved.

The Microbiology Department has a significant program in virology, particularly in virulence determination and development of vaccines. A new vaccine for the fish disease Furunculosis is under investigation. An EEC-funded research project is in progress, using cloning and gene replacement techniques to identify virulence determinants on *Staphylococcus aureus*, the causative agent for bovine mastitis.

In the cancer field, the Microbiology Department is involved in the production and characterization of photosensitizing agents for cancer therapy. Monoclonal-antibody-mediated delivery systems are also being developed to increase the effectiveness of anticancer agents.

The Microbiology Department is also using monoclonal antibody technology to develop diagnostics to a range of animal and human diseases. Assays have been developed for a number of sexually transmitted diseases for Irish diagnostic companies including a rapid diagnostic assay for Chlamydia. A DNA probe test for Chlamydia is currently under investigation.

Specific interests of the scientists in the Department of Microbiology are given here:

- J.P. Arbuthnott – Bacterial toxins. Characterization, mode of action, and role in pathogenesis of staphylococcal toxins; the membrane-damaging cytolysins (alpha-, beta-, gamma-, delta-); toxic shock syndrome; epidermolytic toxin; endotoxins; use of restriction enzyme analysis; DNA probes for typing of staphylococci.
- T. Foster – Molecular genetic analysis of virulence. Genetic analysis of virulence of *S. aureus* and *Aeromonas salmonicida*; use of molecular cloning techniques to generate site-directed mutations in virulence factor genes (for example, *S. aureus* alpha-toxin, gamma-toxin, epidermolytic toxin, coagulase, protein A); molecular genetic analysis of resistance determinants specified by plasmids in bacteria; regulation of resistance genes; assessment of new molecular methods of making attenuated vaccines.
- P. Owen – Structure and function of microbial surfaces. Application of immunochemical methods to characterize novel protein antigens in inner membranes of Gram-negative bacteria; novel glycoproteins in plasma membrane of Gram-positive bacteria; components of aerobic respiratory chain; chemical and biological characterization of protective antigens of *Ps. aeruginosa* as possible components in a new vaccine.
- C. Smith – Fimbriae of pathogenic bacteria. Analysis by immunochemical and molecular cloning techniques of the adhesive fimbrial antigens of human pathogenic strains of *E. coli* and *Gardnerella vaginalis*; characterization of oral streptococci with special interest in antibiotic-resistant determinants.
- G. Atkins – Viral pathogenesis. Use of mutants of Semliki Forest Virus as a model system for study of viral pathogenesis, especially in relation to neurological and teratogenic effects; extension of these methods to study Rubella virus and other pathogenic viruses; cloning the Dengue virus genome; use of SFV mutants and DNA probes to study virus-induced demyelination.
- R. Russell – Immunological and molecular tools in diagnosis. Use of monoclonal antibodies and recombinant DNA technology to devise probes for the rapid detection and characterization of *Chlamydia trachomatis* and other agents; staphylococcal enterotoxins in food; development of computerized impedance-based systems for rapid detection of bacteria in water and food; *in vivo* and *in vitro* chamber systems in infections and cancer; mechanisms of disease, epidemiology, and host response.
- T. McHale – Cellulose degradation. Characterization of the components of the cellulolytic enzyme complex in *Talaromyces emersonii* using monoclonal antibody and rDNA technology; development of new yeast and bacterial strains by rDNA technology; isolation of monoclonal antibodies directed against tumor cells; creation of chimeric antibody/toxin complexes lethal for tumor cells; development of immobilized enzyme production system with a view to their use as artificial organ systems.

In the Biochemistry Department research on antibodies to antidepressants and their biological target sites is in progress. Antisera to tricyclic antidepressants have been characterized with binding properties similar to serotonin carriers. These may be used in drug assays and as source antigens for anti-idiotypic antisera. In the same department, a diagnostic test is being developed for an Irish diagnostic company which will indicate susceptibility to lung cancer.

In the area of enzymology, the Biochemistry Department is developing methods for large-scale purification of enzymes by affinity precipitation using bifunctional ligands and also magnetized affinity resins. Use of a compound composed of two NAD⁺ molecules linked by a

spacer arm has allowed a number of dehydrogenases to be isolated from crude extracts in a single step.

The following deals with the research interests of the staff in the Department of Biochemistry:

- C. Bailey – Mechanistic studies of the multifunctional tryptophan synthetase; molecular activity of epidermolytic toxin; properties of alcohol dehydrogenase from *Bacillus*.
- F.J. Bloomfield – Research interests centered in the area of development and mechanism of action of anti-inflammatory drugs. Biochemical studies carried out on isolated inflammatory cells (neutrophils and monocytes) and lymphocytes, the cells isolated from whole blood of normal and inflammatory disease patients.
- J. Carroll – Investigation of the role of the exterior surface of the cell in the regulation of differentiation and development of the early mouse embryo. Currently, attention is directed to: (1) gene expression in the early mouse embryo, (2) the toxicity of ionizing radiation to embryos and other cells, (3) the masking of trophoblastic antigens to allow attachment of the embryo to the uterus, (4) the factors which promote adhesiveness and invasiveness in the differentiating pre-trophoblastic cells, and (5) the plasma membrane of spermatozoa.
- W.C. Love – Lipid metabolism. Studies on the role of linoleic acid and other polyunsaturated fatty acids in the regulation of lipid metabolism; synthesis of ¹⁴C-fatty-acid-labeled lecithins and their participation in lecithin cholesterol acyl transferase (LCAT) and phospholipase A₂ reactions in plasma and peripheral blood mononuclear cells; separation of lipoprotein subfractions and identification of specific substrate fractions for the above enzymes.
- G. McBean – Assessment of the excitotoxic actions of the amino acid neurotransmitters, glutamate and aspartate, and their agonists using brain tissue-slice preparations; studies on the synthesis, storage, and release of the amino acid; central effects of anticonvulsants.
- M. McKillen – Hemolytic diseases involving a lesion in the red cell membrane; role of thiol groups in energy-transducing membranes; isonitriles as ligands for haem and haemoproteins.
- T. Mantle – Monomeric NAD (P)-linked oxidoreductases as model enzyme systems, with particular reference to biliverdin reductase, aldehyde reductase, and aldose reductase; the nature of the multiple forms of glutathione S-transferase in the rat, with particular reference to the use of cloning techniques in quantifying homologous messenger RNAs; the use of glutathione S-transferase isoenzymes as markers for early neoplasia; the mechanism of action of arylsulphatases; inositol homeostasis and the function of the derepressed beta-lactamase of *Enterobacter* species in promoting resistance to third-generation cephalosporins.
- J. Mason – The effects of molybdenum-sulphur compounds on copper metabolism in animals and upon cuproenzymes *in vitro*.
- B. Orsi – The general field of interest is enzyme kinetics and the molecular mechanisms of enzymes, with particular reference to hydrolases; enzymes catalyzing four electron changes, such as UDP glucose dehydrogenase.
- J. Scott – The function and metabolism of folic acid and its derivatives. Five major lines are being investigated: (1) the breakdown of folates in mammalian cells, (2) the metabolic interrelationship between foliate and vitamin B₁₂, (3) the role of vitamin B₁₂ in neurological tissue, (4) vitamin deficiency and neural tube defects, and (5) use of an amino acid analyzer to study methionine and choline metabolism.
- K.F. Tipton – The metabolism of neurotransmitters in the brain and other tissues and the influence of drugs on these processes as well as the effects of ethanol on metabolism; large-scale purification and novel uses of enzymes.
- P. Voorheis – The long-term objective of the research is to increase our understanding of how membranes, particularly plasma membranes of eukaryotic cells perform their many functions. The functions of membranes of interest include (1) the sequential switching of surface antigens attached to the plasma membrane in bloodstream forms of *T. brucei*, (2) the mechanism by which the plasma membrane potential is generated under basal conditions in different stages of the life cycle of *T. brucei*, (3) the mechanism of calcium ion transport through the plasma membrane and its regulation, (4) the regulation and role of adenylate cyclase in *T. brucei*, (5) the mechanism of amino acid and sugar transport in *T. brucei*, and (6) the interaction of the cytoskeleton with the plasma membrane of *T. brucei* and changes in the cytoskeleton occurring during cell division and differentiation within the life cycle of the cell. The flagellated protozoan, *Trypanosoma brucei*, is used as a model system in these studies.
- C. Williams – Studies on the molecular nature of receptors, mainly gamma aminobutyric acid (GABA) and benzodiazepine receptors; studies on calmodulin (the calcium-modulator protein); studies on the uroporphyrinogen synthetase multienzyme complex; characterization of the molecular properties of the serotonin reuptake site and its relationship to tricyclic antidepressant therapy.

- F. Winter – Most of the current work is on the properties and functions of eukaryotic deoxyribonucleases. Specific investigations include: (1) Mammalian DNAase I (cloning the DNAase I gene with a view to studying its structure and the regulation of its expression), the distribution and roles of DNAase I in the digestive tract, DNAase I in nondigestive tissues; (2) properties and functions of a major class of nucleases from fungi; and (3) the metabolism of derivatives of 5-fluorouracil of potential interest in cancer therapy.

The National Center for Pharmaceutical Biotechnology is now being established in Ireland as a spinoff of Trinity College, Dublin. This center will be part of BioResearch Ireland, a contract research organization established to commercialize the biotechnology expertise of Irish publicly funded research. The new center will involve biotechnology researchers from several of the departments of Trinity College. Projects already underway include genetically modified industrial microorganisms, vaccine, drug slow-release, and enzyme technology.

In collaboration with Trinity College, the Irish diagnostic and laboratory supply firm, Medlabs, has developed Mukit, a diagnostic test for the measurement of a specific blood protein (GST-MU) that may be a marker for smokers at high risk for lung cancer. The test is currently being used in a clinical trial in Ireland to assess a recent report that absence of this protein is associated with an increased risk of lung cancer. To develop further the association between Medlabs and Trinity College, a campus company, Biotrin Ltd., is being formed to pursue research on behalf of Medlabs.

University College, Dublin (UCD). UCD is the largest university in Ireland and has a diverse range of biotechnology interests.

The Pharmacology Department is involved in the investigation of hormonal and tissue-specific regulation of pituitary gene expression. This group has established the enhancer-like nature of glucocorticoid regulatory element in the rat growth hormone gene promoter.

Other research in this department is directed to understanding how cell acquisition, migration, and differentiation are coordinated during normal brain development, and how iatrogenic and ecotoxic perturbations lead to IQ deficit or gross malformation. These studies have led to the development of immunodiagnostic and *in vitro* techniques capable of identifying agents with teratogenic side effects.

In the Department of Medical Microbiology, a range of assays, including a routine means of detecting cell-mediated immune responses to microbial infection are being developed.

In the Botany Department, research is in progress on applications of DNA probe technology to plants, and

transacting factors involved in photoregulation of gene expression in *Pisum* plasmid stability.

Environmental control of extracellular enzyme production and the influence of process parameters is under investigation by the Industrial Microbiology Department.

The Agriculture Department has a significant program in mammalian reproductive technology. The work here concentrates on embryo storage and *in vitro* fertilization and on the precise control of oestrus and ovulation. Recent research has resulted in the development of a technique to "rescue" eggs from ovaries of slaughtered cattle for reimplantation. This technique, which is felt to have good application in third-world countries, will be developed by Ovamass Ltd., Dublin.

The Zoology Department is involved in development of control strategies for insect pests including the identification of natural attractants, repellent, or insecticides and resistant crop varieties. In this Department's immunoparasitology unit, a diagnostic test for liver fluke, *Fasciola hepatica*, has been produced for a client company.

The following paragraphs deal with specific projects of scientists in the various departments at UCD.

Biochemistry Department:

- M.E. Beary – Effects of liver damage on the metabolism of steroid hormones; involvement of phospholipids in the enzymes of steroid catabolism; sterol carrier protein in hyperlipoproteinaemias; prostaglandin biosynthesis in animal tissues, effects of age, of dietary supplements, and of inhibitors on *in vivo* and *in vitro* prostaglandin production; platelet aggregation studies.
- M.G. Harrington – Enzymatic changes occurring in meat and meat products during short- and long-term storage.
- J.J. McDonnell – The influence of media composition on the nature and course of fermentation by yeasts.
- J. Malthouse – Mechanism of action of proteolytic enzymes and pyridoxal phosphate requiring enzymes; nuclear magnetic resonance studies of biomolecules using ¹³C reporter groups.
- J.M. Manning – Extracellular polysaccharide complexes: collagen-proteoglycan interactions studied using biochemical and electron microscopic techniques.
- B.F. Masterson – Process biochemistry of industrial proteins; biochemistry of dissolved oxygen; biochemistry of manganese; studies on biochemical determinants of water quality; blood compatibility of artificial surfaces.
- S.G. Mayhew – Structures and mechanisms of action of flavin- and iron-containing redox enzymes from anaerobic bacteria; hydrogenase, flavodoxin, electron-transferring flavoprotein, NADH-, acyl

CoA-, dihydrolipoamide- and lactate dehydrogenases.

- H. Ryan – Factors regulating the active transport of inorganic electrolytes in yeast – for example, metabolic changes, intracellular pH, etc.
- H. Smyth – Cell membrane glycoprotein alterations in malignancy; examination by gel filtration and isoelectric focusing techniques.
- P. Joyce has developed an assay for *Fasciola hepatica*.

Department of Medical Microbiology: A. Shattock has developed a delta-hepatitis antigen assay which is marketed by Noctech Ltd. as "DeltAssay". Further assays under development include a rapid milk-based assay for mastitis detection and an assay to routinely detect cell-mediated immune responses to microbial infection.

Department of Agriculture. I. Gordon, in conjunction with scientists at the Agricultural Institute, is researching the transfer, *in vitro* fertilization, sexing, culture, and storage of embryos. In 1987, a company called Ovamass Ltd. was formed to commercialize a new technique, developed in Gordon's laboratory, that allows eggs removed from slaughtered cattle to be used for implantation.

Department of Pharmacology: C. Regan's research, on neural tissue differentiation processes has led to development of immunodiagnostic and cell-culture-based assays for identification of compounds with teratogenic effects. Regan and his group have also developed a rapid drug haptenization procedure with application to gentamicin and quinidine. Other interests of this group include studies of the neural adhesion molecule and developmentally regulated neural sialidases. M.P. Ryan, and his group are involved in several projects including the role of magnesium in the prevention and control of hypertension, ion transport in red blood cells of patients with cystic fibrosis, effect of gentamicin on calcium transport in rat renal brush border membrane vesicles, and studies of cisplatin-induced nephrotoxicity in an animal model. These investigators are also looking at other anticancer drugs to ascertain some of the factors involved in their cytotoxicity. F. Martin and his team are investigating hormonal and tissue-specific regulation of pituitary gene expression.

Department of Industrial Microbiology: As this is the only Department of Industrial Microbiology in Ireland, research concentrates heavily on biotechnology and the application of microbiology to industrial processes. Research interests of the staff include:

- Enzyme and fermentation technology (W.M. Fogarty and C.T. Kelly) – Enzyme production, fermentation, isolation, purification, and identification of characteristics of new industrially important enzymes from microorganisms; the

application of soluble and immobilized enzymes in reactor systems.

- Bacteriology (J.B. Gillespie) – The physiology and biochemistry of bacterial endospore formations; control of bacterial contamination in the pharmaceutical and cosmetic industries.
- Microbial genetics and genetic engineering (J.J. McEvoy and E.C. Hussey) – Industrial strain development (genetic and process strategies for optimization of expression of cloned genes).
- Mycology and environmental microbiology (I.J. McEvoy) – Interaction of fungi with their natural environments; the control of fungal spore germination and growth in industrial environments.
- Industrial process design and control (A.J. McLaughlin) – Kinetic and ecological studies on the use of complex substrates by mixed microbial populations; microbial control in meat and other food processing industries.
- Food Microbiology (M.E. Upton) – Food quality control methodology; identification of food-poisoning bacteria; irradiation and other methods of food preservation.
- Culture collection (M.M.P. Devine) – The collection comprises over 500 species of bacteria, yeasts, moulds, and industrially important actinomycetes; methods for the preservation of microorganisms are developed and tested.

National Institute for Higher Education (NIHE). A varied range of research projects is being carried out at the School of Biological Sciences as follows:

- Biochemical Engineering/Industrial Microbiology (F. Daralsi, P. Walsh and O. Ward). The areas studies include computer control of fermentation, immobilized cells and enzymes in biotechnology, enzyme production in fermenters (bacteria, fungi), and large-scale fractionation and processing of enzymes. Much work is being done in the mathematical modeling and design of immobilized cell bioreactors for the production of secondary metabolites. Some of this research has been carried out in conjunction with the Departments of Chemical Engineering and Industrial Microbiology at University College, Dublin.
- Genetics (T. Ryan and M. O'Connell). Research includes cloning and gene expression in yeast and other eukaryotic organisms as well as cloning in bacteria of agricultural importance. T. Ryan is working on genetic control of enzyme secretions in yeast and M. O'Connell on the molecular genetics of bacteria involved in nitrogen fixation.
- Cell Biology, Immunology and Biochemistry (R. O'Kennedy) The research involves studies of monoclonal antibody production, enzyme stabilization, and drug metabolism. O'Kennedy and

his group have produced monoclonal antibodies against activated lymphocytes, apolipoproteins, blood clotting factors, tumor antigens, and drugs.

- Cell Culture (M. Clynes). Clynes and coworkers are involved in studies of primary culture of human cells, large-scale animal cell culture, and purification and characterization of growth factors in relation to biology of cancer as well as use of cells in culture to screen chemicals for their toxic effects. Clynes and his group have also developed an antinuclear antibody assay which is currently marketed by Medlabs Ltd.
- Enzymes (L. O'Connor). O'Connor is studying enzyme immobilization and the biochemistry of steroid hormone receptors.

University College, Galway (UCG). Recombinant DNA (rDNA) research is in progress on cloning, expression, and analysis of eukaryotic genes and on development of transgenic animals. F. Gannon (Department of Microbiology) is involved in these studies. He is also Director of the National Diagnostics Center at University College, Galway. Gannon and coworkers are involved in the development of transgenic animals (including fish) with novel characteristics. J.M. Sreenan of the Agricultural Institute in Galway is a collaborator on this project.

In the same department, L.K. Dunican is applying genetic techniques to the improvement of amino acid production by *Corynebacteria*, while D. Headon has cloned the gene for bovine inhibin. This compound works by selective inhibition of FSH secretion and has application in increasing ovulation and fertility in cattle.

The National Diagnostics Center is located within University College, Galway and its research is aimed mainly at the development of nonradioactive enzyme-linked immunoassays and DNA probes. Examples include assays for indicators of abnormal bone metabolism which are being developed by P. Fottrell, who is also in the Department of Biochemistry at the university. These assays are intended for monitoring of bone healing processes following fractures and for diagnosis of conditions such as osteoporosis, a major problem among older women.

A related area of interest in the laboratories of P. Fottrell and J. Gosling (Department of Biochemistry) is development of assays for specific steroid hormones and their metabolites for use in determination of fertility problems. This research has been in progress at the university for many years and has led to the development of a commercial progesterone assay for pregnancy detection in farm animals. This is marketed by Noctech Ltd. J. Gosling and his group are also carrying out research on solid-phase immunodiagnostic systems with negligible affinity for nonspecific components of plasma and saliva. Research on characterization of blood proteins, and particularly assays for IgG and IgA subclasses is also in pro-

gress in J. Grealey's laboratory. These assays will be an important means of assessing problems in patients suffering chronic or recurring infections. Assays are also being developed by P. Smith for diseases of farmed fish. BioResearch Ireland currently provides the routine disease diagnostic service for 80 percent of Irish salmon farms. The diseases of current interest are pancreatic disease, furunculosis, and bacterial kidney disease.

University College, Cork (UCC). This university has particular research strengths in the fields of food microbiology and chemistry, nutrition, and in plant sciences. BioResearch Ireland has established a Food Biotechnology Center in this university to develop and commercialize this expertise.

In the Microbiology Department the research interests of one team are in the molecular basis of plant microbial interactions with *Rhizobium* and *Pseudomonas* species. This group has genetically engineered strains with improved nitrogen-fixation potential as a result of enhanced carbon utilization abilities. *Pseudomonas* species capable of stimulating plant growth and providing biological control against root pathogens have also been developed and are currently under commercial field evaluation.

In the same department, a second team is applying rDNA technology to accelerated cheese ripening and phage resistance in dairy starter cultures.

The Department of Food Chemistry is actively involved in researching the functional properties of food proteins, enzymology, and the chemistry of dairy products.

The nutritional significance of trace elements, food toxicology and the role of trace elements and vitamins in the etiology of human birth defects are being investigated in the Nutrition Department.

In plant biotechnology the Department of Plant Sciences (UCC) is a major research center and a campus-based company, Plant Biotechnology (UCC) Ltd., has been founded to offer contract research services in this area.

In UCC, genetic engineering research is directed at the development of improved bacterial strains for agricultural and food processing applications. F.O'Gara (Department of Microbiology), who is also Director of the National Food Biotechnology Center, is working on improvements of *Rhizobium* and *Pseudomonas* strains for nitrogen fixation and biological control, respectively. C. Daly (Department of Dairy and Food Microbiology) is developing improved strains of starter-culture bacteria. This research, in association with T. Cogan of the Agricultural Institute has already produced the starter cultures from which 90 percent of Ireland's cheddar cheese is now being made.

The molecular biology of catabolite repression control in bacterial systems is also under investigation with

particular emphasis on microorganisms involved in fermentation. Factors influencing plasmid copy number-control and protein secretion from yeast are also being investigated by J. Atkins (Department of Biochemistry). In the same department, S. Doonan and coworkers are studying structural and genetic relationships between cytosolic and mitochondrial isoenzymes as well as cloning of the gene for the protease from *Armillaria mellea*. This protease is interesting because it is small, has a very high

specificity (it cleaves only at the aminoterminal side of lysine residues), and is very stable to denaturants. These investigators are cloning the gene for protease in order to determine its amino acid sequence and also with a view to obtaining large quantities of the enzyme for use as a tool in protein chemical work. In the Department of Botany, T. Gallagher is investigating transacting factors in the photoregulation of gene expression in *Pisum*.

The Netherlands

Seven years ago, the Netherlands government launched an extensive program to stimulate development work in the biotechnological industry and to create a fertile breeding ground for innovation. This program has resulted in an impressive biotechnological infrastructure. It was 1981 when the government initiated the Innovation-Oriented Research Program for Biotechnology (IOP-B), which was the first of its kind in the Netherlands. The purpose of the IOP-B was and is to coordinate and stimulate all biotechnology-related research with a view to exploiting the commercial potential of new developments. A Planning Commission for Biotechnology (PCB) was appointed to develop and carry out this program. This commission is composed of both academic researchers and representatives from industry.

About half of all available IOP-B funds are set aside for the financing of contracted research. In such projects, the industrial partner, as the body invested with the chief responsibility, indicates the actual research activities to be funded.

Biotechnological research is centered in various research establishments, each focusing on a particular theme within the context of the IOP-B's industry-oriented program. A report on academic/industry cooperative programs in biotechnology in the Netherlands is available in *ESN* 39-12:575.

Research Establishments

In parallel with the universities, the research establishments play an important role in the field of biotechnology in the Netherlands. These establishments are responsible for about 40 percent of all biological research conducted outside industry. They also have links with IOP-B and are represented on the planning and coordination commissions.

Research establishments can be divided into two categories: those supported to some extent by the auth-

orities and those which are semiprivate bodies. Into the first category fall the Netherlands Organization for Applied Scientific Research (TNO), the National Institute of Public Health and Environmental Hygiene (RIVM), and the agricultural establishments. The Ministry of Agriculture and Fisheries has 30 research establishments and testing stations, 12 of which carry out some biotechnological research.

The semiprivate establishments include the Central Laboratory of the Blood Transfusion Service (CLB), the Netherlands Cancer Institute (NKI), and the Netherlands Institute for Dairy Research (NIZO).

The TNO is a large organization employing 5000 persons in the fields of fundamental and applied research. Although the TNO budget is partly funded by subsidies, 49 percent of the budgeting needs are covered by revenues earned from research projects commissioned by government and industry. To ensure that the available manpower is exploited as efficiently as possible, an inter-departmental biotechnology coordination committee was set up to coordinate all research within TNO in the field of biotechnology; at the same time, it serves to ensure that all programs drawn up cater sufficiently to the needs of industry (particularly those of medium-sized and small companies). TNO's biotechnological projects cover a large field - from recombinant DNA (rDNA) research on mammalian cells to research into the breakdown of polysaccharides during the malting process - and are focused on public health, food industry, fermentation technology and environmental aspects. (See *ESN* 40-6:193 for additional information.)

The Netherlands dairy industry has traditionally been an intensive one with the emphasis on cheese production - the Netherlands being the world's largest exporter of cheese. The dairy companies support the NIZO, to which they contribute a tenth of a cent per liter of milk produced. The NIZO is optimizing milk-processing methods in accordance with an important new research

approach whose objective is to improve efficiency by the genetic manipulation of microorganisms in starter cultures. Membrane research also plays an important role in this connection.

NKI's research achievements are now world-famous, and DNA research forms an integral part of current cancer research. Biotechnologically relevant parts of the working program include DNA separation techniques, molecular hybridization techniques, chromosome separation, and the production of Mabs.

In addition to the production of a large number of very different Mabs from both human and murine immunoglobulins for research and diagnostic purposes, the CLB entered the field of medicobiological research a few years ago. One of the objectives is to clone proteins of therapeutic or diagnostic relevance which hitherto has been possible to prepare only from blood plasma or blood cells, such as Factor VIII complex, the histoplasminogen activator, serum albumin, and interleukin-2.

The preparation of vaccines for Dutch vaccination programs and of reagents for diagnostic purposes are two important tasks performed by the RIVM.

The primary function of the Central Veterinary Institute (CDI) is to uphold the interests of the Dutch veterinary world. CDI's biotechnological research is focused on the development of vaccines and the production of Mabs. One line of research pursued relates to the production of synthetic peptides for the detection and reconstruction of antigenic determinants.

The "Schoonard" Institute of Animal Husbandry Research (IVO) develops diagnostic field tests for Third World countries on the basis of Mabs; it has recently devised a pregnancy test for cows. The Royal Tropical Institute (KTI) also makes many reagents and Mabs for diagnostic field tests.

The Institute for the Application of Atomic Energy in Agriculture (ITAL) specializes in developing regeneration procedures for various horticultural crops, extending the range of genetic variations and selecting and propagating key characteristics so as to arrive at better (for example, more resistant) agricultural crop varieties. Further projects include research into the production of fine chemicals from plant cell cultures and bioinsecticides.

At the Institute for the Genetic Improvement of Horticultural Crops (IVT) efforts are being made to adapt recent developments in the field of somatic cell genetics for application in the genetic improvement of horticultural crops. The use of Mabs in the detection of viruses, bacteria, and hormones in plants is one of the directions that research is taking at the Institute for Research into Plant Diseases – another agricultural establishment located in Wageningen. With its agricultural university and its many research establishments and testing stations, Wageningen is the central point for agricultural research in the Netherlands.

Universities

Katholieke Universiteit Nijmegen (KUN) – Catholic University of Nijmegen. The Institute of Cell Biology and Histology has developed several monoclonal antibodies against ovarian carcinoma-associated antigens. The antibodies are specific for ovarian carcinomas and do not react substantially with normal tissues or with other tumors. The researchers in this institute are also involved with serodiagnosis and immunoscintigraphy. One of the Mabs has been licensed by Centocor Europe BV, Leiden. The Mabs against ovarian carcinomas are developed, produced, and characterized in cooperation with the university's Institute of Pathology and Institute of Obstetrics and Gynecology. The research program, under the direction of L.G. Poels, is focused on the significance of tumor antigens for histodiagnosis and serodiagnosis and as a target for therapy.

H.P.J. Biomers and coworkers in the Department of Biochemistry are concerned with the production of antibodies directed against antigens that are difficult to purify. Two methods which are being used for this purpose are the use of synthetic peptides as antigens and methods based on the rDNA technique. W. van Venrooij and coworkers in the department have developed an immunoblotting technique in which a test strip placed in blood can, after processing, give prognosis about certain diseases of the connective tissues.

A.M. van Loon, Department of Microbiology, and coworkers have been investigating the use of IgM-antibody-capture immunoassays for the diagnosis of infectious disease. The specific IgM antibody is measured using a labeled antigen. The labeled antibodies are produced in the laboratory and are available for the detection of specific antibodies against *Toxoplasma gondii*, cytomegalovirus, and varicella-zoster virus. Other applications for the Herpes simplex virus, Epstein-Barr virus, and *Mycoplasma pneumoniae* have been developed. The "hemadsorption immunosorbent technique" is also an antibody-capture method useful for hemagglutinating viruses (rubella, mumps, measles, influenza). The ability of these viruses to agglutinate red blood cells is used instead of the conversion of substrate by enzyme-labeled antigens.

J.H.E.Th. Meuwissen, Institute of Medical Parasitology and J.G.G. Schoenmakers, Department of Molecular Biology, have been working on the development of a malaria vaccine. Malaria research at Nijmegen is focused on two surface proteins of the asexual stage of the parasite. When antibodies raised against these proteins are ingested by a mosquito during feeding on a vaccinated host, these antibodies can block further development of the parasite in the mosquito midgut.

P.J.A. Capel and W.E.M. Tax, in the Department of Nephrology, are investigating diagnostic and therapeutic

Mabs. They are especially concerned with Mabs directed against human T-cell lymphocytes as these Mabs can be used to analyze T-cells and T-cell subsets, which is important for clinical diagnosis in a variety of diseases, including leukemia. The anti-human T-cell Mabs are prepared in the Department of Nephrology.

The Laboratory for Large-Scale and Custom Synthesis of the Faculty of Sciences is specialized in organic chemistry and biochemistry, based on the expertise in the Faculty in such areas as carbohydrates, organosulfur chemistry, epoxides, oxidations, photochemistry, and flash-vacuum-thermolysis. Most of the work is carried out via orders placed confidentially by customers. The main activities of the LGS are in:

- Peptides
- DNA synthesis
- Carbohydrates
- Fine chemicals
- Monoclonal antibodies
- Contract research.

The projects are headed by B. Zwanenburg and G.J.F. Chittenden.

The Dutch National Center for Computer-Assisted Chemistry is situated at the University of Nijmegen. State-of-the-art hardware and software for computer-assisted syntheses (CAOS) and computer-assisted molecular modeling (CAMP) are accessible through user-friendly graphics menus. The Center develops interfaces and elaborates "Help"-facilities, such that all tools can be used with ease by experts and novices alike. Profit-making organizations can gain access to the services of the CAOS/CAMP Center provided that they have obtained appropriate licenses on commercial software. Programs and databases are accessible through the Center.

University of Utrecht. The Institute of Molecular Biology and Medical Technology (IMB) was set up in 1974 with the research focused on fundamental molecular biology. In 1985, several departments at Utrecht University joined forces to concentrate on the field of applied medical microbiology. Since then, the IMB has been the setting for this kind of multidisciplinary research. Among the projects carried out at IMB, two of them are:

(1) The detection and expression of pathogenic and human genes. The purpose of this project is to develop nucleic acid-hybridization assays, useful in a specific and reproducible way to detect small quantities of specific DNA sequences and messenger RNAs (mRNAs); for example, of pathogenic organisms in human tissues, cell smears, and body fluids. Assembly kits being developed should find extensive clinical application in the diagnosis of infectious disease, in endocrinology, and in the recognition of premalignant changes, as well as in the diagnosis and classification of malignant tumors.

(2) Research is also focused on expression of the genes coding for calcitonin and calcitonin-related peptides. The disturbed regulation of the expression of this group of peptides in some lung tumors and sarcomas indicates that these hormones may contribute to the origin, development, and maintenance of growth-tumors. The scientists involved in these studies and those cited above are: P.D. Baas, H.S. Jansz, C.J.M. Lips and J.A.M. van Unnik.

E.J.E.G. Bast and H. Snipper are concerned with the development of versatile tests for viral diagnosis of several human pathogenic viruses (mumps, respiratory syncytial virus, Herpes virus 1 and 2) in terms of rapidity (within 6 hours), sensitivity, and convenience of performance. The leading principle of the tests is the detection of viral antigens in cell cultures of patients' material by use of glycoprotein-specific Mabs in a direct immunoassay. Furthermore, the delineation of *in vitro* methods for the determination of minimal inhibitory concentrations of antiviral agents for therapy and the introduction of simple but sensitive immunoassays for the measurement of antiviral antibodies in serum are also being carried out. Another project is the enhancement of the specificity of diagnostic tests based on Mabs using a method developed for the bioelectronic selection of first- and second-generation hybridomas using a fluorescence-activated cell sorter, independent of classical biochemical inhibitors.

J.L. van den Brande, J.P.H. Burbach, and J.S. Susenbach are studying growth and brain failure in man. The aim of this research is to use rDNA techniques for the synthesis of growth-stimulating and neurohypophysial hormones.

W.H. Gispen and his coworkers are concerned with understanding the basic mechanisms underlying the complex functioning of the brain and to create possibilities of treating brain disease. Thus, research is focused on providing insight into the molecular aspects of communication in the brain and in the molecular regulation of brain repair mechanisms. The group concentrates on two aspects of modern neuroscience; for example, on the significance and mechanism of neuroactive peptides in the functioning of the central and peripheral nervous system and the importance of phosphoproteins in transmembrane signal transduction and axonal sprouting. The studies of Gispen and his group are aimed at development of animal models for studying brain diseases, in the development of new antiepileptics by rational drug design, in insight into the mechanism of action of peptides with putative drug action on the central nervous system, and new leads in the pharmacology of injuries of the central and peripheral nervous system. The project cooperates intensively with the Rudolph Magnus Institute for Pharmacology and the Laboratory of Physiological Chemistry, both of the Faculty of Medicine, Utrecht.

R. de Kruijff and coworkers are engaged in studies of the structure and function of membranes. Current research topics include lipid polymorphism, protein transport, and the mechanism of drug action. Both biological membranes and model membranes are studied with a variety of sophisticated chemical, biochemical, and biophysical techniques. There is a close collaboration with the Laboratory of Biochemistry, Faculty of Chemistry.

A. Osterhaus, H. Snipper, J.F.G. Vliegthart, H.O. Voorma, and P.J. Weisbeek are involved in the development of subunit and peptide vaccines. Peptide vaccines, consisting only of the immunity-inducing epitopes of pathogens, overcome the inherent disadvantages (like serious side-effects, limited application, and limited protection) of live (attenuated) or inactivated pathogens. Peptide vaccines can be constructed by identifying and selecting epitopes on viral components, followed by chemical or biotechnological synthesis of the relevant parts. In this project, vaccines are developed against a series of pathogens based on epitopes of a peptide nature as well as of lipid oligosaccharide conjugates. For testing of immunity-inducing capacity of the new vaccines, both *in vitro* and *in vivo* model test systems were developed.

University of Groningen. The Groningen Biotechnology Center (GBC) was founded in 1981. The Center combined 10 biotechnologically oriented research groups of the Departments of Biology, Chemistry, and Pharmaceutical Sciences of the University of Groningen. The aim of the GBC is twofold: first, to develop and carry out multidisciplinary research programs and second, to coordinate and support biotechnologically oriented teaching.

GBC has also invested heavily in two major programs: the Protein Engineering Program and Extremophilic Industrial Microorganisms. These two programs, established in 1986, will be expanded further in the coming years. (An account of the various projects at GBC is available in *ESNIB* 88-02:22.)

A list of some of the research projects and scientists directing them are given in the following section. The particular section in which the work is being carried out is given since the GBC is a coordinating organization encompassing several laboratories and departments.

W. Harder and coworkers in the Department of Microbiology are concerned with studies of extremeophilic anaerobic microorganisms. Harder and his group are also investigating the use of methanol as raw material for biotechnological processes. The basis for this project is that in industrial fermentations, the price of the raw materials is an important cost factor. Another project, this one led by I. Dijkhuizen, involves studies of the regulation of the expression of genes coding for enzymes specifically involved in primary carbon assimilation in aerobic, facultatively autotrophic, and facultatively methylo-trophic bacteria.

W.N. Konings, also in the Department of Microbiology, is concerned with studies of the mechanism of peptide breakdown in *Streptococcus cremoris*. The aim of the project is to improve the proteolytic activity of starter cultures of *S. cremoris*. Localization of peptidases and mechanisms of peptide transport are being studied. Concomitantly, a genetic study is being carried out with the aim of stabilizing the genetic information coding for peptide breakdown. Project leaders are H. Veldkamp and H. Venema. Konings and coworkers are also studying mixed cultures of lactic acid bacteria which are used as starters in cheese production. The biotic and abiotic factors affecting the growth of individual bacterial strains are being analyzed. Another study by the same group is on the resolution and characterization of components of primary and secondary transport systems in *Bacillus subtilis*. Other projects headed by Konings are studies of the mechanism of energy transduction in anaerobic bacteria and the regulation of membrane-bound processes in bacteria by the proton motive force.

At the Biochemistry Department, B. Witholt and coworkers are concerned with studies of the synthesis of chiral organic compounds with biosystems. These researchers are working with *Pseudomonas* strains which may possess plasmids that encode for the utilization of various organic compounds, such as alkanes and aromatics. Whole cells can be used to carry out reactions of such compounds, such as the conversion of alkenes to epoxides. Optimization of these reactions is being carried out at the genetic, enzymic, membrane, and technical level. Another project by this group is the study of the structure and function of bacterial membranes. Witholt's group is investigating two main problems: (1) synthesis of the outer membrane of *E. coli*, especially with respect to the insertion of proteins into this membrane; and (2) synthesis, structure, localization, and function of *E. coli* enterotoxins.

The Biochemistry Department also has the instrumental facilities for the analysis and synthesis of genes and proteins. This facility is also the nucleus for the supporting section of the Protein Engineering Program of the Biomolecular Study Center (BIOS) and the Groningen Biotechnology Center (GBC). Research on amino acid sequence and molecular evolution is carried out by J.J. Beintema, Department of Biochemistry; gene expression by G. Ab of the same department and synthetic vaccines by G.W. Welling of the Department of Medical Microbiology. G.W. Welling is, in particular, studying integral membrane proteins and proteins produced by rDNA techniques that show a tendency to aggregate and therefore are difficult to purify. Sendai virus membrane proteins are used as model proteins to study high-performance liquid chromatography (HPLC) methods for the purification of these proteins.

The Department of Genetics performs both fundamental and application-oriented research on potatoes and nitrogen fixation by peas, and on two classes of industrial microorganisms (*Bacilli* and lactic acid streptococci). W.J. Feenstra is head of this section on cell and plant genetics.

G. Venema heads the section on molecular genetics of bacteria at the Department of Genetics. The application-oriented molecular genetic research on bacteria focuses in particular on:

- Plasmid instability in *Bacilli*.
- Protein secretion by *Bacilli*. *Bacilli* are the producers of important extracellular enzymes, such as proteases, that are used in detergents and amylases for use in the starch-processing industry. Venema and coworkers are looking for ways to optimize the secretion of particular enzymes; rDNA technologies are frequently used for this purpose.
- Genetics of lactic acid streptococci. Lactic acid streptococci are a dominant component of starters used in the Dutch dairy industry for cheese making. The research project in the department has recently led to the development of a host-vector system for lactic acid streptococci, which allows the researchers to work rationally toward strain improvement.

A.J. Pennings, Department of Polymer Chemistry, heads a section focusing on the development of a new synthetic blood vessel that can serve as a temporary scaffold for the regeneration of a new and functional arterial wall. These researchers have found that only synthetic vascular grafts of a specific polyurethane/poly (L-lactide) composition, pore size, elasticity, and rate of biodegradation can induce the regeneration of a properly functioning new artery. The researchers think that the application of synthetic, compliant blood vessels of the biodegradable type may lead to a major breakthrough in the reconstruction of small-caliber arteries.

The Materials Science Center of the University of Groningen has a longstanding tradition of interdisciplinary research on new materials with interesting physical and chemical properties. The research of the laboratory focuses on two main points:

- The surface characterization of solid surfaces. The influences of pretreatments to increase, decrease, or prevent adhesion are investigated in about 10 projects. Systems investigated involve solid as well as powdered materials. Surface free energies and surface compositions of PVA/PMMA polymer blends are also studied. This includes not only polymers but also inorganic materials as well as metal systems.

- The bulk optical properties of translucent, turbid materials. This research is conducted by J. Arends, J. ten Bosch, and H. Busscher.

The Department of Pharmaceutical Chemistry and Pharmacognosy performs research on pharmaceutical biotechnology, plant cell biotechnology, and production of pharmaceuticals by bioconversion and biosynthesis. The broad aims of the department are the chemical and pharmacological evaluation of medicinal plants, the development of new drugs of natural origin, and the production of biologically active compounds by plant cell biotechnology. Two approaches are being studied to achieve the production of the neurotransmitter precursor L-DOPA (used in the treatment of Parkinson's disease) with suspension-grown cells of *Mucuna pruriens*: (1) the endogenous production of L-DOPA with suspension-cultured cells and (2) the bioconversion of L-tyrosine into L-DOPA by means of alginate-entrapped cells. Upscaling of production by means of fermentor systems is also being investigated. The immobilized cells of *Mucuna pruriens* are being used for the study of kinetic parameters and the production of biologically active compounds (dopamine agonists) and fine chemicals (a number of catechols). In addition, the production of scopolamine by *Datura* and *Duboisia* species is also being investigated. Another topic with practical application is research on eupatoriopicrin derivatives. These projects are under the direction of Professor Th.M. Malingré.

Research on the development of improved delivery devices is carried out at the Department of Pharmaceutical Technology. The researchers in the department design systems for application in dentistry and chemotherapy (parenteral) and in therapy by the peroral route. The megaloporous system, a principle designed for constant drug delivery is already available for licensing (patent pending). The drug release performance has been tested both *in vitro* and in human volunteers. Other scientific topics being investigated are:

- Design of polymeric inserts for controlled ophthalmic availability
- Development of drug dosage forms for oral/intestinal flora suppression
- Improvement of stability and gastrointestinal absorption of drugs by cyclodextrins
- Screening of antibacterial agents on the indigenous flora in animals and humans
- Development and application of systematic optimization techniques in the formulation of drug dosage forms
- Improvement of the properties of drugs and excipients (starch derivatives and lactose) by physicochemical modification

- Development of glucose sensors for the control of diabetes. These research projects are under the direction of P. de Haan and C.F. Lerk.

University of Amsterdam. The University of Amsterdam and the Free University have formed a collaborative program to work together in the field of biotechnology. This cooperation, referred to as BIOTECHNOLOGY AMSTERDAM, has given rise to a strong research group with expertise in a large number of areas. At the same time, it offers students an excellent opportunity to acquire knowledge and proficiency in all the basic disciplines of biotechnology.

Research within BIOTECHNOLOGY AMSTERDAM is focused on microorganisms and their products, plants and plant cells, enzymes, and monoclonal antibodies (Mabs). The research carried out is aimed at the discovery of new scientific principles and at the initiation of new processes.

The yeast *Saccharomyces cerevisiae* has long been an important organism in industrial microbiology, but recent developments in rDNA technology have resulted in an upswing in its popularity as a production organism. Fundamental research on the molecular biology of yeast is carried out by two groups within the framework of BIOTECHNOLOGY AMSTERDAM, that of L.A. Grivell and H.E. Tabak (Department of Biochemistry, Biotechnology Center, University of Amsterdam) and that of R.J. Planta/H.A. Raué (Department of Biochemistry, Free University of Amsterdam). Both groups have long-standing experience in both classical molecular genetic and rDNA techniques with yeast, and both occupy leading international positions in their respective fields. Main research areas of the University of Amsterdam group are the study of the structure and expression of genes in mitochondrial DNA and the elucidation of the rules governing the correct addressing of proteins to unique locations in the cell. Understanding of this latter process is of particular importance for many biotechnological applications in which the gene products must be translocated across specific cell membranes and/or sequestered in organelles.

Use of yeasts in both fundamental and applied studies has been severely limited by the absence of suitable vector systems for the introduction of foreign DNA. The aim of a recently initiated project by J. Meijer and coworkers (Department of Biochemistry, University of Amsterdam Biotechnology Center) is to meet needs in this area by the development of stable vectors, with both broad host range and positive selection features.

Like yeast, bacteria are also widely used in biotechnology, with applications in the production of antibiotics, enzymes, polysaccharides, ethanol, and organic acids such as gluconate, ketogluconate, and lactate. In the groups of O.M. Neijessel (Department of Microbiology,

University of Amsterdam) and K. van Dam/P.W. Postma (Department of Biochemistry) research is being carried out into microbial carbohydrate metabolism and its relationship to the energy balance of the cell with the aim of optimizing the conversion of raw material to end product.

The group of A.H. Stouthamer (Institute for Molecular and Cellular Biology, Free University of Amsterdam) also carries out research into the relationship between biological productivity and the energy balance in microbial cells. The group is particularly interested in the regulation of the efficiency of oxidative phosphorylation during aerobic or anaerobic electron transport and in the manner in which both substrates and energy are distributed over the processes of biomass generation, cell maintenance, and product formation. These areas are of direct importance to many biotechnological processes, and results obtained have found application in a variety of industrial fermentations, including the production of penicillin. Within the framework of BIOTECHNOLOGY AMSTERDAM, the group intends to focus attention on the physiological aspects of growth and product formation by *Bacillus* species. These organisms are industrially important for their ability to produce a number of hydrolytic exoenzymes.

The efficiency of product formation also underlies research into the structure of the cell wall in milk streptococci (J.T.M. Wouters, Department of Microbiology, University of Amsterdam). These organisms play an important role in the souring of milk during cheese-making. A common event during this process is viral infection of the streptococci leading to cell lysis and consequent loss of product. Use of viral-resistant strains would circumvent this problem, and in order to facilitate the isolation of these, knowledge of the structure of the cell wall, in which specific viral receptors are located, is highly desirable. As such, it makes up part of a broad collaborative effort between the laboratories of microbiology of the NIZO (National Institute for Dairy Research), the University of Groningen, and the University of Amsterdam, and is complementary to research carried out by the group of F.K. de Graaf (Department of Molecular and Cellular Biology, Free University of Amsterdam), into protein transport across membranes and the properties of the cell envelope in the Gram-negative bacteria.

A new research line within the area of industrial microorganisms has been initiated as a collaboration between the groups of N. Nanninga, R. van Driel, P.W. Postma, K. van Dam, and H. van den Ende (Departments of Electron Microscopy and Molecular Cytology, Biochemistry, and Plant Physiology respectively). This line builds on expertise available in the areas of bacterial cell division (Nanninga), cell differentiation in lower eukaryotes (van Driel), features of cell membranes (van Dam/Postma), and cell wall structure (van den Ende). The program aims at an analysis of changes in intermediary

metabolism occurring during the cell cycle in yeast. Industrial fermentation processes generally employ cultures in which cells pass through the cell cycle asynchronously. Insight into cell cycle-dependent variation may eventually allow cells to be maintained longer in phases of the cycle that are favorable to production.

Plants have always been an important source of food and of valuable products for industry, agriculture, and medicine. The "Biological Productivity of Plants and Plant Cells" is the central theme for fundamental and applied research at the Free University of Amsterdam. For plant productivity, new molecular and cellular approaches are being addressed to problems that are impossible or very difficult to solve by means of classical plant breeding.

Within the framework of BIOTECHNOLOGY AMSTERDAM, research is carried out at the molecular, cellular, and tissue and plant level and is focused on gene identification and transformation systems for plant cells and the cell organelles (chloroplasts and mitochondria), the production of secondary metabolites, and the production of oils and fats. Disciplines involved are molecular genetics, somatic cell genetics, biochemical genetics, classical genetics, and physiology.

The application-oriented part of the research aims at: (1) the improvement of biomass production (phytopathogen resistance, cytoplasmic male sterility), (2) the optimization of product synthesis in the phenyl-propanoid pathway such as flavonoids and lignans (antitumor products), and (3) the improvement of yield and quality of oils and fats (fatty acid synthesis in European crops with oil-containing seeds and in oil-producing yeasts). These goals can be achieved by identification, mutagenesis, and transfer of relevant genetic material and by optimization of internal and external physiological conditions for growth and production of plants and plant cells.

Plant research is carried out by three groups: H.J.J. Nijkamp, J.N.M. Mol, and F.K. van der Plas (Institute of Molecular and Cellular Biology, Free University of Amsterdam).

The Biochemistry Department of the University of Amsterdam places a strong emphasis on the fields of chemical enzymology and protein chemistry.

With regard to the research on the structure-function analysis of metallo-enzymes, the groups of S.P.J. Albracht, R. Wever, and B.F. van Gelden are experienced in physical, chemical, and analytical methods. These methods are of importance for quality control of rDNA-synthesized proteins when these are used in the pharmaceutical or food industries. These groups also possess a wide knowledge of both chemical and enzymatic reaction kinetics and are experienced in the techniques required for the chemical modification, stabilization, and storage of proteins. Knowledge of kinetics is essential for the optimization of the activity of enzymes used in process tech-

nology, while insight into the relationships between structure, activity, and stability is of importance for the coupling of proteins to carriers or the engineering of improved enzymes by the method of site-directed mutagenesis (molecular design; protein engineering).

Within the framework of BIOTECHNOLOGY AMSTERDAM, a number of aspects of bioprocessing is under investigation in the University of Amsterdam's Departments of Chemical Technology (C. Boelhouwer) and Microbiology. A joint water purification project has led to the development of a two-step method for the anaerobic purification of effluent wastewater from industries that process agricultural products (sugar and potato starch industries, slaughter houses, etc.).

At present, an attempt is being made to concentrate domestic waste effluent water, making it suitable for anaerobic purification. In conjunction with industry, this research is being carried out on both a laboratory and industrial scale.

For an efficient and thus economic procedure for biological processes, it is essential to have active biological matter available in a high concentration. The Department of Chemical Technology, in conjunction with the Department of Electron Microscopy (Nanninga) is investigating the possibility of achieving this by using microorganisms attached to pellet-forming carriers. The development, architecture, and physiology of such biofilms is probably influenced by hydromechanic forces, type of organism, and chemical composition of the reactor environment. Present research is directed to an analysis of these factors.

Research using immunological techniques is being carried out by all departments of both universities. Use is being made of conventional antisera, made and characterized by the investigators involved. These antisera are used to identify, quantify, and isolate biological (macro) molecules, not just of proteins, but also of oligosaccharides, glycosphingolipids, and other small molecules. In addition, increasing use is being made of the hybridoma technique to make monoclonal antibodies (Mabs). In conjunction with the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service and the Netherlands Cancer Institute, facilities have been developed for the production of Mabs. In the group of J.M. Tager (Department of Medical Enzymology and Molecular Biology, University of Amsterdam) a new project was recently initiated to improve the technique for the production of Mabs using *in vitro* immunization.

Biotechnology Delft Leiden (BDL). BDL is the joint biotechnology centre of Delft University of Technology and Leiden University. It covers an integrated program on industrial biotechnology. The input from Leiden comprises formal and molecular genetics, molecular biology, and biochemistry of plants, bacteria, and yeasts. Delft is strong in microbiology, enzymology, and the various tech-

nological disciplines that support biochemical engineering. The integrated program has been reinforced by both universities, the government, science foundations, and industrial contacts. The main body of the BDL effort is organized within six multidisciplinary project-groups. In each project-group, the input from several departments is integrated. Biochemical Engineering (Delft) has a central role. As well as mission-oriented research, most programs have long-term and fundamental components. Many other projects with biotechnological relevance are carried out within the BDL-related departments. Most of them concern improved gene expression or agrobiotechnology or both.

All project groups have contacts and contracts with industry. On average, work covered by more than 20 contracts, is underway, mainly, but not exclusively for Dutch companies. As a result, the BDL Project-Groups are being reinforced with additional researchers. BDL is one of the factors that attract industrial companies to the Bio-Science Park in Leiden. Dutch as well as foreign companies have settled in the area around the laboratories.

BDL Project-Group – Incomplete Microbial Oxidations: The research theme of this group includes incomplete oxidation (dehydrogenation) reactions in microorganisms. These reactions lead, for example, to the production of organic acids. The coenzyme pyrrolo-quinolinc quinone (PQQ), discovered by the group, plays a central role in the novel class of quinoprotein enzymes. Several oxidizing systems in bacteria as well as in higher organisms have been found to use PQQ as their prosthetic group. The bacterium *Acinetobacter calcoaceticus* appears to synthesize glucose dehydrogenase, a PQQ-containing enzyme (quinoprotein) under all growth conditions. With this enzyme, extremely rapid conversions of glucose into gluconic acid are possible. The bioenergetics of this process are studied in continuous culture in order to achieve maximal efficiency.

Research is also being carried out on the development of biosensors, primarily for medical applications.

The scientists heading the projects described above are: J.A. Duine and J.G. Kuenen (Department of General and Applied Microbiology, Delft Technical University) in collaboration with K. Ch.A.M. Luyben (Department of Biochemical Engineering, Delft University of Technology). P. van de Putte of the Department of Biochemistry, University of Leiden, is also a collaborator in the research described above.

Another BDL Project-Group study is concerned with the regulation of metabolism in yeasts. Redox balances in the cell play an essential role in this regulation. Hence, basic research is focused on the relationship between redox balance and physiology, and on the genetic manipulation of metabolism. The results of this fundamental approach are applied in specific industrial fermentations and in the development of new processes.

In large industrial fermentations, gradients of oxygen, nutrients, and pH occur in the fermenter. Hence, the yeast cells encounter continuously changing environments. In order to optimize fermentation, integrated studies on "transient state" physiology, growth kinetics, reactor design, and mass transfer are being conducted.

The researchers heading the above programs are the same as stated in the preceding section on incomplete microbial oxidations.

Plant cell biotechnology is another BDL Project-Group program. Plants are capable of producing a wide range of secondary products, many of them being of economic value (for example, as drugs, flavors etc.). They often have complex chemical structures that make them inaccessible to chemical synthesis on a commercial scale. The BDL group is studying the possibilities of producing such compounds in large-scale cultures of cells in bioreactors. The course of biosynthetic pathways and their epigenetic and genetic regulation is being analyzed, genetic manipulation of biosynthesis being one of the important goals of the BDL group. The influence of various nutritional and hormonal factors on the rate and the efficiency of growth is also being studied. The choice and further development of suitable types of bioreactors interacts directly with the study of the parameters mentioned above. Isolated enzyme systems and regeneration of cells to complete plants are important spin-offs of the plant cell studies.

The *Cinchona* alkaloids, quinine and quinidine, are well-known drugs. The pathway of their biosynthesis is simple relative to the terpenoid-indole alkaloid synthesis in other plants. Thus, for the BDL group, *Cinchona* was an interesting model system for the study of the epigenetic and genetic regulation of biosynthesis. Meanwhile, one of the procedures for epigenetic regulation has been patented. The group has also discovered anthroquinones in *Cinchona*. The production of these phytoalexins can be induced in cell cultures by various elicitors.

The BDL group is also studying the physiology of cultured cells of *Catharanthus roseus*. Within the rather young field of plant cell biotechnology, periwinkle is one of the most studied species. This plant produces valuable anti-neoplastics: dimeric indole alkaloids. However, so far only monomers have been found in cell cultures. The group uses periwinkle cells for the study of physiological parameters relevant for large-scale culture, such as respiration, uptake of nutrients, hormonal control of growth and production, and transmembrane transport of alkaloids. Moreover, it appears to be a suitable model for the study of cryopreservation.

Construction of plant vectors and transformation of plant cells are also being carried out by the BDL group. Bacteria of the genus *Agrobacterium* are able to genetically transform plant cells, with tumors as a result. With subtle techniques, the bacteria can be manipulated to in-

corporate desired genes into the plant cell genome. Procedures developed by the group in this and related fields have led to several international patent applications.

In close collaboration with the other projects, the genes coding for the biosynthesis of secondary metabolites and the regulation of secondary metabolism are being studied in order to be able to increase production by plant cell cultures via genetic engineering.

The researchers concerned with the above projects are: R. Verpoorte, A. Baerheim-Svendsen, and J.J.C. Scheffer (Section on Pharmacognosy, Center for Bio-Pharmaceutical Sciences, Leiden University); R.A. Schilperoort and K.R. Libbenga (Department of Plant Molecular Biology, Leiden University); K.Ch.A.M. Luyben (Department of Biochemical Engineering, Delft University of Technology); and J.A. Duine (Department of General and Applied Microbiology, Delft Technological University).

Another important BDL Group-Project being carried out at Delft University of Technology deals with bioreactor design and downstream processing.

One of the research projects of the group at Delft deals with immobilized living cells (*Clostridia*) for the production of an isopropanol/butanol/ethanol (IBE) mixture. Another is devoted to immobilized enzymes. The first deals with the modeling and design of a process for solvent (butanol) production, while in the other the reactor design (fluidized bed) is more specifically studied.

Diffusion rates and concentration profiles within the particles are being estimated and short-cut mathematical models for process kinetics are being developed. There are many interactions with other BDL project-groups.

Transport phenomena in bioreactors, especially the transport of gases to and from the bulk liquid (mass transfer) and in the liquid (mixing) form the subject of a project on reactor development. Important aspects are bubble swarm phenomena, bubble size distribution, bubble breakup, and coalescence in large-scale apparatus (for example, tower loop reactors, multi-impeller stirred tank reactors). Gradients in concentration of oxygen and substrate as a result of insufficient mixing in large-scale apparatus, and their influence on the micro-environment of the organisms are also studied. There are several interactions with other BDL project-groups, especially Physiology and Genetics of Yeast and Control.

The first stage in downstream processing is usually the separation of biomass from the fermentation broth by, for example, centrifugation or filtration. In the project on biomass separation, the researchers are studying classical filtration: the influence of the cell disruption technique, the use of filter aids and the use of high-frequency backwashing with cross-flow filtration to increase the filtration fluxes. For these investigations, a reproducible model system is needed, for which the use of yeast is being tested.

Continuous product recovery during fermentation is a way to prevent inhibition by the product itself. It can also lead to a larger yield per time and/or volume. Researchers at Delft are studying butanol recovery by perstraction or pervaporation via membranes.

In addition, the adsorption of protein on ion-exchange media or affinity-adsorbent in fluidized bed columns is being studied with emphasis on hydrodynamics, adsorption kinetics, and column design. Other subjects of research are the adaptation of packed columns for extraction from fermentation broths and the possible use of a porous membrane in which one of the phases is captured.

The scientists involved in the above projects are: K.Ch. M. Luyben, Department of Biochemical Engineering, Delft University of Technology; J.A. Wesselingh and J. de Graauw (Chemical Technology); J.G. Kuenen and J. Duine (General and Applied Microbiology) and M.M.C.G. Warmoeskerken, dealing with transport phenomena.

Another BDL Project-Group is concerned with control of biotechnological processes. The project-group control develops and implements control strategies on digital computers for processes ranging from laboratory- to production-scale.

In the optimal control of biotechnological processes, emphasis is laid on the use of mechanistic models, the estimation of model-parameters and state estimation (off-line or online). Among others, a control strategy for a butanol production process with immobilized *Clostridia* is being developed. The glucose concentration, which cannot be measured online, is estimated using an observer technique. The butanol concentration is influenced by a temperature-controlled pervaporation unit that withdraws butanol selectively.

A user-friendly program, called BIOSIM, has been developed for the implementation of control structures that can be used during simulation or during real-time experiments. A model for bioprocess production, the control structure and input-output functions can be generated using pre- or user-defined blocks. After implementation of the simulation or real-time control, the user interacts with the control system via a command interface. Flexible graphical display facilities are supported. The program is implemented on several minicomputers.

Another part of the project on control is the monitoring and control of wastewater treatment. Quality standards for the effluent flow of wastewater treatment reactors necessitate thorough control.

The researchers concerned with the above projects are: K.Ch.A.M. Luyben (Department of Biochemical Engineering, Delft University of Technology); G. Honderd and H.B. Verbruggen (Department of Con-

rol Engineering); and A. Johnson (Department of Transport Phenomena).

The BDL Project-Group on Environmental Biotechnology concentrates on the application of fundamental knowledge of microbiology and modern fermentation principles to develop innovative technologies for the treatment of (industrial) wastes and for clean technologies. Particular effort is put into the removal of sulfur and nitrogen compounds.

In order to develop biotechnological processes for the removal of metals from wastewater, the biochemical mechanisms are being studied. Microbial manganese transformations are being used as a model system.

Activities have also focused on a further development of the Up-flow Anaerobic Sludge Blanket (USAB) reactor system by using, for example, mathematical modeling.

By application of modern fermentation principles, high conversion rates are being obtained on solid organic waste from breweries, etc. Three-phase slurry reactors for the biological decontamination of polluted soil are also being developed and tested at the Delft University of Technology.

The scientists concerned with the above projects are: from Delft University of Technology, J.G. Kuenen (Department of General and Applied Microbiology), and K.Ch.A.M. Luyben (Department of Biochemical Engineering), collaborating with L. Bosch (Department of Biochemistry, University of Leiden).

In addition to the multidisciplinary project-groups, several other biotechnological projects are being carried out within the departments that constitute BDL. Most of them deal in one way or another with gene expression, with agrobiotechnology, or with both. Moreover, the departments contain several important service units.

Within Leiden University's Department of Biochemistry, the expertise of various areas of molecular biology (for example, bacterial genetics, protein biosynthesis, and plant virology) is used to solve problems of biotechnological relevance. Some of these efforts are integrated in BDL Project-Groups work described in the previous sections.

Viral infections are responsible for considerable losses of agricultural crops. Within the project of viral studies, this problem is approached in various ways. The expertise on "pathogenesis-related proteins" and "cross protection" is used for the immunization of plants. One of the results has been the construction of plants resistant to alfalfa mosaic virus. Another line of research concerns the diagnosis of viral infections in ornamental bulbs (tulip, narcissus, lilies) and food crops. Routine detection and identification procedures based on cloned DNA copies of the viral RNA are being developed.

The controlled secretion of proteins from *E. coli* is also being studied. RNA bacteriophages encode a small

protein that is responsible for cell lysis at the end of the infection cycle. The gene involved has been cloned. Controlled expression of this gene in *E. coli* may lead to controlled secretion of proteins. The system can also serve as a model for the function of peptide antibiotics.

Another study is concerned with the elevation of kirromycin production by *Streptomyces*. The production of kirromycin by *Streptomyces ramocissimus* is hindered by the fact that it inhibits its own synthesis by binding to one of the so-called "elongation factors." The researchers involved in this project are attempting to relieve this inhibition by site-directed mutagenesis without affecting the product itself.

In the protein engineering project, the relationship between the biological function and the three-dimensional structure of a bacterial protein is being studied both with classical procedures and by site-directed mutagenesis. This extensive project is part of the Research Action Program Biotechnology of the European Community.

Another study is concerned with the modification of blue copper proteins. Some of these redox enzymes are promising candidates for application in biosensors. Site-directed mutagenesis is being used for modification of the standard redox potential as well as the surface characteristics. The latter is important for the immobilization of the proteins in biosensors.

The scientists directing the above projects are: L. Bosch and P.H. van Knippenberg (Department of Biochemistry, University of Leiden); G.W. Canters (Department of Inorganic Chemistry, University of Leiden); and J.A. Duine (Department of General and Applied Microbiology, Delft University of Technology).

Industry

A relatively large number of prominent companies engaged in biotechnological research are located in the Netherlands. Owing to the limited size of the domestic market, these companies are internationally oriented. The major markets for biotechnology have been extensively developed in the Netherlands, viz, health care, food, agriculture, fine chemicals, the environment, and (also constantly increasing) instruments.

Human and veterinary health care is of a high standard in the Netherlands. Because of the high population density of the Netherlands (in terms of both man and beast), a relatively large and fertile market has been created which is eminently suitable for innovations.

AZKO-Pharma is one of the pioneers in the field of diagnostic tests. Organon, AZKO-Pharma's largest operating company, manufactures medicines, oral contraceptives, diagnostic aids, and psychopharmaceutical products. Organon was the first to launch an improved form of pregnancy test based on Mabs. Intevet, another oper-

ating company, is specialized in the field of veterinary medicines such as vaccines for poultry and hormone preparations for veterinary use. It produced the first commercial biotechnological product in the world, a veterinary vaccine against infectious diarrhoea in pigs and calves. Diosynth, another of AZKO-Pharma's companies, has invested in a major expansion of its fermentation production facilities with a view to obtaining a feedstock for the production of steroids by newly developed microbiological manufacturing routes. Organon Teknika recently acquired three American companies: General Diagnostics, Nuclear Medical Laboratories, and Litton Bionetics. Organon Teknika's latest biotechnological development is an antibody test for the AIDS virus.

Gist-Brocades operates in such fields as those of veterinary vaccines, antibiotics, and steroids. One of Gist-Brocades' most successful research achievements has been the optimization of penicillin manufacture. As a result of improvements in mould formation and processing conditions operating efficiency has been increased threefold to fourfold over a period of 15 years. The company cooperates with other organizations in many fields. For instance, Gist-Brocades and the Central Laboratory of the Blood Transfusion Service work together to establish an economic route for the manufacture of the coagulant, Factor VIII.

Duphar, one of Solvay's companies, is active in the vaccine field. In cooperation with bodies such as the State University of Utrecht, research is being carried out to develop veterinary vaccines against corona viruses. Duphar is Europe's largest manufacturer of influenza vaccine.

In April 1984, **Promega**, one of the Promega Biotech, USA, group was launched; it was the first biotechnological company to come to Leiden and is now located in the Leiden Bio-Science Park. Promega is developing its own products in the Netherlands, for example, restriction enzymes, but also other molecular biological products.

Holland Biotechnology (HBT) was set up in 1985 because many academic establishments in the Netherlands were insufficiently exploiting the commercial potential of their biotechnological research. In the coming years HBT will be engaged in the manufacture and sale of reagents for use in rDNA research and Mabs for use in human diagnostics.

Centocor Europe, a member of the American Centocor biotechnology group, opened its new establishment in Leiden's Bio-Science Park in 1986. The aim is to develop and market biotechnological products for *in vivo* medical applications. Most of the new products are Mabs for routine injection into humans. They will be used for *in vivo* diagnosis of heart and vascular disease and cancer. Plans for the therapeutic application of Mabs are in an advanced stage.

Food and luxury goods industry. Dairy companies, breweries and the other concerns making up this industry in the Netherlands are run on modern lines, have an international name, and enjoy a prominent share of the world market in their field. The Netherlands food industry contributes about 25 percent to the gross national product, biotechnology accounting for 12 to 15 percent of this percentage. The world-famous Heineken beer is fourth in the world ranking in terms of sales, being responsible for 7 percent of the world beer production.

Gist-Brocades are very experienced in the field of large-scale fermentation processes. In the food sector, Gist-Brocades is Europe's top yeast manufacturer. This company is also the world's second largest producer of commercial enzymes.

Unilever is also actively engaged in the agricultural foods sector. One of the activities for which it is well known is the use of enzymes, notably lipases, in food processing. Furthermore, continuous fermentation processes are being developed, for example, for the production of yoghurt. Unilever's researchers were the first in the world to clone the genetic information for a plant protein in yeast, namely, the sweet-tasting protein, thaumatococin. Unilever and Gist-Brocades were jointly successful in reproducing the genetic information for chymosin in yeast, chymosin being an enzyme which is used for the curdling of milk in cheese production. Biotechnology consumes at least 10 percent of Unilever's total research program.

Naarden International is an independent Dutch company operating in the field of aromatic and flavoring essences and is one of world's market leaders. This company's biotechnological research and development work is chiefly centered in the following areas: (1) applicational research on industrial enzymes, (2) the formation of special enzyme complexes, and (3) the development of new industrial processes in which these enzymes can be employed and the commercialization of the developed enzymes together with the relevant know-how. In addition, they are involved in microbiological aroma production. One of the most important fields in which Naarden has performed a great deal of research is the application of enzymes in brewing. An equally important field is that of enzymes for the starch and alcohol industries. This manufacturer of aromatic and flavoring essences has obtained international patent coverage for the enzymatic treatment of liquid wheat starch waste.

Agriculture and horticulture. A biotechnology coordination commission approved by the National Agricultural Research Council (NRL) coordinates the agriculture-oriented aspect of the government-initiated Innovation-Oriented Research Program for Biotechnology (IOP-B).

Vanderhave is a leading company, both nationally and internationally, in the genetic improvement, produc-

tion, and sale of agricultural sowing seeds. **Nuhema Zaden**, a producer of vegetable seeds, is a medium-size company actively engaged in plant biotechnology research. **Zaadunie**, a company employing 1200 people, develops, produces, processes, and sells vegetable and flower seeds and young plants. This seed improvement company has also recently begun construction of a plant biotechnology laboratory.

In January 1985, Molecular Genetics, US, signed an agreement to establish a plant biotechnology group in the Netherlands under the name of **Mogen International**. Mogen is now located in Leiden's Bio-Science Park. This company is concentrating its efforts on the development of new plant varieties of agricultural interest to Western Europe and the rest of the world.

Multiplan Holding BV, launched in 1986, is one of the companies of the ACF Chemiefarma NV group. This company is engaged in a number of agricultural activities of a biotechnological nature. In the field of tissue culture it is engaged in the cultivation of ornamental plants for the domestic market and tropical plants in the ACF tradition such as quinine, spices, and cardamon. Somaclonal techniques are also being developed with a view to the genetic improvement of these tropical plants. Multiplan has also concluded joint working agreements with US companies intending to establish themselves in the Netherlands.

Environment. The biotechnology of environmental conservation is in an advanced state of development in the Netherlands. It is a field in which several important innovations also having an impact on the international market have already been developed. Many Netherlands-based companies have succeeded in securing a prominent international position for themselves.

DSM (Dutch State Mines) have already for some years been operating the second largest aerobic/anaerobic wastewater treatment plant in Europe especially designed for removing urea from wastewater, making use of a countercurrent, multistage, fluidized-bed enzyme reactor.

Gist-Brocades developed an anaerobic reactor operating according to the fluidized-bed principle. There are plans to erect a total of six reactors at the operating site and to develop post-treatment fluid-bed reactors for nitrification purposes. An important breakthrough in the field of wastewater treatment was the development of the upflow anaerobic sludge blanket (USAB) reactor, which represented the joint efforts of various universities and the sugar manufacturer CSM. This work was taken over by Gist-Brocades. At least 40 such plants have now been constructed in the Netherlands and elsewhere.

De Ruiter Milieutechnologie has accumulated a vast fund of experience and know-how in such fields as soil conservation (for example, microbiological soil decontamination) and air pollution (for example, air purifica-

tion by microbiological means). In cooperation with the IWACO engineering bureau, a land reclamation optimization study is being carried out on a semitechnical scale on soil contaminated by oil, on the one hand, and phenols, on the other.

Boemsanering Nedeland BV, with the cooperation of DSM, is working, as part of a test project in land reclamation, on soils contaminated with such substances as polycyclic aromatics.

Zegwaard, a waste processing company, and the Institute for Storage and Processing of Agricultural Products (IBVL) some years ago initiated a project for treating organic waste. The project was supported by the Netherlands Government and the EEC. The anaerobic two-stage reactor which they developed is being built in the "Westland," a large market-gardening region, where it will be used to convert rejected vegetables into biogas.

Industrial chemicals. The Netherlands exports considerable quantities of chemicals, many prominent biotechnological companies contributing to this trade.

AVERBE is Europe's largest manufacturer of potato flour. The company's researchers recently developed a cleaner biotechnological process for the production of fermentation broths. Other biotechnological developments include the enzymatic production of cyclodextrins from starch and the start-up of an anaerobic wastewater treatment plant. **Glucona**, a joint venture between AZKO and AVEBE, is the world's largest supplier of gluconates. These are the product of enzymatic and fermentative processes with starch as the feedstock. This company was the first in Europe to operate enzymatic processes.

CCA Biochem is the world's largest producer of lactic acid and its derivatives by the fermentative route. **Oce-Andeno**, an offshoot of Oce van der Grinten, is one of the few companies in the Netherlands to specialize in fine chemicals. It is an important supplier of intermediates to the pharmaceutical industry, producing, for example, key intermediates for the preparation of semi-synthetic penicillins and cephalosporins such as D-phenylglycine. It is also very actively engaged in research into new methods for the preparation of optically active compounds, particularly enzymatic processes. The commercialization of these processes is expected to be completed within the next 3 years.

DSM is an international concern with its head office in Heerlen. Its most important sphere of operation is in chemistry and its strategic efforts are being increasingly directed toward the development of new, high-value products and the manufacture of specialty chemicals requiring intensive know-how. As far as the diversification toward the latter is concerned, biotechnological processing methods are intended to play an important role. In the recent past, one of the developments was an enzymatic process for the preparation of optically active

amino acids. Using DSM's enzymatic process, a series of D- and L-amino acids of high optical purity can be produced on the basis of simple commercially (and readily) accessible feedstocks. For the development of biocatalysts for this purpose, DSM is engaged in a long-term joint research project with the Danish company, NOVO.

The production of peptides is another field in which enzymatic processes are becoming increasingly important. DSM and the Japanese company, TOYA SODA, entered into a joint venture in April 1985, covering the enzymatic synthesis of the dipeptide sweetener "Aspartam." An Aspartam plant has been built recently in the Netherlands.

However, DSM is engaged in even more biotechnological projects. For instance, in a joint project with researchers from the universities of Amsterdam and Wageningen, the possibilities are being gauged of halogenating aromatic compounds stereo- and regio-specific by means of enzymes. Work is also being done on the biodegradation of lignin, etc.

Royal Dutch Shell is also interested in microorganisms. In a microbiology related study, researchers are investigating topics such as the possible use of bacteria in metal extraction, detoxification of spent metal catalysts, and enhanced oil extraction.

Instruments. The innovatory approach has benefited the Netherlands' position as a manufacturer of biotechnological instruments. In addition to instruments used in the environmental sector, many other types of instruments are also being developed by Dutch companies. Gist-Brocades is actively engaged in the development and construction of reactors in accordance with the fluidized-bed principle which are intended specifically for use in anaerobic wastewater treatment. The sugar manufacturer CSMO developed the upflow sludge blanket (USAB) reactor and Gist-Brocades has taken over this development activity.

ClairTech was set up by the Technological University of Eindhoven and two other participants for the pur-

pose of marketing an advanced biofilter, called Bioton. Van Tongeren International BV, which is operating in the same field, manufactures and develops biofilter equipment in which microorganisms scavenge gaseous waste streams.

Applikon Dependable Instruments has developed a complete range of instruments for use in biotechnological processes: fermenters, on-line analyzers, computerized systems for bioprocesses, biosensors, and sterile samplers. Contact Flow specializes in the design and construction of fermentation systems which are employed to produce bacteria and cell cultures for the human and veterinary health sector. This company is, furthermore, intensively engaged in the development of computerized control systems for use in bioprocesses. Bio-Intermediar is a young company specializing in the production of Mabs. For the large-scale production of relatively pure Mabs, efficient fermentation systems are needed, synthetic media being used for the breeding process. Bio-Intermediar possesses considerable expertise in this area.

Wafilin Company specializes in the production of hollow membranes and in the design and construction of membrane filtration units for the food, chemical, environmental, and medical sectors. Membrane Technology Consultants BV is an advisory engineering bureau in the membrane technology field. It is a small company which is also engaged in research into membrane systems for use in biotechnology.

A small but important aspect of instrument research is that focused on the development of suitable biosensors. Netherlands research establishments, universities, and industrial companies are cooperating to an increasing extent in this field, particularly with respect to medical biosensors, a specialized area in which Netherlands research is playing a leading role. Both the Honeywell Medical Electronics and Sentron (a joint venture between Cordis Europa NV and NOM) are actively engaged in medically oriented research into the subject of biosensors.

Belgium

The biotechnology scene in Belgium goes back in the preantibiotic era to the brewing industries to which, in terms of biotechnology, industrially made citric acid was added in 1919 on the initiative of two engineers from the Catholic University of Louvain. This resulted in the company S.A. Citrique Belge.

Industry

In the antibiotic era, the company Recherche Industrielle Therapeutique (RIT) started antibiotics manufacturing. This company extended its range of biotechnological products to viral and bacterial vaccines, of which the chemically pure meningococcal vaccines are

especially noteworthy. RIT merged with the US company Smith Kline and French (now Smith Kline Beckman) and is well equipped for work with pathogens and recombinant DNA; for example, in the field of Hepatitis B, cholera, and colibacillus vaccines.

In the food industry, Amylum holds a strong position as the third starch manufacturer in Europe and is one of the few European producers of high-fructose corn syrup (HFCS).

Belova (lysozymes) and major dairy producers (milk derivatives) export a great part of their products.

The Belgian breweries number approximately 100. More and more of their products are finding their way to foreign markets, not only Stella Artois but also many of the local beers.

In the chemical industry, the major companies have more recently become interested in biotechnology. Solvay, through the Biochem Products Division has been engaged for several years in developing the agrochemicals with pesticides – Bactospein and Bactimos – derived from *Bacillus thuringiensis* to combat Lepidoptera and Diptera's grubs. The company occupies an important position at the international level in animal immunology. Solvay has extended its research through collaboration with Belgian and foreign universities and through the setting up of research units specialized in fermentation, enzymology, genetic engineering, and the creation of a pilot-plant center for fermentation.

Biotech S.A. is involved in the research and development of original molecules implicated in cellular processes. In the pharmaceutical sector, Jansen Pharmaceuticals is active in the field of veterinary vaccines like, for example, for hog cholera and pseudorabies.

The pharmaceutical activities of Union Chimique Belge (UCB) are now concentrated in the company UCB-Bioproducts with four main product lines: amino acids, synthetic peptides, immunological products, and enzymes. One of the recent products, Penzym, is a kit for penicillin detection in milk. The Petrofina group extended its interests into yeast genetics directed, among other applications, to industrial enzymes. The subsidiary Oleofina holds an important position in the fields of transformation and refining of natural raw materials – mainly triglycerides – and is developing enzymatic processes in this area.

Plant Genetics Systems N.V. was founded in 1982 as a genetic engineering company applying its technologies primarily to agriculture. Professor Marc van Montague, Scientific Director, was the founder of the company and was instrumental in obtaining start-up funding. He is also still a professor at the University of Ghent and has gained worldwide acknowledgement for his research work on *Agrobacterium tumefaciens* and Ti plasmids. M. Zabaeau, formerly at the European Molecular Biology Laboratory (EMBL) at Heidelberg, is Laboratory Di-

rector. His specialization is concerned with different aspects of gene manipulation in bacteria. He is also a part-time professor at the University of Brussels. J. Leemans, coordinator for plant engineering has gained international acknowledgements for his research on vector systems as a means to transfer foreign DNA into plant cells. S. Wodak is a consultant in protein engineering and heads the Molecular Modeling Laboratory of Plant Genetics Systems at the University of Brussels and coordinates the research program of the company in the field of protein engineering.

In December 1982, Plant Genetics Systems entered into an agreement with Advanced Genetic Sciences Inc. (PGS) of Greenwich, Connecticut. Plant Genetic Systems and Advanced Genetic Sciences share the essential contribution of the same Scientific Board. This Board was established by Advanced Genetic Sciences Inc. in 1979 and groups some of the world's leading specialists in the fields of molecular biology and biochemistry, plants, and soil bacteria. Advanced Genetic Sciences has founders' shares in Plant Genetics Systems and is represented on its Board of Directors and Management Committee. Plant Genetics Systems is located in Ghent on the Science campus of the University of Ghent. The company also has a second laboratory at the University of Brussels which houses the molecular graphics activities of the Protein Engineering Program of the company. The administrative offices are located in Brussels.

Plant Genetic Systems has long-term development contracts with major industrial companies in Belgium, France, Sweden, the US, Japan, and Brazil. The research and development activities of the PGS laboratories are centered around three major themes: the genetic engineering of plants, soil microbiology, and protein engineering. Due to the close association with the research activities at the Laboratory of Genetics at the State University of Ghent (J. Schell and M. van Montague); PGS is particularly well-suited to tackle the challenging field of plant genetic engineering. The Laboratory of Genetics developed efficient gene vector systems for plants which allow the regeneration of the engineered plant cells into normal and fertile plants. These systems are based on an adaptation of the Ti plasmid of *Agrobacterium tumefaciens*.

The current objectives of the plant engineering program are to construct:

- Insect-resistant plants producing proteins that are toxic to insects, for example, the *Bacillus thuringiensis* endotoxins
- Leguminosus plants with higher nutritional value through the expression in the seeds of high-sulfur-containing storage proteins
- Virus resistant plants which produce antiviral agents that block the proliferation of viruses.

In January 1985, PGS announced the successful engineering of plants for insect resistance. This achievement constitutes a first example of the transfer of an agriculturally important trait into crop plants using recombinant DNA technology.

The present activities involve the construction of tissue-specific expression vectors in order to limit the synthesis of new compounds to either roots, the leaves, the fruits, or the seeds of the engineered plants. Besides the development of improved vectors, the research is centered around the identification of the plant genes that give advantageous properties to particular cultivars, such as growth in adverse conditions, better plant development, disease resistance, and improved nutritional value. Although the strategies vary from case to case, the approaches are based on the capacity to tag chromosomes and plant movable DNA elements with antibiotic resistance genes by means of the T-DNA vector system.

A third focus of activity, which may influence plant development, is aimed at introducing and expressing specific bacterial genes in plant cells. It has been shown that this approach can be important for the improvement of the regenerative capacity of some plant species by altering the level and composition of secondary metabolites in plants. The goal at PGS is that this activity will lead eventually to the commercialization of highly valuable secondary metabolites from medicinal plants.

In the area of soil microbiology, one of the main objectives of the research program at PGS is the identification of efficient root colonizing bacteria, which could be engineered genetically and used as vehicles for the engineering of genes that determine properties beneficial for plant growth. In this program, the identity and the properties of the major groups of bacteria that colonize the ecto- and endorhizosphere of some major crops are being evaluated. Among the efficient colonizers, those that are most accessible to gene transfer manipulation are being examined in detail.

Another program involves the isolation and characterization of bacteria that produce antifungal compounds that inhibit the growth of major plant pathogenic fungi, with the aim of developing systems for controlling fungal diseases in major crop plants.

The protein engineering activities aim at the modification of industrially important enzymes so as to improve their catalytic properties and to optimize their use in industrial processes. In the long run, the goal is to exploit this know-how to design novel enzymes tailored to catalyze reactions that now can only be performed chemically. Such modified enzymes will have very large industrial applications in the food and feed industry, the food and feed processing industry, and the chemical industry.

The close cooperation between PGS and the universities and research institutes allows them to actually transfer new technologies to fields of practical application (the

classic role of an R&D company) and to make long-awaited improvements. Thus the outlook seems very bright for PGS. A report on PGS is available in ESN-40-5:151.

Eco-Bio (abbreviation of *Ecology* and *Biochemistry*) was set up in May 1982, by E. Brier in Hasselt, Belgium, and production was started in October 1982 with commercial activity begun in April 1983. One year later, the firm had already conquered about 40 percent of the Belgian market for microbiological preparations. One of Eco-Bio's pioneering new products reduces the current very long 18-hour bacterial reaction time to a mere 15 seconds. This gain of time can be very important when dealing with some deadly diseases. Eco-Bio is also developing diagnostic DNA probes; i.e., detecting bacteria with a replicating technique. To do this the double DNA strand is untwisted to form a single one. Using synthetic DNA probes with a fluorescent or radioactive tag, the sought-after DNA particle can be found easily because it only pairs with its predestined synthetic counterpart. The firm's basic diagnostic products are blood and its derivatives (for example, defibrinated horse and sheep blood) and egg yolk. The ready-to-use products include petri dishes and disposable bottles and tubes. At the same time, colorants, reagents, and additives (antibiotic and enrichment mixes as well as sterile solutions) are manufactured. These preparations are used in hospitals and clinical laboratories to detect pathogenic germs. To prevent diseases in hospitals, the sterility of materials and of special examination treatment areas is checked by means of diagnostic preparations. They are used in clinical laboratories to detect and isolate germs, and to look for an efficient antibiotic to contain the disease as quickly as possible. Diagnostic preparations are also used in the pharmaceutical industry to determine whether the outgoing product contains any germs. Diagnostic preparations are also used in the cosmetic and food industries as well as to make sure that the products do not contain microorganisms that may be harmful to humans.

Government

The Services for Programming of Scientific Policy (SPPS) is the governmental body of the Ministry of Scientific Policy. The annual budget is about \$130 million. The aim of these services is, among other things, to exploit the best of Belgian biological science by reinforcing fundamental research in key sectors, within the framework of concerted research programs. Some important activities are the linking of academic research to commercial exploitation, the creation of national collections of microorganisms, and the participation in international programs such as the European Commission's Biomolecular Engineering Program.

The Ministry of Agriculture has focused on a number of research projects in the biotechnology field for agricultural purposes; for example: plant cell culture and gene transfer for improvement of crops and forest species, improved resistance to plant diseases, genetic engineering of bacteria and yeasts for fermentation of agricultural products and monoclonal antibodies for the diagnosis of Foot and Mouth disease, and porcine pests. Some weak points of biotechnology in Belgium exist in the field of biotechnological instrumentation.

Universities

The life sciences have absorbed in the course of the past decade, more than one-third of the research budget that the government allows to universities. This has resulted in a number of university teams of international standard in branches such as molecular and cellular biology, immunology, and microbiology. The major universities are engaged in the field of biotechnology and offer courses in biotechnology, integrating biosciences and engineering with emphasis on genetics of microbes, animal and plant cells, and industrial and environmental processes.

The central points of research at the University of Ghent are based on interferon, gene transfer for the modification of plants, and anaerobic waste fermentation in the food industry. Research in plant genetics has already been described in the previous section. M. van Montague and his group have made important contributions in this area and he has founded the Plant Genetics Systems, a company for exploiting the commercial applications of their work. E.J. Vandamme (Laboratory of General and Industrial Microbiology, University of Ghent) and coworkers are concerned with immobilized biocatalyst technology for peptide antibiotic production (see ONRL Report C-13-85).

W. Fiers and coworkers (Laboratory of Molecular Biology, University of Ghent) are concerned with molecular biological approaches to anticancer treatment as one of their projects. (See ONRL Report C-10-86.) Another project deals with satellite viral RNA expression systems for manipulation in *E. coli* and replication and expression in plant cells.

A study on the quantification of hormones with chemiluminescence is under the direction of J. DeBoever (Department of Gynecology, University Hospital, University of Ghent). De Boever and his group have also developed a method for the measurement of estriol in saliva. The assay is simple and fast and is nonisotopic. The assay uses a monoclonal antibody bound to the wells of microtitration plates and estriol labeled with the chemiluminescent marker molecule, isoluminol (E3-APEI). (See ESN 41-10:544.)

Belgium now has the second largest bacteria bank in Europe. It is located at the Laboratory of Microbiology and Microbial Genetics, University of Ghent. Only Sweden has a larger collection, but Sweden's is mainly for medical purposes, whereas at Ghent University, the emphasis is on biotechnology. The bacteria bank, the life-work of Professor J. De Ley, contains more than 7000 species. For more than 40 years, De Ley has been keeping all the bacteria that he has isolated and collected in the course of his work. Over the years, the number of staff has expanded, enabling more and more bacteria to be studied in greater detail. The value of the collection is, therefore, not only in its diversity, but in the extensive knowledge of the characteristics of these microorganisms which it affords. The attention in Ghent focuses on those characteristics that are or soon will be of biotechnological value.

At the University of Liège, the curriculum and research interests are focused on biochemistry with projects on peptidases and biomethanation.

The University of Brussels teaches the basic disciplines – the main (and relative) research topics being bacterial genetics, immunology, and genetic engineering in eukaryotic systems. Molecular modeling and protein engineering are of recent research emphasis.

S. Wodak (U.C.M.B. CP 160, University of Brussels) is well known for her research on studies of the mechanisms of conformational changes in proteins using molecular modeling. She is a consultant for Plant Genetics Systems and receives some support for her research from this company. (See ONRL Report 7-007-C.)

A. Bacolla and coworkers at the University of Brussels-IRIBHN, are engaged in studies of the characterization of the promoter region of the thyroglobulin gene using recombinant DNA technology.

J. Davison (Department of Cellular and Molecular Biology, University of Brussels) and coworkers are engaged in studies cloning genes of lignocellulose in *Pseudomonas*. Studies of the degradation and processing of lignocellulosic material are being carried out by F. Brunel and coworkers (Unit of Molecular Biology, Institute of Cellular and Molecular Pathology, Brussels). Brunel collaborates with J. Davison in some aspects of the research.

In the area of genetic engineering of microorganisms important for agrofood industries, E. Schoonjans and coworkers (Laboratory of Genetics, University of Brussels) are engaged in studies of the genetic analysis of pectinolysis and cellulolysis in *Erwinia chrysanthemi*.

In the same general area of research as above, M. Grenson and his group are involved in studies dealing with the construction of transformed yeast strains for agrofood applications and the development of systems for stabilizing the genetic material introduced by genetic engineering into the food yeast *Saccharomyces cerevisiae*.

F.R. Opperdoes (International Institute of Cellular and Molecular Pathology, Research Unit for Tropical Diseases, Brussels) is engaged in studies of glycosomes which may provide clues to the import of peroxisomal proteins. Glycosomes are microbodies unique to the *Trypanosomatidaek* – kinetoplastid protozoa parasitic to both animals and plants. Peroxisome research has recently gained impetus owing to the role these organelles play in the biosynthesis of ether lipids, wax esters, phospholipids, cholesterol, bile acids, and dilichol, as well as the notion that has emerged that impaired peroxisomal function may be at the basis of a whole variety of inborn errors of metabolism. Thus, the research being carried out by Opperdoes and his group has many potential biotechnological implications.

The Institute of Cellular Pathology and the Rega Institute are quartered in the Catholic University of Louvain. P. Rouxhet at the Faculty of Agronomic Science and his group are engaged in various biotechnological projects. One project deals with the immobilization of microbial cells for use as a biocatalyst. Immobilization of whole cells by adhesion (also called adsorption) on a carrier was studied extensively. Some of the microorganisms studied – in addition to yeast cells – are *Xanthommas compestris*, *Arthobcater simplex*, *E. coli* (A223), and *Moni-liella tomentosa*.

Institutes

Three State Research Institutes are engaged in some field or other of biotechnology. IRSIA (Institute for the Encouragement of Research in Industry and Agriculture)

in Brussels, as research promoter, has created a biotechnological committee comprising 32 companies belonging to various industrial sectors and university laboratories specialized in the field of monoclonal antibodies, fermentation, immunology, and genetic engineering. The results of these researches would be exploited subsequently by the industrial sector.

The Nuclear Energy Center in Mol (CEN/SCK) has a Radiology Department which has over 18 years' experience in fundamental research on DNA. The work also includes applications concerning the production of antibiotics by bacteria and the introduction of genetic data in widely cultivated plants.

The Institute of Radioelements of Fleurus (IRE) at Fleurus, focuses its research on monoclonal antibodies under a contract with the regional authorities in Wallonie.

In Flanders, under the auspices of the TIRF (Third Industrial Revolution in Flanders), the two research companies, Artemis Systems and Plant Genetics Systems NV (described above) have been founded on the Ghent University campus.

In Wallonie, the SRIW (Regional Society of Investments) has also created two R&D companies, one in the food and plant breeding sectors for the exploitation of biomass, valorization of plants, and manipulation of seeds (the company named C.D.A. [Company for Agro-Alimentary Development]). The other, named C.D.B. (Company for the Development of Biotechnologies) specializes in pharmaceuticals and fine chemicals such as monoclonal antibodies, hormones, peptides, and fermentation products.

Denmark

This small country has an ancient tradition with products of the pre-Pasteur era. Typical examples are in the dairy, brewing, and meat industries. This stems from the important position of agriculture in the Danish economy, both directly, and indirectly through the industries using agricultural produce as raw materials.

Industries

During the antibiotic era a number of Danish fermentation and pharmaceutical industries of international importance emerged. Probably the first purified enzyme preparation to be used in industry was developed by the Danish pharmacist Chr. Hansen, who launched his cheese

rennet, produced by extraction of calves' stomachs, in 1874. Chr. Hansens Laboratorium A/S is still the world leader in the production of rennet and has diversified so that it also produces starter cultures of pure lactic acid bacteria used in the manufacture of cheese, butter, yogurt, etc., as well as in certain fermented foods derived from vegetables and meat. The company also develops products for treating allergies. Chr. Hansens currently has factories in Osterbro and Anger, while the administrative offices are located in Copenhagen. The firm has recently leased space in the new research park in Horsholm and after construction of new buildings, to be finished this year, will consolidate its administrative offices and plants in the Science Park at Horsholm.

Another very important development took place during the latter half of the nineteenth century at the Carlsberg Laboratory where Emil Chr. Hansen pioneered the use of pure yeast cultures in brewing. The research tradition created then has been continued by the two leading Danish breweries, Carlsberg and Tuborg, which after merging into De forende Bryggerier (United Breweries) account now for 80 percent of the Danish beer production. Besides problems directly related to the brewing process itself, the research laboratories of the United Breweries are working on the development of new barley varieties for brewing whereby the latest techniques of molecular biology are utilized.

The Alfred Jorgensen Laboratory for Fermentation supplies technical know-how to biotechnological industries, primarily breweries. It produces cultures of pure yeast cultures for breweries and cultures of *Penicillium roqueforti* for dairies.

De danske Spiritfabrikker (Danish Distilleries) have been active in biotechnology for more than a century and are today the sole Danish producer of fermentation alcohol and baker's yeast. Grain, potatoes, and molasses are used as raw materials. The residue from the alcohol production (stillage) is used as cattle feed. Recently, the company has taken up production of dry yeast for wine-making in cooperation with a US company.

Dansk Gaerings-Industri (Danish Fermentation Industry) was established around 1920 to exploit the so-called Z-method, developed by Soren Sak, for the production of baker's yeast. The principle involves the fed-batch method, which is now used all over the world. Sugar and other nutrients are added as they are consumed whereby a constant, low concentration of nutrients is maintained. The company now acts as a research center for the companies in the Danisco group. Biotechnical research based on fermentation technology is carried out especially for Grinsted products, one of the leading manufacturers in the world of aroma and food additives.

Fermentation techniques for the manufacture of antibiotics (for example, penicillin G and V, semisynthetic penicillins, cephalosporins, streptomycin, tetracyclines) have been developed by a number of Danish pharmaceutical companies such as Lovens kemiske Fabrikker (Leo), Novo Industri, Dumex, H. Lundbeck & Co., and Rosco. An example of original Danish achievement in this area is the antibiotic fucidin, developed by Leo, to combat staphylococci resistant to other antibiotics.

As a natural extension of Novo's experience in antibiotics fermentation, methods for the production of microbial enzymes were developed. This development gained momentum during the 1960's when the first enzymes preparation especially designed for use in detergents was launched. Since then Novo has introduced a range of enzymes for use in the starch, brewing, dairy, protein, wine, juice, and other industries. The company

has a leading position in this area with a global market of about 50 percent.

Biological materials are the basis for another important industry in Denmark: the manufacture of insulin and other hormones from animal glands. The two Danish insulin producers, Novo and Nordisk, have a world market share of more than 40 percent. Both companies have developed methods for enzymic conversion of porcine insulin to human insulin, and, in 1982, Novo became the first company to market such a product. Production of human insulin by recombinant DNA methods applied to microorganisms has recently been developed by Novo. Using molecular modeling, computer technology, and genetic engineering, scientists at Novo Industri A/S (Bagsvaerd) have recently developed a series of new insulin molecules that the company states can help diabetics control their blood sugar more effectively. The first products, which are in early clinical trial in Europe, are a fast-acting insulin and a soluble long-acting insulin. According to Dr. Ulrik Lassen, chief science officer at Novo, the new insulins have been designed to overcome the problem of subcutaneous tissue absorption which delays the onset of the action of insulin delivered to a patient suffering from diabetes mellitus. Novo claims that its long-acting insulin mimics the normal basal insulin secretion in a more predictable manner with less variation than present long-acting insulin preparations. These soluble long-acting preparations crystallize after being injected subcutaneously, allowing for a protracted absorption. The company plans to couple the use of the insulin to its NovoPen, an insulin delivery system that looks like a fountain pen. However, the first commercial product resulting from Novo's research in rDNA is an enzyme — maltogenic amylase from a *Bacillus* strain. As far as is known, this represented the first marketing of a technical enzyme made by genetic engineering. The enzyme is used by the starch industry to manufacture syrups high in maltose.

De danske Sukkerfabrikker (Danish Sugar Factories) and its subsidiaries, Niro Atomizer and Pasilac, produce equipment for the biotechnological industries (for example, drying and ultrafiltration equipment, and machinery for the dairy industry). Except for research at the laboratories of the United Breweries and vaccine production, the Danish industry lacks experience with plant and animal cell culture techniques.

Dansk Gaerings-Industri carries out research in Denmark, primarily in wastewater treatment, especially in the field of anaerobic digestion, for the engineering company, I. Kruger. This cooperation has led to the construction of full-scale plants for the treatment of wastewater from food production, primarily from slaughter-houses and from potato processing operations.

The need for close interplay between research and industry has been strengthened through technological developments. Recent studies have shown that high-tech-

nology industrial products most often have their basis in basic research, and that there is a direct connection between a firm's productivity and its research effort. The results of basic research in Denmark have been utilized to too small a degree in the past. Experience from abroad and in other European countries has shown that the contact between universities and industry is best established in research complexes. Therefore, Science Parks are now being established in Denmark with close collaboration between academic and industry. These Science Parks are being established in Aarhus and Copenhagen. The research complex in Copenhagen is called Symbion. An association was formed for the establishment of a research center in conjunction with industry, financial institutions, and science centers. The firms that have signed contracts with the research complex include Novo, along with several newly started firms in biotechnology and computer technology.

Industry's desire for the rapid commercial application of research results was the driving force behind the plans for the establishment of a research park in Aarhus. Unlike the "university model," where the initiative comes from higher educational institutions, in Aarhus it was seven firms and institutions that founded an independent institution that paved the way for construction of the research park. They are: Aarhus University, Jutland Telephone, Aarhus Oil Refinery, Jutland Technologies, the Computer Exchange, the Business Communication Committee, and the English Senetic biochemical firm. Fifty firms and private individuals have signed up for several million dollars worth of shares.

Aalborg also has plans to establish a science and industrial park associated with the Alborg University Center, AUC. The project will be a part of the North Jutland Nordtek industry promotion program.

In order to give Funen – the island between Zealand and Jutland – a needed technological lift, a number of enterprising Funen business people have made plans for a science and research center in the vicinity of Odense University and Odense Technical College. The starting point is IFAD (the Institute for Advanced Computer Technology), financed by industry on Funen and in South Jutland. The center would focus strongly on engineering and production know-how. The Technology Center, which is an independent institute unit under the Technology Institute has been inaugurated in Odense. The aim is to create a development environment that can attract highly qualified associates to Funen. The partners in the venture are, in addition to the Technology Institute, Jutland Technologies, the Funen Technology Information Center, and local research and educational institutions. The goal is to help Funen's industry to advance with the introduction of new technology, in production processes, products, and control systems.

Government

The government supports biotechnological research including research in genetic engineering through the Science Councils (Statens naturvidenskabelige Forskinsrad, Statens teknisk-videnskabelige Forskskingarad, Teknologistyrelsen). This support has been budgeted at about Kr8 million (\$1.1 million) per year. The Danish state is directly involved in biotechnological production through the Statens Seruminstitut, the sole producer of human vaccine in the country. Vaccine and serum against foot-and-mouth disease is produced at the Veterinary Institute for Virus Research (Ministry of Agriculture). Recently Danish biotechnology has received a governmental infusion of Kr500 million (\$68.8 million). This investment is an attempt to introduce a new element into Danish research policy: an effort to steer research toward fields that promise economic growth. New research centers are being established at technical universities and private firms at a cost of Kr410 million. New scholarships will be established for Kr70 million and another Kr20 million will be spent on information and technology evaluation.

Universities

The most complete program in biotechnology is offered by the chemical engineering faculties at the Technical University of Denmark and at The Engineering Academy. A range of courses from biochemistry, microbiology, and genetic engineering to biological technology, fermentation kinetics, and mathematical modeling in applied biochemistry and fermentation are incorporated into the teaching and research programs. Other courses related to biotechnology are given at the Royal Veterinary and Agricultural University, at the sanitary engineering faculty of the Technical University of Denmark, and at the Aalborg University Center. A special education program in brewing science and technology is offered by the Scandinavian School of Brewing in Copenhagen. Although courses in microbiology, biochemistry, and genetics are offered at the universities of Copenhagen, Odense, and Aarhus, they are rarely combined with more applied courses.

The Technical University of Denmark (Danmarks Tekniske Højskole or DTH) is situated (in a campus setting) in Lyngby, a suburb of Copenhagen. The university has extensive teaching programs in all of the engineering disciplines as well as in biotechnology. Last year, with the infusion of government funds for biotechnology research in Denmark, the various departments and divisions dealing with research in biotechnology were designated as a Center for Biotechnology and received additional government funding. The study of enzyme reactor systems using flow injection analysis coupled with computer systems is being carried out by J. Villadsen and

coworkers. R. Cotterill and his group are investigating the structure and dynamics of biological membranes and have initiated a new program on the study of neural mechanisms and brain function by computer simulation.

Some of the projects carried out in the Department of Structural Properties and Materials at the Technical University are:

- Study of the atomic structure of materials with special emphasis on mechanical and thermodynamic properties
- Experimental study of materials by transmission electron microscopy, field microscopy, and optical microscopy and of strengthening mechanisms in metals and alloys and of mechanical failure
- Research into fatigue (such as in high-temperature materials), melting, and other phase transitions, and into structure and stability of metallics and glasses
- Theoretical studies of crystal defects and noncrystal condensed matter
- Computer simulation of properties of materials at the atomic level
- Study of the structure and dynamics of biological membranes
- Theoretical studies of protein conformation and protein/lipid interactions
- Investigation of inorganic ion transport through nerve membranes.

The physical constraints on the evolution of the plasma membranes of eukaryotic cells is being explored by O. Mouritsen and his group. They have proposed a novel interpretation of the influence of cholesterol content on membrane fluidity. This group is also studying lipid-protein/polypeptide interactions in membranes. Building upon ideas of a recently developed phenomenological model of lipid-protein interactions, they are studying a class of model systems consisting of lipid bilayer membranes with embedded synthetic amphiphilic polypeptides. Aspects of protein aggregation and crystallization are also being investigated by Mouritsen and coworkers.

A report on the Technical University at Lyngby is given in *ESN* 41-6:299.

Aarhus University, founded in 1928, was the first Danish university to be established outside Copenhagen. The university was a private university until 1970 when it became a state university. Some of the research projects in the life sciences which, although basic research work, have potential biotechnological implications are:

- Study of human epidermal cells in culture and factors affecting this parameter (L. Bolund, Institute of Genetics)
- Evolution of human repetitive DNA sequences (A.L. Bak, Institute of Medical Microbiology)
- Humoral and cell-mediated immunity to Herpes Simplex Virus (HSV) (A. Møller-Larsen)
- Studies of leghemoglobin genes from soybean (K.A. Marcker, Department of Molecular Biology and Plant Physiology)
- Pathogenesis of *Mycoplasma hominus* (G. Christiansen, Department of Medical Microbiology).

A report on Aarhus University is available in *ESN* 41-7:361.

Institutes

Research within the area of biotechnology is performed at the Carlsberg Research Center, at the universities, and at several institutes under the Danish Academy of Technical Sciences (the Biotechnological Institute, the Water Quality Institute, the Genetics Group). However, most of the Danish research has been performed at the laboratories of industrial companies. This situation should be changing in the future with the large amount of funding being provided recently to universities and institutes by the Danish government as well as the development of science parks combining industry with academia, as described above.

Sweden

The Swedish government has identified biotechnology as an industrially strategic area and is quietly promoting it as best as it can. The biggest problem in commercialization, as in Denmark, is the lack of trained personnel and the adverse public image of recombinant DNA techniques. Although the very strict guidelines of earlier years have been relaxed, Sweden retains one of the toughest regulatory regimes in the world, which hampers

large-scale development and, in particular, inhibits multinational cooperation.

Government

The Swedish government funds biotechnology through the academic research councils such as the Academy of Engineering Science (IVA) and the Swedish

Natural Science Research Council. The government is also funding a new biology laboratory at the University of Stockholm at a cost of \$20 million.

The most prominent body for support of biotechnology in Sweden is the Technical Research Council (STU). It works through joint governmental/private ventures, providing 50 percent of the R&D funding as provisional grants. The STU provides resources for industrial applications of gene technology and cellular biology, separation and extraction techniques, immobilized biocatalysts, and computer control. STU also collaborates with the Biotechnology Research Foundation. The aims of this foundation are to initiate and coordinate research and development within the field of biotechnology. About 30 Swedish, Finnish, Norwegian, and Danish companies contribute to this foundation.

Universities

Six universities are involved in biotechnology-oriented research and courses. Some of them emphasize the basic disciplines such as the those of Medicine and Natural Science faculties at the University of Umeå and the Microbiology Department at the University of Stockholm.

Research at the University of Uppsala emphasizes separation technology (also using monoclonal antibodies) and molecular biology.

The University of Lund has a chemical center that integrates the chemical departments of the technical and natural science faculties. Immobilization of enzymes, downstream processing (including membrane technology and two-phase separations), and microbial physiology related to defined mixed cultures are the core of the expertise.

The following paragraphs deal with specific projects at the University of Lund.

Professor Klaus Mosbach is head of the Department of Pure and Applied Biochemistry, the Chemical Center, at the University of Lund. The research activities of the department cover a broad area including:

- Affinity techniques
- Bioprocess control
- Biosensors (including enzyme thermistors)
- Development of new carriers and new immobilization procedures for small molecules and for enzymes and cells (including animal and plant cells)
- Gene technology (including construction of fused proteins)
- Processes based on immobilized catalysts (enzymes, bacteria, fungi, plant and animal cells)
- Construction of organic polymers with enzymelike properties

Since the isolation of products generated in bioprocesses is often difficult, new chromatography materials are being developed for downstream processing.

A list of the scientists and research projects in the Department of Pure and Applied Biochemistry are:

(1) P.O. Larsson is studying submicron silica fibers with attached ion exchange ligands.

(2) Larsson, K. Mosbach, and K. Nilsson are researching macroporous gel-based supports.

(3) Larson is working on composite supports with solid core and gel coating.

(4) Aqueous two-phase systems such as dextran-polyethylene glycol have considerable potential in downstream processing, according to K. Mosbach. He says the methodology is easy to scale-up and, most significantly, it is insensitive to particulate impurities/fouling. A technique is now being developed where one of the phases is made magnetic because phase separation may then speed up by a factor of 10 to 100 in a magnetic field. Larsson is the project leader of this research also.

(5) Biologically active carbohydrates are generating increasing commercial interest. Efficient ways of production must, however, be generated. A group headed by Larsson is presently developing enzymatic methods for the synthesis of oligosaccharides using free and immobilized enzymes.

(6) A group headed by B. Danielsson and C.F. Mandenius is concerned with a special emphasis on biosensors. Analytical methods are developed for use in biotechnology, clinical chemistry, and environmental control. Immobilized biocatalysts such as enzymes or whole cells are combined with various physical measurement techniques for specific and rapid, usually direct, analysis, even of crude samples. Continuous monitoring and control of biotechnological processes are major fields of interest. The current activities of this group include:

- Enzyme calorimetry – the combination of a thermistor as heat transducer with immobilized enzymes or cells (the enzyme thermistor); for example, studies on recycling enzyme combinations
- Enzyme transistors – the combination of biocatalysts with hydrogen- or ammonia-sensitive semiconductor components
- Process monitoring and control
- Development of miniaturized biosensor systems
- Bioanalytical application of biocatalysts under unusual conditions as, for instance, in organic solvents
- Biochemical applications of optoacoustic spectroscopy and optical waveguides
- Ethanol sensor for process control
- Optical surface techniques for biomolecular studies.

(7) Another group is involved in protein engineering projects. The project leaders are K. Mosbach and L. Bülow. The project is divided into three areas:

enzyme-antigen fusions, bifunctional enzymes, and genetically fused enzyme-peptide conjugates for special purposes. The researchers are using recombinant DNA techniques to fuse an enzyme to an antigen. The product has advantageous properties as a reagent in ELISA assays. The fused proteins are, for example, well-defined and easy to produce in large scale in contrast to conventional, chemically prepared conjugates between enzymes and antigens, according to Mosbach and Bülow.

(8) Bifunctional enzyme conjugates of sequentially operating enzymes are also being studied by Mosbach and Bulow and are expected to be catalytically more effective than a mixture of the two enzymes. These researchers have recently reported on the preparation of a soluble bifunctional enzyme by gene fusion as well as the characteristics of an artificial bifunctional enzyme, beta-galactosidase/galactokinase, prepared by gene fusion.

(9) Mosbach and Bülow are also fusing polypeptides to enzymes in order to give the enzymes superior properties – ease of purification, for example, and increased stability. They have recently reported on enzyme purification by genetically attached polycysteine and polyphenylalanine affinity tails.

(10) Yet another project in Mosbach's department is research on the immobilization of animal cells. Mosbach said that despite the very high potential of animal cell culture (for example, production of high-value therapeutics, interferons, etc.), only a few industrial processes have been established. This is mainly due, he said, to two reasons: first, the lack of cell wall makes animal cells sensitive to mechanical stress and second, as the majority of these cells are anchor-dependent, a high surface area is required for large-scale culturing. These problems have been reduced by newly developed methods for immobilization of such cells. The methods comprise a special macroporous carrier of gelatin. Similar techniques can be used for plant cell immobilization. These studies are headed by Mosbach and K. Nilsson.

(11) Mosbach is also the project leader for research on immobilized recombinant cells. Recombinant *Bacillus subtilis* and *E. coli* cells containing the gene for proinsulin and a signal sequence for excretion have been immobilized. These studies emphasize the aspects of reducing cell leakage and of optimization of products. In addition, immobilized Chinese Hamster Ovary cells (CHO) are being studied as a means of producing immune interferons and tissue-type plasminogen activator (TPA) which is used to dissolve blood clots in a heart attack. Focus is on reducing serum concentration and screening of various carriers.

(12) E. Szwajcer-Dey and Mosbach are project leaders for a research program on D-amino acid oxidase for cephalosporin production. This project involves the purification and characterization of a D-amino acid oxidase from the yeast *Trigonopsis variabilis*. They are also

investigating the potential of this enzyme as a catalyst for the preparation of cephalosporins.

(13) Mosbach and D. O'Shannessy are project leaders in studies of polymers with enzymelike properties. By a new technique called molecular imprinting, it is possible to make imprints of various molecules into polymer matrices. Such imprinted polymers then recognize the type of molecule used in the imprinting process. A practical use of the polymer matrices is as selective adsorbents. These researchers have developed polymer supports that are able to efficiently separate enantiomers of amino acid derivatives.

(14) M.O. Mansson is the project leader for a program called synthetic biochemistry. He and his group have recently reported on site-to-site-directed immobilization of enzymes with bis-NAD analogues.

The Department of Biotechnology at the University of Lund's Chemical Center, is located in the largest academic research unit for chemistry in northern Europe. The department has focused its activities on a few technologies that are used in many different situations. This leads to good interaction between the different research groups and gives the department members the ability to treat larger projects by collaboration between different groups. Besides the competence within the department, additional expertise is added by collaboration with other departments both inside and outside the Chemical Center. There are direct collaborations as well as contacts on a discussion level both nationally and internationally. The department also has broad contacts with industry, primarily Swedish, but also from other countries. The joint projects may be collaborations on a research project, financial support for a project run at the department or a contract made on a specific research project.

The research activities of the Department of Biotechnology can be divided into the following areas:

- Fermentation technology
- Environmentally related biotechnology
- Enzyme technology and bioorganic synthesis
- Biocatalysis and process control
- Immunotechnology
- Downstream processing

Biotechnical processes are characterized by taking place at low temperature, low pressure, and in dilute aqueous solutions. This leads to low productivity and dilute product streams which severely influences the possibilities for biotechnology to compete with traditional chemical processes. The research in the Department of Biotechnology in the area of fermentation technology is aimed at improving the productivity and also the product concentration in order to improve the process economy. This is achieved through operation at higher concentrations of catalyst (cells or enzymes) and with better control of environmental factors. Techniques used, among others, are immobilization, membrane tech-

nology, and extraction in aqueous two-phase systems. A newly installed pilot-plant fermenter makes it possible to study scaleup as well.

B. Mattiasson and M. Larsson are studying extractive bioconversions with emphasis on solvent production.

O. Holst, L. Hansson, A.C. Berg, and Mattiasson have been carrying out studies on continuous culture with complete cell recycling to obtain cell densities in product-inhibited cultures such as cultivation of *Streptococcus lactis* for the production of superoxide dismutase.

O. Holst, R. Kaul, and Mattiasson and Larsson have carried out model studies on the integration of bioprocesses and downstream processing.

L. Nielson and Larsson, Holst, and Mattiasson have recently reported on adsorbents for extractive bioconversion applied to acetone-butanol fermentation.

A.C. Berg and Holst and Mattiasson are also studying continuous culture with complete cell cycle: cultivation of *Pseudomonas cepacia* ATCC 39351 on salicylate for the production of salicylate hydroxylase.

An area where biotechnology seems to have a good potential is environmental technology, which includes the use of enzymes from microorganisms to degrade toxic compounds that cannot be degraded by microorganisms. Thus, the environmental biotechnology group is working on the selection of the proper organisms to degrade various types of chemical compounds and thus make them harmless. Holst, Mattiasson, and H.T. Karlsson, G. Olsson, B. Nilsson, and I. Eriksson have recently reported on the prospects for microbial desulfurization of coal for CWM production.

The Department of Biotechnology is also concerned with enzyme technology and bioorganic synthesis. Mattiasson and P. Adlercreutz are the project leaders. This area involves the use of enzymes or cells for production and analysis. The biocatalysts are used in free as well as immobilized form or in aqueous two-phase systems, or in membrane reactors. Bioorganic synthesis is an offshoot of enzyme technology. It includes work with enzymes and cells in organic synthesis. A major part of the application deals with stereospecific synthesis. By utilizing organic solvents, a higher solubility of the reactants is achieved and in some cases, new activities can be obtained, according to Mattiasson. Work is performed both in the area of increasing our understanding of the basic conditions for creating a successful bioorganic system and in more applied fields; for example, in designing reactor systems for specific purposes. The enzymes used most often be isolated in the laboratory.

In the area of enzyme technology, R. Kaul, P. Adlercreutz, and Mattiasson have reported on the co-immobilization of substrate and biocatalyst as a method for bioconversion of poorly soluble substances in a water milieu. Another recent report by R. Kaul deals with extractive bioconversion in aqueous two-phase systems studying

the production of prednisolone from hydrocortisone using *Arthrobacter simplex* as catalyst.

M. Larsson, V. Arasaratham, and Mattiasson have also recently reported on the integration of bioconversion and downstream processing investigating starch hydrolysis in an aqueous two-phase system.

In the area of bioorganic synthesis, P. Adlercreutz and Mattiasson have been studying the aspects of biocatalyst stability in organic solvents.

M. Reslow, P. Adlercreutz, and Mattiasson are also involved in the optimization of parameters for a chymotrypsin catalyzed process.

Another study by Larsson, P. Adlercreutz, and Mattiasson deals with the activity and stability of horse liver alcohol dehydrogenase in sodium dodecyl sulfosuccinate/cyclohexane reverse micelles.

M. Reslow, P. Adlercreutz, and Mattiasson have recently reported on the importance of support material for bioorganic synthesis, studying the influence of water partition between solvent, enzyme, and solid support in water-poor media. These investigators are also studying the influence of water on protease-catalyzed peptide synthesis in acetonitrile/water mixture as well as the activity and operational stability of immobilized mandelonitrile lyase in methanol/water mixture.

Other areas under investigation in the Department of Biotechnology are bioanalysis and process control. Bioanalysis consists of exploiting the inherent specificity of biomolecules. By using antigen/antibody interactions, sensitive immunochemical assays may be set up. Likewise, enzyme/substrate interactions form the basis for enzyme assays. These assays and several others may be performed as discrete analyses in a laboratory or, provided the technology is available, under field conditions. Combinations of biochemical interactions with various transducers form the basis for biosensor units that may be used in the automated laboratory as well as in process control. Activities within the department, under the direction of Mattiasson, have focused on three aspects: field-adopted bioassays, biosensors, and process control for biotechnological processes. Mattiasson, in the area of field-adopted bioassays, has reported on a partition affinity ligand assay (PALA) for quantifying haptens, macromolecules, and whole cells as well as a simple, rapid method for quantifying microorganisms by the metabolic activity when bound to a specific adsorbent.

Several bioassays have been developed at the department. These include: enzyme-based sensors, immunoelectrodes, cell-based sensors and, recently, some nonspecific membrane gas sensors, gas flow meters, and a device for sampling from complex biological materials. Immunochemically based sensors have attracted special interest and Mattiasson and coworkers are now developing a unit based on flow injection technology for assaying discrete samples with a frequency of more than 30 sam-

ples per hour and one continuously monitoring unit based on streaming potential measurements.

Control of biological processes to make them run under optimal conditions is of growing importance. This is valid both for fermentation/bioconversion processes and for downstream processing. When the cell density in a fermentation reactor is increased, the need for control increases. This is especially clear when dealing with genetically modified organisms and with cells growing on toxic substrates. The use of sensors for substances or products in the reaction mixture makes it possible to control the process properly according to O. Holst. Control strategies is an area where much work still remains. Such problems are addressed in projects in collaboration with the Department of Automatic Control. C.F. Mandenius, Mattiasson, J.P. Axelsson, and P. Hagender have been studying the control of ethanol fermentation carried out with alginate-entrapped *Saccharomyces cerevisiae*. Axelsson, Mandenius, Holst, P. Hagen Jer, and Mattiasson are also working on the use of an ethanol sensor to control molasses feed-rates in Baker's yeast production.

Studies in the area of immunotechnology are under the direction of C. Borrebaeck. Knowledge of cells and molecules that participate in the immune system is the basis for applications in areas like immunotherapy, diagnosis, and analysis. An essential part of the work is devoted to antigen-specific *in vitro* activation of both human and mouse B-cells. This is called *in vitro* immunization and is used for the production of monoclonal antibodies (Mabs). Since different characteristics are important for antibodies used in *in vivo* therapy/diagnosis as compared to analysis/affinity chromatography, an important aspect is antibody engineering that allows the making of tailor-made antibodies for a specific application. The efforts of Borrebaeck and coworkers are mainly concentrated on the production of therapeutically valuable human Mabs. C. Borrebaeck and S.A. Møller have, for example, been studying *in vitro* immunization, investigating the effect of growth and differentiation factors on antigen-specific B-cell activation and the production of Mabs to autologous antigens and weak immunogens.

L. Danielsson, Møller, and Borrebaeck are studying the effects of cytokines on specific *in vitro* immunization of human peripheral B-lymphocytes against T-cell-dependent antigens as well as the production of L-leucine methyl ester treated and *in vitro* immunized peripheral blood lymphocytes. They are also studying the production of human Mabs by primary *in vitro* immunization of peripheral blood lymphocytes.

Another project of the Department of Biotechnology deals with downstream processing in biotechnology. A group under the direction of T.G.I. Ling and Mattiasson is concerned with the development of new procedures for affinity-based purification. Ling says that separation based on affinity between different biological macro-

molecules has been shown to be a powerful technique. The efforts of Ling and Mattiasson are devoted to making them applicable in large scale and in continuous processes. To monitor these processes, fast as well as continuous immunological sensors are being developed by these investigators. They have reported on their efforts to integrate affinity interactions with conventional separation technologies studying affinity partitioning using biospecific chromatographic particles in aqueous two-phase systems.

R. Kaul and B. Mattiasson are working on the affinity elution of almond oxynitrilase from an affinity support based on Eupergit C, also on Reppal PES – a new starch-derived polymer for applications in aqueous two-phase systems.

C. Sensted and Mattiasson are working on affinity-precipitation using chitosan as ligand carrier.

Kaul, U. Olsson, and Mattiasson are studying interactions in free solution as an initial step in downstream processing.

Additional information is available in: ESN-41-8:415; ESNIB 88-02:5 and 11; ONRL Report C-1-85; ONRL Report R-2-85; ONRL Report 7-001-C; ONRL Report 7-032-C; ONRL Report 8-001-C; ONRL Report 8-002-C; and ONRL Report 8-003-C.

Institutes

Research within the area of biotechnology is conducted at a number of Swedish institutions. At the Karolinska Institute, located in Stockholm, research is conducted in close cooperation with the pharmaceutical industry. Extensive basic research is carried out in genetics, immunology, and biologically active substances related to prostaglandins.

The Royal Institute of Technology or Lungliga Tekniska Hogskolan (KTH) in Stockholm, has a Department of Biochemistry and Biotechnology which is located in the School of Chemical Engineering. S. Gatenbeck is head of biochemistry and S.O. Enfors is head of biotechnology. The research programs of the department are concentrated in the following areas:

- Microbial metabolism
- Recombinant DNA technology
- Bio-organic synthesis
- Plant tissue culture
- Fermentation technology
- Extraction of intracellular enzymes.

In the area of fermentation technology, Enfors and his group study sensors and computer strategy for process control and biological responses to mixing during scale-up of anaerobic processes.

L. Häggström and her group are working on the control of immobilized nongrowing cells for the continuous production of metabolites. A nutrient dosing technique

was developed for maintaining constant activity in non-growing cells. The work is focused on the development of adsorption techniques, reactor construction, mass transfer problems, and metabolic regulation in amino acid production in *E. coli*.

Enfors, L. Strandberg, and B. Nilsson deal with scale up of recombinant DNA (rDNA) processes. Processes with rDNA organisms produced by the rDNA group of the department are studied in scale-up experiments in the pilot plant with respect to fermentation and separation of the products. Production of the fused proteins *E. coli*-beta-galactosidase-*Staphylococcus aureus*-protein A produced by *E. coli* and *S. aureus* protein A-human IGF-1 produced by *S. aureus* are being studied.

A.L. Smeds and Enfors have been investigating the large-scale production of chromatophores (membrane-bound enzymes) from *Rhodospirillum rubrum* by light-fed batch cultivation.

A. Veide, T. Lindback, and Enfors have studied the continuous extraction of beta-galactosidase from *E. coli* in an aqueous two-phase system concentrating on the effects of biomass concentration on partitioning and mass transfer.

U. Björkman has been investigating the properties and principles of mycelial flow dealing with rheology and flow mechanisms in a mycelial mash and using mathematical modeling for explanation of experimental results.

New methods for the production of polypeptide hormones have been developed by S. Josephson (KabiGen AB, Stockholm) in collaboration with S. Gatenbeck at the Royal Institute of Technology as well as with B. Nilsson and M. Uhlén (Department of Biochemistry and Biotechnology, University of Lund) using rDNA technology. These researchers have worked on human insulin-like growth factor-1 (IGF-1) which appears to be a major regulating hormone of postnatal growth. The production and purification system has been scaled up to 1000 liters. The production system is also being used for the production of other peptide hormones such as vasoactive intestinal peptide (VIP), brain IGF, and IGF-II. This work is a collaborative project of the academic scientists and KabiGen. Josephson has said that the production system can also be an excellent way of preparing new vaccines since the production level of the fusion protein obtained has a high level of production as well as a strong immune response.

Industry

Biotechnology-oriented companies constitute only a small part of Swedish industry. They mostly emerged during the postantibiotic era and some now occupy a leading position in the pharmaceutical, analytical, medical technology, and equipment industries.

Industrial developments in biotechnology are dominated by the pharmaceutical companies. This is also re-

flected by the biotechnology research and development efforts in industry in which the pharmaceutical industry accounts for about 75 percent followed by 9 percent for the food industry and less than 1 percent for the chemical industry.

The most important companies are Pharmacia, Alfa Laval, LKB, the Cardo group, and Kabivitrium. Pharmacia is one of the most prominent companies in biotechnological separation technology. Pharmacia is a subsidiary of the larger pharmaceutical/medical products group A.B. Forta. Pharmacia is closely connected with Uppsala University and is jointly funding with the Swedish government an Institute of Cell Research within the university. It is a specialist producer of chemical reagents for isolation and purification, and has developed affinity chromatography techniques using antigen/antibody characteristics as a means of specific isolation. Pharmacia sees its role substantially as a service role to firms like Novo who are selling biologically manufactured products and need help with problems of scaleup, extraction, and purification. Pharmacia's interests in this area have also taken it into the design and manufacture of equipment and instrumentation.

KabiGen is a subsidiary of the state-owned pharmaceutical group Kabivitrium. KabiGen is, more strictly speaking, a biotechnology firm, its main interests being in research into drugs and vaccines which can be produced by recombinant DNA technology. It also sees its main role as one of service – to cell breeders. Kabivitrium, its parent company, is the world's largest producer of human growth hormone, which until recently was derived from human cadavers. However, more recently, KabiGen, to protect its market, has been actively developing a bioengineered product derived from Genetech's (US) initial engineering. KabiGen's contract was Genetech's first non-US contract for recombinant DNA work. KabiGen is also carrying out research on interferon and plasminogen/activators (substances that dissolve blood clots). Forty percent of KabiGen's stock was sold off in 1983 and its shareholders now include Volvo; Korsnas Marma, the forestry and wood products group; and Alfa Laval.

Alfa Laval has wide interests in fermentation equipment for biotechnology – they are the foremost European group here – and in ethanol production techniques.

LKB holds an international reputation in analytical instruments and Cardo has a considerable impact on the biotechnology industry in Sweden through its subsidiary companies such as Hilleshög for the production of clonal seedlings of forest trees, and Sorrigona in the field of pollution control systems.

As the Swedish industry is small in an international perspective, it has to find very special areas of application instead of covering the whole field of activities in biotechnology, as indicated in the preceding sections.

Biotechnology has attracted venture capital as it has, for example, in the US. A number of small companies have been started by scientists attached to different universities. At the University of Uppsala, the Pharmacia company has sponsored joint ventures with research workers in the area of cell biology. At the University of Lund, a science park has been developed which serves as a growing point for companies emerging from research within the university laboratories. One of the biotechnology companies at the science park is Biocarb, which specializes in the production of complex carbohydrates with biological activity. The subsidiary, Monocarb, produces and markets monoclonal antibodies. Another company, Biovent, has been successful in developing techniques for *in vitro* immunization of human cells. These companies were founded by academic scientists, and the close contact between the company and the university are said to be part of their success. Other high-tech business parks

that have been important for technology transfer have been founded at other universities such as: Uminova in Umeå, Teknik Centrum in Linköping, and Teknikhojden in Stockholm. Of these, only Uminova is recognized as a center for biotechnology. Also, Huddinge Hospital, south of Stockholm, is now developing a biotechnology center in which academic research and industrial products are being developed side by side. A company, Karobio, was recently created to exploit the research of the scientists.

Environmental biotechnology has attracted a considerable amount of research effort and industrial development during the past 10 years in Sweden. AC Biotechnics and Puras AB offer systems for anaerobic and aerobic wastewater treatment on the international market. Alfa Laval has developed new and sophisticated techniques for ethanol production from cellulose and grain.

Norway

Industry

Until recently Norwegian industry has been involved mostly in the traditional biotechnologies of the pre-Pasteur era, such as the manufacture of dairy products, beers, etc. In the past couple of years enzyme technology has been successfully extended to fish processing. Fish is an important resource, and fish processing as well as production of fish oils and fish flour represent a big industry in Norway.

The pharmaceutical industry in Norway is characterized by few and relatively small companies. Apothekernes Laboratorium is involved in fermentation processes, mainly in the production of antibiotics. This is the only company that has established a recombinant DNA group. Nyegaard & Co. A/S is producing diagnostics and drugs. They are now increasing their activities within immunology, directing them particularly at various applications of monoclonal antibodies. The Biotechnology Group at Norsk Hydro A/S has concentrated their activities on the development of fermentation-based fine chemicals but no new products have yet been launched.

In the fish industries there has been the application of enzymes to fish processing, particularly the enzymatic removal of skin and membraneous material from squid and herring. The technology was developed at the University of Tromsø, and several companies in the northern part of Norway are applying the new process. The increasing fish breeding industry (salmon) in Norway has

resulted in an increased need of special feed, and this will probably represent a growing field in the near future.

The utilization of potato starch has a long tradition. The laboratory of the Norwegian Potato Starch Industry plays a central role in product as well as in process development within this industry.

In 1987, Dyno Particles A/S, Lillestrøm, opened its new research center, which houses the following three departments: polymer and surface chemistry, specialty chemicals, and biotechnology. The method of making monosized polymer particles marketed under the trade name DYNOSPHERES was developed by J. Ugelstad. These particles are used for a variety of applications such as fast, accurate counting of T-cells, immunomagnetic separation, reversed phase chromatography, etc.

Environmental Biotechnology. The Laboratory of the Norwegian Potato Starch Industry is responsible for the introduction of the first and only anaerobic wastewater treatment process.

Government

The major part of the biotechnological research done by the research councils (salaries for university staff, etc.) is funded by the government at a cost of about \$2 million per year. The Royal Norwegian Council on Science and Technology (NTNF) has supported a research program since 1977 at the Foundation for Scientific and Industrial Research at the Norwegian Institute of Technology (SIN-

TEF). The NTNf has recently engaged business consultants in its efforts to find interesting business areas for Norwegian industry in biotechnology.

The research councils which are responsible for agriculture (NLVF) and fishery (NEFR) also support biotechnology projects. Research projects related to the fish breeding industry such as the development of fish vaccines represents an important field. The NEFR plays a central role in the funding of this research.

By means of an action plan with a funding of several million dollars, the government is providing support for the development of biotechnology within various fields and industries in Norway. Biotechnology in Norway is, however, still far behind other European countries except for Spain and Portugal. In 1985, a research laboratory for genetic engineering was established at the Norwegian National College of Agricultural Engineering. The research emphasis is on the new methods of biotechnology. In addition to independent research, the laboratory was planned to be a service agency and a workplace for other institutes which are involved in biotechnology research.

Biotechnological research linked to veterinary medicine is expected to be established on a somewhat more decentralized model at the Norwegian Veterinary College and the Veterinary Institute. There are also plans for cooperation between the universities in Tromsø and Oslo with respect to agricultural research and biotechnological research on plants.

Universities

University courses in Bergen, Oslo, and Tromsø are mainly in biological sciences. At the University of Trondheim, basic as well as applied courses in microbiology, microbial genetics, and biochemistry are given. Research in biochemistry is directed at biosynthesis of cellulose, microbial degradation of hydrocarbons, fish technologies, and marine biochemistry, which includes polysaccharides and cultivation of marine organisms (fish and feed). Research at the University of Bergen is concentrated on microbiology, immunology, plant physiology, and DNA biochemistry. A great number of departments at the University of Oslo are engaged in research in botany, plant physiology, biochemistry, and medical sciences. Besides Tromsø University's work in medical biology, its Institute of Fisheries, devoted to enzyme technology and fish processing, is noteworthy. Unfortunately,

not many of the scientists are applying recombinant DNA technology. Thus, the activity within molecular biology is much too low. This lack should be mitigated, to some extent, under the present government emphasis and support for biotechnology, as mentioned above.

Institutes

Five Institutes cover the fields of industrial research, environmental toxicology, and health care. Industrial research is carried out at two Institutes, The Norwegian Institute of Technology (SINTEF) at Trondheim (fermentation technology) and the Central Institute for Industrial Research at Oslo (fine chemicals, microbial transformations). The Division of Environmental Toxicology of the Norwegian Defense Establishment is involved in DNA repair. In the health sector the Norsk Hydro Institute for Cancer Research works on monoclonal antibodies for diagnostics and therapeutic use. The National Institute of Public Health is a vaccine producer and has research interests in hybridomas.

The following paragraphs deal with a few research projects on various topics in Norwegian establishments. This information is very limited since I have not yet made a liaison visit to Norway.

G. Halmø and coworkers (Department of Microbiology, University of Trondheim) are engaged in studies of environmental microbial degradations at low temperatures. (See *ESNIB* 88-03:12.)

S. Olsnes, J.O. Moskaug, H. Stenmark, and K. Sandvig (Institute for Cancer Research, Norwegian Radium Hospital, Oslo) are carrying out studies on diphtheria toxin. This is a protein that binds to cell surface receptors and then enters the cytosol where it inactivates elongation factor 2, thus inhibiting protein synthesis. It was found that translocation of the enzymatically active part of the toxin across the plasma membrane can be induced at low pH. Receptor molecules appeared to be involved in the translocation process, which also requires an inwardly directed H^+ -gradient and permeant anions. Transient cation-selective channels were formed upon toxin entry.

J. F. Storm (Institute of Neurophysiology, University of Oslo) and his group are studying temporal integration by a slowly inactivating potassium current in hippocampal neurons.

Finland

As a small country with limited resources—especially manpower—Finland has one major advantage: close cooperation and interactions between different research groups is easy and has proven very fruitful, mainly in biotechnology. This can be seen from some promising results in Finnish research institutes and industry.

Biotechnical research is carried out at several universities and institutes mainly in the Helsinki area but also in Turku, Tampere, Kuopio, and Oulu. The number of Finnish companies applying biotechnology is still limited. Many of them use traditional biotechnology, while actively doing research in molecular biology and gene technology.

The Academy of Finland takes care of the training of scientists and supports basic research. The Technology Development Center (TEKES) is responsible for applied research in the precompetitive field, and different ministries are financing research work for special applications of biotechnology in their own areas.

National Technology Programs

TEKES is supporting R&D in biotechnology within national technology programs and in some smaller projects. The programs are jointly financed by TEKES, participating institutes, and industry and are carried out in close cooperation. Two 4-year programs were terminated by the end of 1987: "Utilization of Gene Technology" and "Wood as Raw Material for Process Industry."

The gene technology program focused on two important areas: the development of new proteins by protein engineering and development of expression systems for production of proteins.

Two methods were developed in protein engineering: a new random mutagenesis method by the biotechnical laboratory of the Technical Research Center of Finland (VTT) and the application of random mutagenesis by the University of Turku. At the Recombinant DNA Laboratory of the University of Helsinki new vectors for protein production in mammalian cells have been developed. The VTT biotechnical laboratory cooperated with Aiko Ltd in the development of a new fungal vector system to produce different proteins in *Trichoderma reesei*.

The wood technology program included biotechnical applications with two subprojects: VTT biotechnical laboratory studied biotechnical degradation of lignin and, in cooperation with the Finnish Pulp and Paper Research Institute, investigated the potential for biotechnical pulp bleaching to reduce chlorine.

TEKES started a new biotechnology development program in 1988 comprising five subprograms: biotechnology in pulp industry, bioprocess technology, plant biotechnology, cultivation of mammalian cells, and protein engineering. It will be carried out in close cooperation between research institutes and industry. Other technology programs include biotechnology as, for example, in the paper and chemical technology programs.

Biotechnical Research Institutes

Biotechnical research is being concentrated in regional centers. All main areas of biotechnology represented at the University of Helsinki and their related disciplines at the different faculties are proposed to be combined in a new science park in Vikki.

Bioprocessing and related technical areas are studied at the Helsinki University of Technology, which is situated in Otaniemi close to the Technical Research Center of Finland (VTT), which represents another regional center for biotechnology.

VTT's biotechnical laboratory is one of the most important biotechnical research units in Finland. It is able to develop complete bioprocesses starting from strain development with conventional methods or gene technology to pilot-plant trials including fermentation and downstream processing.

Research into vaccines carried out by the Public Health Institute is versatile and of high standard. A modern health care system in Finland and the potential of biotechnology should allow a considerable expansion in the use of new vaccines.

In Turku, two universities are active in biotechnology. The cooperation between the University of Turku and the Swedish University of Turku (Åbo Akademi) and industry is close and will get additional input when Biocity in Turku will be in operation.

In Oulu, different facilities, combining their activities in the field of biotechnology, have established the Biocenter Oulu, which is an administrative unit in the University of Oulu. Its main research activities are in the field of medical biotechnology and plant biotechnology.

The university of Kuopio started education in biotechnology in 1987. The main areas are medical and environmental biotechnology and toxicology. In Tampere, the University of Tampere, the Tampere University of Technology, and some VTT laboratories carry out biotechnical research in medical biotechnology (diagnostics and biosensors) and in environmental biotechnology.

Industry

It is not surprising that the food industry is the leading area for biotechnology application. Chymos and Huhtamaki Ltd Marli produce wine from Finnish berries, all breweries use fermentation in beer production, and Alko Ltd produces alcohol by fermentation.

Pressed baker's yeast is produced by Alko Ltd and Lahden Polttimo. Alko also produces distiller's yeast and "bioyeasts", which are enriched with selenium, chromium, and other trace elements. The Finnish Dairies Association, Valio, utilizes biotechnology for production of traditional milk products and has also developed new products based on whey and lactose.

Enzyme technology plays a major role. Alko and Finnish Sugar produce industrial enzymes and develop new applications for them in close cooperation with universities, research institutes, and industry. Silaging is very important in Finland where the growing season for grasses is only a few months. Several companies are developing new biological preservation methods for green fodder.

Pharmaceutical industries (Orion Co. Ltd, Farnos Group Ltd, and Huhtamaki Ltd Pharmaceuticals) utilize biotechnology both in production of drugs and for diagnostics. Some small companies developing diagnostic methods have recently started in Finland.

Plant biotechnology is an important area in Finland for agriculture, forestry, and raw material plants. Kemira Ltd is newly involved in this area: in plant cultivation and production, in plant protection, and in biotechnical production of some chemicals. Hortus Ltd produces horticulture plants by latest micropropagation techniques in a modern production unit. Kemira and Hortus together with Enso-Gutzeit are developing this technology for forestry plants.

In the pulp industry, biotechnology has been used for waste treatment. The wide application of new biotechnical processes is still in the development phase.

The rapid development of new biological methods in clinical analysis, in health care, and other major fields creates a growing demand for new analytical instruments and methods. The most well-known Finnish companies in this field are Labsystems Ltd and Wallace Ltd.

Kemira Ltd is a Finnish state-owned company, founded 65 years ago to provide a secure source of sulfuric acid and superphosphate for domestic fertilizer use. However, the company has expanded greatly in recent years and has acquired several firms in the US, the UK, the Netherlands, etc. They have also recently signed a barter deal with the USSR to purchase Soviet fine chemicals and fertilizer feedstocks and supply the USSR with about \$615 million worth of pesticides and their components.

The following paragraphs include some specific research projects (and the scientists involved) at various establishments in Finland. This is a limited list since the information was obtained from biotechnology meetings I attended because I have not, as yet, made a liaison visit to Finland.

Y.Y. Linko and P. Linko (Laboratory of Biochemical and Food Engineering, Helsinki University of Technology, Espoo [Helsinki]) are working on methods for the entrapment of microbial cells in cellulose gels.

T. Kohonen (Laboratory of Computer and Information Science, Helsinki University of Technology, Espoo [Helsinki]) and his group have been active in the area of neurocomputing. Their emphasis is on the study of associative memories and representations of knowledge as internal states in distributed systems. A report on studies of a genuine associative memory, the internal state of which is directly determined by the received input signal patterns, was published a short time ago by Kohonen. He is well-known for his research in the area of neural networks. (See ONRL Report 8-010-C.)

The Recombinant DNA Laboratory at Helsinki University was created in 1982 with L. Kaariainen as Director. The institute represented an unusual consortium between the university, the government, and industrial firms. The Laboratory is conceived primarily as a research center with current research programs in the following areas:

- Structure and physiology of enveloped viruses including structure and biosynthesis of Semliki Forest virus, biogenesis of Uukunemi virus, and synthesis of Rubella virus structural proteins
- Expression of foreign genes in *Bacillus subtilis*
- Construction of recombinant (rDNA) molecules for expression in yeast
- Developmental studies in *Drosophila*.

The laboratory is initiating programs in screening of genetic diseases in Finland and in development of gene expression systems in animal cells. The project areas cover a number of important research questions going the full spectrum from bacterial membrane transport through virology to developmental biology. Work on the Semliki and Uukunemi viruses is fairly unique to Finland and bears some relevance to forestry. The keystone of the laboratory is the *Bacillus* project under I. Palva, a highly respected bacterial geneticist. At the present time, foreign genes can be expressed in *B. subtilis*, but the foreign proteins are produced in low yield presumably due to protease activity. A solution to this problem could make *Bacillus* the system of choice for industrial production of many proteins since they would be exported out into the growth medium. Palva and his group have also been involved in a project in collaboration with Alko Ltd. The project involves alpha-amylase, which is used industrially to break down starch as an early step in fermenta-

tion. The enzyme from *B. licheniformis* is thermostable, which would make it an excellent candidate for industrial applications. However, it is produced at low levels in the parent organism. Using rDNA techniques, Palva and coworkers inserted the gene for this thermostable amylase into a secretion vector under the control of the highly efficient promoter of the *B. amyloliquefaciens* amylase. This construct was then introduced into *B. subtilis* where the synthesis of this enzyme was increased 500-fold. P.M.A. Nybergh (Research Laboratory, Alko Ltd, Helsinki) was the industrial collaborator on this project. (See ONRL Report C-1-85.)

A.C. Syvänen, M. Laaksonen, and H. Söderlund (Orion Genetic Engineering Laboratory, Helsinki) have developed a novel approach for the quantification of nucleic acids. These investigators developed a hybridization technique for the quantification of nucleic acids in which a probe pair is allowed to form sandwich hybrids with the target nucleic acid in solution. (See ONRL Report C-10-86.)

R. Lundell, R. Oy, A. Mustranta, E. Kaila, and J. Karpinen (VTT biotechnology Laboratory, Espoo

[Helsinki]), are working on bioprocessing of fine chemicals and pharmaceuticals. They have developed a novel process for the production of enzymes. They used the *P. varioti* strain, TPR-220 (a mycelium-forming microfungus) in their work. The procedure combines the production of single-cell protein (SCP) and extracellular enzymes for industrial and pharmaceutical use in a continuous process which is fast and economical. (See ONRL Report C-1-85.)

M. Karp and coworkers (Department of Biochemistry, University of Turku) are studying stable-light-producing *E. coli*. Stable-light production in *E. coli* is achieved by cloning the genes encoding bacterial luciferase from *Vibrio harveyi*. To gain advantage of sensitive detection of light, these researchers transferred the genes under the control of a regulatable promoter system and searched for growth and buffer conditions where bacteria emitted stable light. Their results showed that an automated biosensor system can be developed to monitor the effects of biologically active compounds against stable-light-producing bacteria.

Switzerland

In contrast to biotechnology research in the countries described in the preceding sections, three-quarters of Switzerland's biotechnology research is conducted by private firms—primarily the giant pharmaceutical companies such as Hoffmann-La Roche, Ciba-Geigy, and Sandoz. The headquarters of these companies are based in Basel but they have numerous branches throughout Western Europe as well as the US. It appears that in contrast to the other Western European countries (West Germany, France, Sweden, the Netherlands, and the UK), growth in private research as well as academic research has declined. As of 1985, Switzerland was in tenth place among industrialized nations for research and development (R&D) expenditures in high technology. Reports indicate that the competitive position of the Swiss economy, and in particular industry, is liable to deteriorate in the future if Swiss firms do not put greater effort into innovation and diversification. The Swiss biotechnology industry is relatively weak in the know-how of plant operation because all its multinational companies operate their production facilities abroad. This represents a handicap for Swiss universities and research institutes in the realization of their innovations.

Government

The Federal and Cantonal governments support research in biotechnology, mainly by providing funds for the research institutes at the Federal Institute of Technology in Zurich and Lausanne as well as the universities of Basel, Geneva, and Zurich.

Federal research includes that by the Federal Institute for Milk Products at Liebefeld (near Bern) which deals with research in the field of dairy products, an important sector of the Swiss agricultural economy. Also, a project for generating energy from agricultural waste is operated by several federal research institutes.

In addition to covering operating costs for these specific projects, annual budgets for biotechnology projects by nongovernmental organizations are provided by national funds. However, the funds for financing research in biotechnology have not been increased sufficiently and are considered to be too low to permit significant advances in this area. Only 25 percent of the total national spending in scientific research is financed by the government. Biotechnology is no exception, and the main efforts in basic as well as applied research are made by industrial enterprises.

Universities

Over the years, a complete academic curriculum leading to a degree in biotechnology has evolved at the Swiss Federal Institute of Technology (ETH) in Zurich – complete courses and degrees in biotechnology are offered by the Department of Biotechnology. Biotechnology-related courses are also offered by the Department of Chemical Engineering (*bioreactions and kinetics*), by the Department of Microbiology (*bioenergy, genetic engineering, degradation of recalcitrant compounds*), and by the Department of Process Engineering (*reactor design*). Further courses in the basic disciplines of biotechnology are offered at the University of Zurich's Institute for Plant biology, at the Biozentrum of the University of Basel, Department of Microbiology, and at the University of Geneva Department of Biology.

Swiss Federal Institute of Technology (ETH). The Department of Biotechnology at ETH was established in 1982. It was proposed toward a concept established in 1974-1975 – the promotion of biotechnology research in Switzerland. The intent of this concept was to determine the basics for the technical use of living cells and their components and to further develop their possible applications. Besides microbes, the cells of higher organisms (plant and animal cells) would also be studied. The resulting strategy included the establishment of a pilot plant at *Hönggerberg* (a suburb of Zurich), which would allow investigations in the development of bioreactors, scaleup of processes, process development, computer applications, and processing. Thus, pure biology was deliberately combined with technical methodology. From 1979-1981 the biotechnology group was located in small buildings in central Zurich but moved in 1981 to ETH.

The goals of the Department of Biotechnology are:

- Research and development for the improvement of basic knowledge in areas of health, nutrition, and environment
- Assurance of a supply of raw materials through research and development with the aim of fully utilizing the biochemical potential of cells
- The general acquisition of knowledge

Research in the area of bioprocesses is under the direction of A. Fiechter. The various programs are:

- Mass cultivation of living cells
- Improvement of process kinetics
- Mass transfer
- Scale-up
- Process development
- Measurement and control
- Computer applications
- Direct-Digital-Control strategy.

Enzyme technology was under the direction of K. Mosbach, who held a joint appointment at ETH and

the University of Lund, Sweden. However, Mosbach has recently relocated full time to Lund and a new director at ETH has not yet been appointed. The various programs in the section on enzyme technology are:

- Enzymology
- Immobilization of enzymes
- Alteration of enzymes
- Process development
- Analytics
- Clinical testing.

Research in the area of wastewater biology is under the direction of G. Hamer. The various projects in this area are:

- Water biology
- Water pretreatment
- Sludge treatment
- Biogas
- Thermophilic sludge treatment.

In addition, ETH's Institute for Molecular Biology and Biophysics and Institute for Molecular Biology are engaged in basic research in areas such as neuropeptides and hormones (R. Schwyzer), protein structure and enzymology (H. Zuber), spatial structure and internal mobility of biological molecules in solution using NMR (K. Wüthrich), gene function, interferons and molecular virology (C. Weissmann), and genetically oriented molecular biological research (M. Birnstiel, who has just recently relocated to Vienna, Austria, as Director of the new Molecular Biology Institute). Detailed reports of the research at these departments as well as at the Department of Biotechnology are available in *ESN-39-7:293, 298, and 304.*

Institutes

Battelle-Geneva Research Center, Geneva. Battelle-Geneva is an R&D contract organization. Established in 1952, it encompasses today the Industrial Technology Center, the Center for Toxicology and Biosciences, and the Applied Economics Center. The staff of some 20 different nationalities numbers more than 420 scientists, engineers, and supporting scientists whose training and experience embrace the physical, life, social, and behavioral sciences. The research volume is over F40 million (about \$24.3 million) a year.

In the section of *Biotechnology and Applied Biochemistry* at Battelle-Geneva, the emphasis is on the practical aspects of applied genetic engineering and enzyme technology as well as on the large-scale isolation of bioproducts. Other research areas include peptide and polypeptide synthesis for the development of new drugs and drug delivery systems. Immunochemical methods using monoclonal antibodies and other new diagnos-

tic procedures are investigated and developed, in some cases leading to the design of instrumentation.

Battelle-Geneva has recently extended its activities to include the clinical investigation of psychotropic drugs. Phase II, III, and IV studies can be carried out in various centers worldwide subject to approval by an ethics committee.

In the area of drug receptors, the measurement of specific binding of drugs to receptors includes: alpha and beta adrenergic receptors, dopamine, serotonin, Diazepam, gamma amino butyric acid (GABA), glycine, imipramine, acetylcholine, adenosine, opiates, and histamine. Receptor regulation is also being investigated as well as (^3H)-ligand binding and determination of drug plasma levels by radio-receptor assay.

Recently, Battelle sold the biotechnology part of the Geneva Research Center to C.E.L. Industries, in which the Kuwait Investment Office has a 60-percent holding. C.E.L. Industries, headquartered in Vancouver, Canada, hasn't disclosed the price of the acquisition, to be named "Intracel," but will spend more than \$8 million in the next 2 years bringing products under development to the marketplace and will double the research staff. P.J. Bromley, who has headed biotechnology at Geneva since 1982, has been named president of Intracel. The Geneva Research Center was set up by the Battelle Memorial Institute (based in Columbus, Ohio) in 1954.

Biogen S.A., a Swiss research and development laboratory, affiliated with Biogen NW and based in Basel (with new laboratories in Geneva as well as a research group in Zurich), has been involved in research and development of pharmaceuticals. It can claim a few firsts (alpha interferon and Hepatitis B vaccine). It has also been involved in collaborative projects at Swiss universities. However, Biogen has been recently purchased by Glaxo (a UK company), and the Geneva research center is now called the Glaxo Institute for Molecular Biology. I do not have up-to-date information on the activities of this research center except to mention that J.F. Ernst, at the Division of Molecular Biology, is concerned with research on codon usage and gene expression.

The other research institutes based in Basel are: Biozentrum, the Basel Institute for Immunology, and Friedrich Miescher Institute.

Biozentrum. Biozentrum is closely linked with the University of Basel and has a reputation for research in genetic engineering, among other fields. The research activities at the Biozentrum serve to train young research workers. The Biozentrum is divided into six departments: Biochemistry, Biophysical Chemistry, Microbiology, Pharmacology, Structural Biology, and Cell Biology.

In the Department of Biochemistry, research is concentrated on studies of the function, the biogenesis, and the structure of biological membranes. M.M. Burger is concerned with research on several functions of the cel-

lular plasma membrane. G. Schatz's group is involved in the study of the transport of proteins into mitochondria. The recognition sequences in the transported proteins have been investigated by cloning, sequencing, and alteration of the corresponding nuclear genes. The goal of these studies is to learn how a protein recognizes a particular intracellular target and penetrates across one or even two membranes. H. Trachsel and coworkers are interested in the mechanism and regulation of eukaryotic protein synthesis. They study the structure and function of individual initiation factors and are cloning the genes coding for these factors.

In the Department of Biophysical Chemistry, important structure-function relationships are studied at the molecular level by a variety of physicochemical methods with a focus on biological membranes. J. Engel's group works on the structure, function, and assembly of components of the extracellular matrix, including basement membranes, and on components of the complement system. In K. Kirschner's group, research concentrates on interactions between active sites in multienzyme complexes and multifunctional proteins. H. Schindler and his associates are studying ion transport in membranes using reconstitution assays. G. Schwartz's group follows various research projects on the physical chemistry of protein-DNA interactions and membrane-active compounds. J. Seelig's group studies the structure and dynamics of biological membranes. R. Hopman studies thiamine-dependent enzymes. G. Hänisch runs the departmental workshop and both develops and improves instrumentation needed in many of the research projects.

In the Department of Cell Biology, E. De Robertis and his group are using the frog oocyte with its giant nucleus and a stockpile of materials to study fundamental questions such as assembly of the nucleus, selective accumulation of macromolecules in the nucleus, and the sorting out of nuclear and cytoplasmic components. Cloned genes coding for small nuclear RNAs and antibodies from patients with autoimmune disease against these RNAs and the proteins binding to those RNAs are used as a tool to approach these fundamental problems. W. Gehring and his group are interested in the genetic control of development in *Drosophila* (fruit fly). Homeotic mutants that transform one part of the body into another part and affect the segmentation of the embryo have been cloned and analyzed by a sensitive method for localization of transcripts in tissue sections. Cloned genes, which can be inserted into the germ line of the fly by transformation using the P transposon as a vector, enable better studies in developmental genetics. M. Noll and his collaborators analyze the relationship of chromatin structure and gene activity; they also study homeotic genes.

The main (although not exclusive) research interests of the different groups in the Department of Cell Biology are:

- W. Arber – transposition in prokaryotes and its role in bacterial evolution
- T. Bickle – mechanisms and control of DNA restriction and modification, site-specific recombination
- A. Engel – the development of scanning transmission electron microscopy (STEM) for biological applications
- E. Kellenberger – bacteriophage morphogenesis and form-determining mechanisms and the elaboration of new techniques to increase the resolution and analytical power of biological electron microscopy
- P. Philippsen – the structure of the yeast nuclear genome with particular reference to transposable elements and centromeres
- J. Rosenbusch – the structure and function of the bacterial outer membrane with the major interest centering on pore-forming, transmembrane proteins.

Some of the research activities of the Department of Pharmacology are:

- The elucidation of the molecular mechanisms by which genetic and environmental factors control the biotransformation of drugs, carcinogens, and other xenobiotics to inactive, active, and toxic metabolites and polysubstrate monooxygenases (cytochrome P450) (U.A. Meyer)
- The investigation of the primary molecular defects and the clinical applications of several pharmacogenetic diseases (for example, porphyrias, malignant hyperthermia)
- Mechanisms of biosynthesis and the sorting of digestive enzymes and other proteins of intestinal cells (H.P. Hauri)
- Ontogenetic development and function of peptidergic sensory neurons (U. Otten)
- Neuronal plasticity (J. Nichols)
- Lipid bilayer membranes, thermodynamics of energy conversion (D. Walz).

The Department of Structure Biology consists of two research groups headed by R.M. Franklin (working in the field of animal virology and immunopathology) and J.N. Jansonius (engaged in structural and functional studies of proteins – mainly using crystallographic techniques). Research in theoretical biology (E.L. Mehler) is concerned with studying the relationship between the biological activity of small molecules and their electronic structure and conformation. Another area of study concerns the influence of solvent on protein structure and function, emphasizing the development of methods that can account for the dielectric effects of the medium in which macromolecules are embedded.

A general review of the Biozentrum is available in *ESN-39-6:239*.

The Basel Institute for Immunology. This institute is a research center wholly owned by Hoffmann-La Roche. Its research efforts are concentrated on immunologically oriented projects. (See *ESN-39-6:239*).

Friedrich Miescher Institute. This institute was established in 1970 as an independent foundation by Ciba-Geigy Limited. The aims of the Foundation were (1) to engage in basic research, originally in the fields of biochemistry and medicine and later also in plant science, and (2) to provide an international center for research, study, and training for young scientists. The Institute occupies laboratory space within the Ciba-Geigy complex in Basel. Research in the Institute spans a wide range of subject matter in cell and molecular biology of eukaryotic organisms.

Two of the research activities of the Institute are:

(1) Study of glia-derived modulation of neurite outgrowth in neuronal cells, project leader is D. Monard. A factor inducing neurite outgrowth has been isolated and purified, and antibodies have been made to this factor.

(2) Investigation in neuronal microdifferentiation. The molecular mechanisms which regulate the process of microdifferentiation in the developing brain are studied, focusing on microtubule proteins and microtubule-associated proteins (MAPs) which have been shown to be effective promoters of tubulin polymerization *in vitro*. Antibodies are used to study synaptic junction proteins with the aim of establishing markers which can be used to investigate the regulation of synapse formation in the developing brain. As part of this approach, the researchers are characterizing acidic amino acid binding sites in brain synaptic membranes which correlate with excitatory neurotransmitter receptors with the intention of producing monoclonal antibodies against the receptor protein. The aim is to use this combination of antibodies against axonal, dendritic, and synaptic junction proteins to determine what influences, hormonal and sensory, regulate the molecular mechanisms which underlie neuronal differentiation in the developing brain. The researchers involved in this project are: G. Huber, A. Matus, B. Riederer, and G. Fagg.

Another section deals with translational control mechanisms (M. Minks, G. Milchev, and J. Gordon) and clinical immunology. Autoimmunity in mice and humans is studied by J. Gordon and coworkers, and allergy diagnosis (focusing on the measurement of IgE-class antibodies) by M. Dérer and J. Gordon.

Human oncogenes are being studied by Ch. Moroni, Ch. Gämbke, and D. Wächter. This group is investigating the putative role of oncogenes in human leukemia. Their approach is to identify and clone activated genes directly from human patients, study the correlation between gene expression and the clinical source of the disease, and examine the function of cloned genes in experimental systems.

Studies of human interferon (IFN) genes are being investigated by H. Weideli, M. Caravatti, and A. Egg. This group has focused its interest on two kinds of IFN: leukocyte IFN (IFN-alpha) and immune IFN (IFN-gamma).

They are interested in the regulation of the different IFN genes using cloned IFN-gene sequences as probes for the isolation of regulatory proteins.

Gene expression in plants is being studied by B. Chattoo, N. Grimsley, L. Graf, and Z. Nicola-Koukoulkova. The genes under study are chloroplast genes – in particular, those regulated by the nucleus as well as genes of cauliflower mosaic virus. For the reintroduction of genes into plants, transformation with an engineered *Agrobacterium* Ti plasmid is being used in addition to a direct DNA-mediated transformation system. For the rescue of genes from transformed plant cells, the transforming DNA is tagged with the necessary lambda sequences and the desired genes are isolated by *in vitro* packaging.

Other research areas being investigated at the Friedrich Miescher Institute are:

- Hemopoietic cell differentiation and transformation
- Biochemistry of fibrinolysis
- Molecular aspects of protein phosphorylation
- Gene expression in yeast
- Regulatory events of the cell cycle
- Mechanisms of DNA repair
- Structure, function, and hormonal regulation of specific eukaryotic genes
- Biochemical genetics of cultured plant cells
- Plant development
- Culture and genetic modification of cereal protoplasts
- Hormonal regulation of gene expression, regulation of tumor function
- Structure and function of plasma proteases
- Desensitization of beta-adrenergic receptors
- Regulation of protein synthesis and S6 phosphorylation
- Regulation of storage proteins in *Zea mays*.

(See ESN-39-6:240.)

Industry

Biotechnology in the pharmaceutical industries came to the front in the antibiotic period after the Second World War (for example, Vitamin C synthesis at Roche, antibiotics and steroid transformations at Ciba-Geigy and Sandoz). In the postantibiotic era all three companies have been heavily involved in research and production in a variety of new products. Hoffman-LaRoche and Sandoz have used their respective US and Austrian sub-

siidiaries. These companies as well as Ciba-Geigy are operating in Basel as well as in the US.

Ciba-Geigy. Having started its biotechnological research in 1955, Ciba-Geigy concentrated in the beginning on antibiotics and steroids. The company now operates production facilities for antibiotics near Naples, Italy, and a number of successfully developed biotechnology products are marketed today. Research concentrates on interferons and antibiotics as well as products for agricultural pesticides. Genetic engineering groups have been established at the Ciba-Geigy research centers in Basel as well as in the US.

Hoffman-La Roche. This internationally active company is devoted to the development and production of products for health of humans, animals, and plants. Its activities encompass the fields of pharmaceuticals, vitamins and fine chemicals, diagnostics, fragrances and flavors, medical and scientific instruments, and plant protection. Roche is one of the world's leading pharmaceutical companies and is one of the world's major manufacturers of vitamins. Roche has always given high priority to pharmaceutical research, and the company spends more than 20 percent of its turnover on R&D. Roche pharmaceutical research is highly international, but with emphasis on four main centers: Basel, Switzerland; Nutley, New Jersey; Welwyn Garden City, UK; and Kamakura, Japan. In addition, some other important countries such as West Germany and France, have their own highly committed and relatively autonomous clinical development units that undertake work on active substances originating from Roche research. A notable feature of Roche is that, in addition to its own centers of applied and project-related research, it supports two independent institutes involved purely in basic research: the Basel Institute of Immunology and the Roche Institute of Molecular Biology (RIMB) in Nutley. These institutes, which were founded by Roche in the late 1960's and have been financed entirely by the firm ever since, have complete academic freedom in their own research activities. The Basel Institute for Immunology is now a world-famous center of immunological research, its cofounder and first director, Professor Niels Jerne, having been a co-winner of the 1984 Nobel Prize for medicine together with G. Köhler and C. Milstein (University of Cambridge, UK). In 1987, another former member of the Institute for Immunology was honored with the Nobel Prize. Japanese scientist Susumu Tonegawa received this award for research conducted at the Institute between 1975 and 1981, which led to an explanation for the genetically determined variety of antibodies in the immune system. At the RIMB in Nutley, molecular biologists had already started research into interferons in the 1970's. Thus, the Roche group has become a world leader in the development and genetic engineering of promising immunological substances.

Modern methods of molecular and cellular biology, and protein engineering and, in particular, genetic engineering and the use of monoclonal antibodies have given pharmaceutical research at Roche new and versatile tools to effectively complement the classical chemical methods of pharmacological synthesis. At Roche, molecular biologists, immunologists, protein chemists, synthesis chemists, and computer modeling specialists have been working in close cooperation on numerous projects for quite some time. In cardiovascular research, for example, computer models have been used to develop an ACE-inhibitor – i.e., a substance that blocks the conversion of the pressor tissue hormone, angiotensin, from its inactive into its active form. The findings obtained so far in the clinical testing of this new substance, cilazapril, suggests that its molecular structure has been optimized to give a more specific action and hence improved tolerability. In the closely related field of inhibition of platelet aggregation and prevention of arteriosclerosis, some important factors have already been isolated and characterized to the point where the search for specifically acting substances has been initiated.

One research team using genetic engineering to construct a complete benzodiazepine receptor of the brain cells has met with considerable success. Thus, it may soon be possible to have active substances with selective anxiolytic properties. Earlier work in the field of molecular biology led to the discovery of the first benzodiazepine antagonist, flumazenil, which was introduced in Switzerland in 1987. This preparation has no intrinsic pharmacological action of any significance, but when it is given intravenously, it immediately displaces all other benzodiazepines at the receptor in the central nervous system. This compound is used primarily in anaesthesia and in cases of benzodiazepine overdose; it is also of fundamental interest in a great deal of neurobiological research.

In the field of endogenous signal substances of the immune system, work at Roche is currently focused on certain interferons and interleukins. Additional oncological and virological indications for interferon-alpha-2a are currently undergoing clinical testing. Interleukin-2 is being used for the activation of natural killer cells and is being tested selectively in the treatment of various tumors. Where interleukin-2 is concerned, interest is centered not so much on the substance itself – which is involved in numerous inflammation processes and some autoimmune diseases – but rather in the search for effective substances to counteract its effect. Certain substances found in Roche laboratories in the course of rheumatological research exhibit this type of activity *in vitro*. Since some types of rheumatic disease are now seen as disturbances of the immune system, increasing importance is being attached to the role of molecular biology and immunology in the search for a causal treatment for rheumatism.

AIDS constitutes a considerable challenge to Roche research teams working in the fields of molecular biology and immunology. Scientists in the four research centers are currently exploring a number of different avenues in their intensive search for substances capable of blocking major retrovirus-specific mechanisms involved in the penetration of viruses into the host cells and in viral replication. In 1987, Roche received a license for the clinical development and subsequent marketing of dideoxycytidine (DDC), the virostatic action of which was discovered at the US National Cancer Institute. Since DDC is as yet unlikely to be the agent for treating AIDS, Roche research is not only continuing its search for more effective substances but is also making a considerable effort to develop a vaccine against AIDS.

The first notable success in the quest for a malaria vaccine was recently scored by a group of Roche scientists working together with scientists from academia and with specialists from the vaccine research unit in Maryland, US. In volunteer trials, the jointly developed sporozite antigen for prophylaxis against the first blood form of the parasite was found to be well tolerated and in some cases immunogenic. Since an effective vaccine against malaria – by far the most common and most dangerous infectious disease in the world – will require a defined mixture of different antigens, there is still a considerable amount of research work to be done in this field.

Sandoz Ltd. Sandoz has been active for some time in the field of biotechnology. The company conducts basic research in its wholly owned research institute in Vienna and operates plants for fermentation through the Biochemie Kundl GmbH in Austria. Through this company, Sandoz holds an important position in the manufacture of antibiotics, mainly penicillin and modifications thereof. The Institute in Vienna has built up a considerable capacity in molecular biology and genetics which is further supported by collaboration with the Boston-based Genetics Institute. This fits with the company's strategy of developing new immune modifiers to combat immunological disorders. Other goals include new cancer treatments, and using genetic engineering to produce hybrid antibiotics. Sandoz researchers are also working on the development of drugs to improve the cognitive and affective disorders typical of senile dementia – to which dementia of the Alzheimer type belongs – as part of their gerontology program. Parkinson's disease and osteoporosis are other diseases that are being studied at Sandoz. The company has also set up the Sandoz Foundation for Gerontological Research. The Foundation awards scholarships with the aim of encouraging innovative research especially among younger scientists. Another point of concentration is research in the field of immunology – in particular, immunodeficiency diseases. Another area is that of organ transplantation in which the immune system must be prevented from rejecting the foreign organ. This

is achieved by selective inhibition of the cells responsible for the rejection reaction without affecting the rest of the immune system. Cyclosporin, which was isolated by Sandoz research workers in 1970, is the first substance that selectively inhibits the activation of certain immunocompetent cells. This enabled a decisive step forward to be made in transplantation surgery, particularly in the field of heart and kidney transplantation. It took 12 years for the substance to be developed into Sandimmun, the drug first registered in Switzerland. This drug is now widely used in organ transplantation.

Sandoz researchers are also working in the field of autoimmune diseases, which include diabetes, multiple sclerosis, and severe forms of psoriasis.

The agricultural division of Sandoz has expertise in plant tissue culture and cloning. The acquisition of Zoecon, US, strengthened the position in agricultural technology. The molybdenum chelating peptide produced by *Bacillus thuringiensis* is commercially available from Sandoz as an insecticide for *Lepidoptera* larvae.

Other Companies. In the field of nutrition, Nestlé S.A., the biggest Swiss company, was one of the first (together with Exxon) to produce single-cell protein. However, the project was abandoned, as uneconomic, as was similar R&D on food additives and colorants from microbes, because such products require extensive toxicological testing.

Now Nestlé is applying fermentation and continuous culture know-how to research in microbial physiology, particularly with *Lactobacilli* that are permitted in foods. Also, the company has set up a genetic engineering facility and is concentrating on improving their milk products, infant feeding formulae, etc., applying modern molecular biological techniques.

In the more traditional biotechnologies, Attisholz Ltd., the largest Swiss pulp mill established in 1870, produces Candida yeast and ethanol from sulphite liquor wastes. The yeast is mainly for feed but a small part is used as a food additive. Attisholz has developed a continuous fermenter of the airlift type. It is also, as a spin-off, marketing its know-how in the field of environmental biotechnology and wastewater treatment.

The Swiss mechanical industry is represented in the sector of biotechnological equipment by a number of well-known companies, holding a strong position worldwide. Names like Chemap, Bio-engineering, MBR, and Giovanola stand for fermenters, whole plants, and even process know-how ranging from lab-scale units to large production equipment.

The most traditional biotechnology, beer manufacture, is very well represented in Switzerland by three large breweries and some 25 small companies. However, their brands are only of national or local importance.

Austria

Industry

Austria has an old tradition in Biotechnology dating back to the era in the field of yeast and alcohol fermentation on a technical scale. The old "Vienna Skimming Process", which forms the basis of the worldwide know-how of Vogelbusch today, was introduced in 1849 by Mautner and Reininghaus. Another famous bioprocess is carried out by Biochemie Kundl, which has produced Penicillin G since 1946 and, using its own patents, Penicillin V (Ospen R) since 1952.

Biochemie Kundl, now affiliated with Sandoz, the Swiss Pharmaceutical Company, is engaged in the production of several antibiotics (5-percent world production in Penicillin, Cephalosporin, Streptomycin, Chloramphenicol, Tetracyclin, Pleuromulin), alkaloids, hormones, and enzymes. This company developed its own system of biological wastewater treatment. The research from their genetic laboratories led to the biotechnological production of the antiviral alpha-interferon and the immune-modulating interleukin-2 on an industrial

scale. The first stages of the immune suppressant Cyclosporin A are fermented at Biochemie Kundl.

Vogelbusch still holds its main position in the production of baker's and fodder yeasts on different media, worldwide as well as ethanol production including distillation and filtration (for example, recythyrryse vacuum filtration for the production of active dry yeast). Other areas of important Vogelbusch activities are the production of acetic acid and the innovation (in collaboration with the engineering center in Böhlen, East Germany) of the plunging jet loop reactor (VB-IZ-12). The company is also now involved in membrane technology. Research is concentrated on the following topics:

- Dehydration of solvents by pervaporation
- Dealcoholization of mash, wine, and beer by pervaporation
- Biomass recirculation by microfiltration in continuous fermentation processes
- Biomass concentration (product removal/purification)
- Clarification and concentration of fruit juices

- Seawater desalination
- Membrane and module development
- Organization of engineering and operation data.

Many of these projects are carried out in collaboration with scientists at the Technical University of Vienna.

Two other firms of some importance are Wagner-Biro (yeast and ethanol production, design of bench- and pilot-scale fermenters; biodegradation of pentoses for the production of fodder yeast, fats, and solvents) and Steyermühl (cellulase production with *Trichoderma reesei* for enzymatic hydrolysis of paper and straw in pilot scale).

Chemie Linz AG is a large, state-owned chemical plant and has biotechnological activities in biopolymers (polyhydroxybutyric acid). The company has also become involved in two other biotechnology projects: transferring genes for herbicide and pesticide resistance into crop plants, and using biological catalysts to produce plant-protection components and pharmaceuticals.

Jungbunzlauer uses pentoses for the production of citric acid, and Hemoderivate (in Vienna) is an important manufacturer of vaccines and blood derivatives.

The Austrian mechanical industry is represented in the sector of biotechnological equipment by the Arbeitsgemeinschaft für Biotechnologie for the design of fermentation sensors, computer control systems and general consulting for bioprocessing and the Anstalt für Strömungsmaschinen, which specializes in the design of pilot- and technical-scale fermenters and yeast processing.

The Austrian position is relatively weak in enzyme technology, amino acid production, fodder proteins, leaching, downstream processing, cell tissue cultures, and fermentation apparatus with auxiliary equipment.

Environmental Biotechnology. In this field, biotechnology efforts are concentrated on anaerobic plants for biogas production from agricultural waste and aerobic wastewater treatment with conventional activated sludge systems. The latter includes a new design of tubular reactor and trickling filter. The following companies can be mentioned: Andritz-Ruthner (membrane fermentation, reactor design, biological wastewater treatment, biological air filters) and Biologische Verfahrenstechnik (biogas fermenters and anaerobic wastewater treatment).

Government

Since 1982, the Ministry of Science and Research has been engaged in the coordination of biotechnological activities. The main aim of the committee is the coordination and enhancement of collaboration between industries and universities in Austria.

A project team, "Biotechnology and Gene-technique," elaborated an integrated concept for research in Austria recommending special support for the bioprocess technologies (fundamentals of reactor kinetics and

process control for fermentation and enzyme production) and several biological disciplines (in plant and animal cell culture, strain collections). Unfortunately, the government support for research and development is only 1.3 percent of the gross national product, a much lower figure than in the US or West Germany. The estimate for 1990 is still only 1.5 percent GNP, coming in roughly equal parts from the state and industry.

Universities

The microbiology tradition in Austrian universities goes back to 1897 when the first institute for "Technical Microbiology" was founded at the Technical University of Vienna. Complete courses in biotechnology were among the first in Europe when, in 1970, special branches with 2.5 years of study were incorporated into the existing studies on chemical technology at the Technological Universities of Graz and Vienna and at the University of Agriculture (UA).

The research programs at the Technological University of Vienna deal primarily with industrial fermentations including computerized analysis and controls, isolation and purification of enzymes, biological cellulose degradation, and soil microbiology.

The main research activities at the Agricultural University of Vienna are waste recycling, ethanol, and yeast production including software in fermentation control, food and enzyme technology, monoclonal antibodies for diagnosis, genetic engineering for strain improvement, and the culturing of plant cells.

At the Graz University of Technology, research is focused on bioprocess engineering, biopolymer production, environmental biotechnology, plant cell culture for insecticides, and strain improvement by genetic engineering. The University of Graz is engaged in basic research on enzyme characterization, cellulose degradation, and analysis of raw materials.

Institutes

The Austrian research center, Seibersdorf, especially the Institute for Biology and Agricultural Sciences, has its activities in the following fields:

- Optimization of the production of hybridomas
- Isolation of monoclonal antibodies and tumor antigens
- Culture and fusion of protoplasts
- Selection of special yeast strains
- Development of microprocessor-controlled instruments for environmental technology.

Several institutes are engaged in related fields of genetic engineering in research and education: the Universities of Vienna, Innsbruck, Salzburg; the Techno-

logical University of Graz; the Austrian Academy of Sciences; the Sandoz Research Institute in Vienna, and the E. Boehringer Institute.

The Austrian Research Institute of Molecular Pathology (IMP) was officially inaugurated in Vienna in May 1988. The new "biozentrum" is sponsored jointly by Genentech (US), Boehringer Ingelheim (West Germany), and the city of Vienna. The city of Vienna has contributed 20 percent of the \$35 million for the first 5 years. Although the ultimate purpose of IMP is to produce product ideas for the two companies in the area of cancer therapy, the institute's brief is to carry out basic research. The companies believe IMP is the first basic research institute to be set up as a joint industrial venture.

Professor Max Birnstiel, formerly at the ETH in Zurich, Switzerland, is the Director of IMP. The scientific advisory board of IMP includes Dr. David Baltimore, nobel laureate and Director of the Whitehead Institute in Cambridge, Massachusetts. Five senior scientists have now been recruited within Europe and all will be in post by the end of 1988. Among the attractions for new staff are high salaries, generous transferable pensions, and the provision of a service department for protein and DNA sequencing. Senior appointments are for 2 years plus 3 years rolling tenure. While IMP has an initial 12-year life-span, it can be considered as "permanent," according to Clifford Orent, Genentech's director of international operations. Permanency, however, is likely to depend on the successful emergence of product ideas.

The following section deals with the various research projects at universities and research institutes in Austria. The scientists listed for these research topics are project leaders.

M. Kadletz and coworkers (Department of Surgery, University of Vienna) are working on improving biocompatibility of vascular graft materials by *in vivo* lining with autologous endothelial cells. Kadletz and her group established human saphenous vein endothelial cultures, and cells were seeded onto artificial grafts. According to Kadletz, the results of these studies indicate that *in vitro* lining offers a promising technique to improve the biogenic surface of artificial vascular grafts and that it could soon develop into clinical routine wherever a cell laboratory is available. (See ONRL Report 7-032-C.)

O. Wolfbeis (Institute of Organic Chemistry, Karl Franzens University of Graz) and his group are working on fiber-optic sensors and have developed an optical sensor for hydrogen peroxides (HP) based on the finding that HP is able to penetrate polymer membranes. These investigators are also working on an optosensor for alcohol. Wolfbeis and his very productive group have also constructed an oxygen fiber-sensor that is based on the measurement of the decay-time fluorescence as a function of oxygen pressure. (See ESN 41-10-544.)

At the same university, but in the Institute (Department) of Physical Chemistry, J. Schurz and his team are engaged in molecular biology and gene technology studies. E. Schaunstein and coworkers in the Natural Science Faculty, Institute of Biochemistry, are also carrying out studies in the same areas. G. Hoegenauer, Institute of Microbiology, and his colleagues deal with research in gene technology and studies in microbiology utilizing prokaryotes.

At the Medical Faculty of the Karl Franzens University of Graz, W. Rosenkranz and A. Holasek head teams involved in human genetic studies and various aspects of medical biology.

F. Poltau and his group (Erzherzog [Archduke] Johann University of Graz, Technical-Natural Science Faculty, Institute of Biochemistry and Food Chemistry) are engaged in studies of food chemistry and technology as well as biochemical research. At the same university, in the Institute for Biotechnology and Microbiology, R.M. Lafferty and colleagues are carrying out research in the areas of microbiology and biotechnology including microbial degradation of ligninsulfonates.

E. Heinzle and colleagues (Research Institute Johanneum, Laboratory of Biotechnology and Biochemistry) are engaged in studies of the utilization of raw materials (cellulose), production of biopolymers, environmental biotechnology, and methods for the development of biotechnological products.

P. Laggner (Austrian Academy of Science, Institute for X-Ray Microstructure) and coworkers are concerned with studies of the fine structure of the formation of supramolecular complexes with specialized structures of small organic molecules and their biological function (membranes, micelles) and thermodynamic and spectroscopic methods.

G. Wick and colleagues (Leopold Franzens University of Innsbruck, Medical Faculty, Institute of General and Experimental Pathology) are working in the areas of molecular biology and gene technology with emphasis on human autoimmune diseases. In the same university (Institute of Medical Biology and Genetics), Monika Schweiger and her group are involved in human genetic studies. In the Institute of Biochemistry, Manfred Schweiger and colleagues are studying hereditary and molecular mechanisms of DNA repair using molecular biological techniques and gene technology. G. Stoeffler (Institute of Microbiology) and his colleagues are involved in microbiology and biotechnology as well as biohydrometallurgy. O. Blobler (Institute for Radiochemistry) and coworkers are involved in biomass processes for enzymatic carbohydrate and cell material production.

W. Beck (Federal Experimental Research Institute of Linz) and colleagues are involved in work in agrarian

sciences including research on antibiotics, pesticides, and mycotoxins.

The Austrian Academy of Science, Institute of Molecular Biology, Salzburg, has three research divisions:

- Chemistry, directed by G. Kreil. The research includes biosynthesis of biologically active peptides in amphibian skin, structure of cDNA and genes, characterization of the enzymatic process, gene transfer in plants, isolation of genes, and regulation of developmental processes in plants.
- Physics, headed by J.V. Small. Research involves immunocytochemistry of muscle and other cells and investigation of components of the cytoskeleton.
- Biology, directed by K. Kratochwill. Projects include studies of the role of collagen 1 in the organ development of mouse embryos and cell/cell interaction during brain development.

A. Jungbauer (Institute of Applied Microbiology, University of Agriculture of Vienna) and colleagues are engaged in studies of downstream processing (purification) of animal cell products. They developed an in-line steam-sterilizable process line for the purification of animal cell products since biologicals produced by transformed cells must be recovered in a closed sterilizable process line. (See *ESNIB* 88-02:5.) In the same institute, H. Katinger and coworkers are concerned with methods for scale-up engineering in animal cell technology.

P. Gunhold (Federal Experimental Institute of Agricultural Chemistry, Vienna) and colleagues are carrying out studies of plant nutrition, soil chemistry, animal nutrition, and fertilization methods.

F. Paschke and coworkers (Ludwig Boltzmann Institute for Biochemistry, Vienna) are working on biotechnological methods.

Scientists at the Sandoz Research Institute in Vienna are carrying out studies in biochemistry, molecular biology, and gene technology. There are three research divisions at Sandoz:

- Immunostimulation (A. Stuetz and E. Lichl). These investigators are working on immunomodulators, isolation and characterization of cytokines, and

pharmacological evaluation of compounds with respect to hematopoiesis and increased resistance to infection (Rhinovirus) and tumors (cancer).

- Antibodies (H. Loibner and H. Bachmayer). These studies involve development of monoclonal antibodies for use in therapy of malignant solid tumors, development of anti-idiotypic antibodies (both polyclonal and monoclonal) as potential vaccines for prophylaxis and therapy of malignant tumors, and isolation and characterization of tumor antigens.
- Dermatology (A. Stuetz and H. Mieth). The dermatology studies include tests for synthetic and natural products for treatment of infections and for fungus in humans.

M. Roehr (Institute of Biochemical Technology and Microbiology, Technical-Natural Science Faculty, Technical University of Vienna) and colleagues are engaged in biochemical, molecular biology studies, and gene technology. Also in the same university, at the Institute of Food Chemistry and Technology, J. Washuettl and colleagues are engaged in studies of food chemistry and food technology.

C. Steffen (Department of Immunology, Medical Faculty, University of Vienna) and coworkers are emphasizing studies on immunological gene technology. At the Institute of Molecular Biology, E. Wintersberger and colleagues are engaged in research in molecular biology and gene technology.

W. Ruecker and colleagues (Institute of Pharmacology, Natural Science Faculty, University of Vienna) are working with plant cell cultures and products obtained from such cultures using methods of molecular biology and gene technology.

E. Bamberg and his group (Institute of Biochemistry, Veterinary Medical University of Vienna) are developing radioimmunoassay and enzymatic techniques for pregnancy tests in animals. At the same university, at the Institute of Animal Research and Genetics, W. Schleger and his groups are concerned with genetic studies in animals.

Italy

Up to 1986, Italy had been remiss in its coordination of bioengineering research in terms of adequate financing and its readiness to finance by way of venture capital. Now the situation appears to be changing. The government has become conscious of this important area of in-

novation. Industry has already progressed further. Here collaboration exists with US and British firms.

In 1986, a new biotechnology association, the National Association for the Development of Biotechnology (ASSOBIOTEC), was founded. Any company interested in biotechnology products and processes in Italy can join

this association. Federchimica, which had already shown its interest in biotechnology products and processes in the new biotechnology seeks to help out those companies that work or will work in this field, in solving technical, economic, and legal problems. This goal will be achieved by participating with the appropriate ministries for the formulation of national research and development programs by preparing proposals favoring this type of new technology through financial and tax assistance, and which follow regulations issued for the production and marketing of substances resulting from biotechnology. The association also concerns itself with the development and execution of EC-sponsored programs.

Industrial biotechnology in Italy dates back to the Pasteur era for a range of classical products such as wine, dairy products, ethanol, baker's yeast, vinegar, and citric acid. After World War II, Italy was one of the first European countries to develop antibiotic production through the activities of the Istituto Superiore della Sanità—founded in 1948—under the leadership of the Nobel laureate, E.B. Chain. As a result, antibiotic production was started in the 1950's at Leo, Squibb, and Farmalita. With favorable liberal patent legislation in drugs, the number of companies operating in this field increased in the 1960's. A great deal of original research resulted in many new discoveries including rifamycin and derivatives at Lepetit, Daunorubicin, and Doxorubicin at Farmalita, and fermentation processes for the production of ergot alkaloids.

Industry

Farmalita-Carlo Erba SpA, the largest Italian pharmaceutical enterprise is now using bioengineering for the manufacture of a human hormone, calcitonin, which is important for the assimilation of calcium into bone substance. It was developed jointly by the US company, Unigene Laboratories, and the Lark SpA in Mailand. Lark, like Farmalita, belongs to the Erbamont NV, the common pharma-holding of the Italian Montedison SpA (73 percent) and the US Hercules Inc. (13 percent). Farmalita is also involved with cancer chemotherapy, collaborating with the US research firm, Cytogen Corp. This company specializes in the area of monoclonal antibodies and has experience in their applications to produce diagnostic means and substances which conduct the pharmaceutically active substances into the diseased cells.

The enzyme field is ruled by Soreni Co. — a research organization belonging to ENI — which has obtained several patents concerning enzymes entrapped in fibers.

Four companies that are especially advanced in biotechnological R&D are Farmalita, which is active in protein chemistry and genetic engineering, Sclavo SpA (protein chemistry, recombinant DNA, hybridoma technology, molecular biology, and molecular immunology),

and the Gruppo Lepetit SpA (genetic engineering and monoclonal antibodies) as well as Sorin Biomedica SpA (protein chemistry, monoclonal antibodies, and immobilization of enzymes). Another enterprise involved in biotechnology is the Industrie Farmaceutiche Menarini in Florence. For its bioengineering research, this company is expanding its research center in Pomezia, south of Rome. They are working on the production of beta-interferon, the plasminogen activator (tPA) and, in competition with Farmalita, on calcitonin.

Sclavo, the pharmaceutical enterprise of the government EniChem SpA is not only carrying out bioengineering research in the above-mentioned areas, but also research in fermentation, in the production of monoclonal antibodies, in cell cultures and in gene expression. Sclavo has already come on the market with monoclonal antibodies and special proteins of the cytoskeleton, the most important antibodies for immuno-diagnostics, as well as with atoxic diphtheria toxin, human beta-interferon and beta- and gamma-interferon from yeast and human cell cultures.

The Dow subsidiary, Lepetit, like the Genetic Institute of the National Research Council (CNR) in Pavia, is involved with the production of urokinase. This anticoagulant is obtained by *in vitro* cloning.

The Sorin Biomedica, which belongs to the Fiat conglomerate, is specialized in the production of artificial organs as well as diagnostic systems. The company is also involved in the development of a diagnostic system for Hepatitis B. One of the main target directions is the development of immuno-diagnostic reagents and methods. Together with Farmalita and Sciavo, Sorin Biomedica participates in the Tecnobimedia, a company for applied research founded by the government special credit institute, IMI.

The following companies are also conducting bioengineering research:

- The Recordati SpA (monoclonal antibodies)
- The international Ares-Serono group with its Istituto di Ricerca Cesare Serono (genetic engineering)
- The Soc. Prodotti Antibiotici SpA, a subsidiary of the US G.D. Searle & Co., but now owned by Monsanto (immobilization of enzymes)
- The government ENI group.

The ENI group's research company, EniRicerche SpA, also does research in protein chemistry and plant-cell cultures. Its predecessor firm, Assoreni, received the first Italian gene engineering patent in 1983 for protein production by means of soil bacteria. The EniChem Agricoltura SpA, a specialty company for fertilizers and pesticides cooperates with the Fererconsorzio, an umbrella organization of agricultural societies which is spending about to 25 billion lira (\$18.2 million) over the next 3 years

for bioengineering research products concerning plant growth and plant protection.

Government

The government is interested in biotechnology through the Ministry of Scientific Research and the National Research Council (CNR). This body is heavily involved in feasibility studies on the production of basic chemicals by the new biotechnologies. A number of companies, including Soreni, are state-owned through the ENI.

The Italian biotechnology lag (as compared with countries such as West Germany, the UK, Sweden, France, and the Netherlands) does not so much concern the engagement of industry but coordination based on specific objectives and the corresponding financial subsidies by the government. The government has finally recognized this and in 1985 founded the National Board for Bioengineering (Comitato Nazionale di Biotecnologia, CNB). The objectives are: the application of bioengineering methods in the pharmaceutical industry and in agriculture, collaboration both on an international level as well as with the Institute for Gene Engineering, which UNIDO has founded in Trieste, and the special funding of interdisciplinary projects. The other common market countries are the primary cooperation partners. However, one of the first specific results was a contract between the Italian Ministry of Health and the US Food and Drug Administration (FDA). This provides for a regular exchange of information concerning research, production, and the registration of new drugs obtained by bioengineering methods as well as bioengineering process technology.

Recently, several billion lira have been made available by the government agencies for biotechnology research, with an emphasis on genetic engineering. To be eligible for this funding, the research must be coordinated between the industrial enterprises and the universities as well as the public and private sectors. Besides the National Research Council (CNR) other agencies include the National Society for Alternative Energies (ENEA), the Mialand Cancer Research Institute, the Pharmacological Research Institute Negri, and the Grain Research Institute Casaccia.

Universities

The universities mainly involved in biotechnology are those at: Pavia, Naples, Milan, Rome, Bologna, and Genoa. Only partial biotechnology courses in the basic sciences are given. The main research areas covered by the universities are genetic engineering, bioengineering, including model studies, ethanol, bio-methanation, dairy products, and pharmaceuticals.

Verona University has recently introduced a course of studies for bioengineering and is striving to erect a science park similar to the pattern followed in other European countries as well as in the US. In the pharmaceutical area, Verona University hopes to be able to profit from enterprises resident in the region – especially Glaxo in Verona and Fidia (in Abano Terme), whose research is focused on neurobiology.

F. Parenti and coworkers (Lepetit International Research Center, Milan) are concerned with the development of methods for searching for novel glycopeptide antibiotics. They have recently developed a method for screening of these compounds which involves immobilization of the D-alanyl-D-alanine residue of bacterial cell wall on an insoluble matrix such as cellulose, sepharose, glass, etc. This compound was found to be a powerful probe for the detection of glycopeptide antibiotics even at low concentration and in the presence of other antibacterial activities, (see *ESN-41-2:63*).

M. Soria and his group (Biotechnological Research, Farmalita Carlo Erbe, Milan) are concerned with studies on recombinant strategies in the development of targeted pharmaceuticals. One of their projects deals with the chemical conjugation of plant and bacterial toxins to monoclonal antibodies to obtain immunotoxins.

G. Carrea and his group at CNR, Milan, are involved in studies of steroid transformation by immobilized steroid dehydrogenases.

R. Rappuoli and coworkers at the Sclavo Research Center, Sienna, are involved in epitope mapping of the S1 subunit of pertussis toxin by monoclonal antibodies (Mabs) and have obtained several Mabs which are being used for characterization of the functional and antigenic properties of the S1 subunit. (See ONRL Report 8-001-C.)

P.G. Righetti and his group (Department of Biomedical Sciences and Technology, University of Milan) are working on large-scale electrophoresis for protein purification using isoelectric focusing. They have developed a modified version of isoelectric focusing which provides high rates of sample processing, purification, and recoveries.

A. Fontana (Institute of Organic Chemistry, Biopolymer Research Center, University of Padua) and his group are involved in studies of thermophilic enzymes. The interest of biotechnologists in thermophilic microorganisms is their potential use in biotechnological processes because enzymes from these microorganisms are much more resistant to heat and other protein-denaturing agents than their counterparts from mesophilic sources. (See ONRL Report C-1-85.)

The formation, reactions, and toxicity of aldehydes produced during the course of lipid peroxidation are being studied by A. Benedetti and coworkers (Institute of

General Pathology, University of Sienna). (See ESN-41-5:239.)

L. Cazzador (LADSEB-CNR), Padova and co-workers are engaged in studies of bioreactor control and modeling using a simulation program based on a structured model of budding yeast. This is a collaborative project with L. Mariani (Department of Electronics and Information, University of Padova) and L. Alberghina and E. Martagani (Department of Physiology and General Biochemistry, University of Milan).

Research on methodologies for cell culture, cryopreservation, mutant isolation, and transformation is being carried out by M. Terzi and his group at the CNR unit in Pisa.

In the area of biomaterials, M. Grattarola and co-workers (Department of Biophysical and Electrical Engineering, SGS Microelectronics, Genoa) are engaged in studies of cell adhesion to silicon substrate. According to Grattarola, the controlled growth of cellular assemblies on integrated circuits is a challenging goal with far-reaching implication in both biology and electronics. (See ESNIB 88-01:16 and ONRL Report 7-032-C.)

P. Costantino and coworkers (Department of Genetics and Molecular Biology, University of Rome) carry

out research aimed at the definition of the role of auxin, *A. rhizogenes* auxin genes, and TL-DNA genes in the induction of hairy roots. This work involves mapping and structural characterization of Ri-plasmids.

Institutes

In 1948, the Istituto Superiore della Sante, with the help of E.B. Chain became involved in biotechnology and thereafter, the research institute called Centro Internazionale di Chimica Microbiologica, was created in Rome. The research in this center has included the following fields:

- Biosynthesis of penicillins
- Alkaloid production from *Claviceps purpurea*
- Single-cell protein (SCP) and organic acid production
- Studies on biotechnology and bioengineering (mass transfer, continuous fermentation, and bioreactor configurations).

By the 1950's, the center operated one of the largest biotechnology pilot plants in Europe, with fermentors ranging from 5 up to 3,000 liters.

Spain

Industry

Biotechnology in Spain, as represented by wine-making, predates the Pasteur era. Sherry wines from Spain's southern provinces are particularly renowned.

In the antibiotic period, the fermentation industry advanced greatly, encouraged by government support. Two antibiotic companies, CEPA in Madrid and Antibiotics S.A. in Leon, were established in 1949, and since then two novel antibiotics – phosphomycin and Mirocina-17 have been developed. This industrial expansion was favored by the Spanish patent legislation. Various other fermentation industries are developing at present, such as for the production of amino acids, organic acids, alcohol, and yeast and for the transformation of steroids. The local pharmaceutical industry was stimulated to some extent by restrictions on imports. The brewing industries have flourished since the 1950's and many new breweries are scattered over the country, mainly in the cities, to serve local markets. The dairy and other food products fields have also been expanded considerably during recent decades. Two petrochemical industries have recently become involved in the biotechnological field. CEPA is engaged in the development of biologically active sub-

stances (steroids) and EMPETROL has started activities in the area of immunology.

Environmental Biotechnology. Municipal wastewater treatment that leads to energy recovery in the form of biogas has found general application in nearly all major cities. Study programs and projects oriented to the use of residual agricultural wastes for biological energy production have been underway since 1978 by ENADIMSA in cooperation with one of the institutes of the National Research Council in Seville.

Universities

A great deal of biotechnological research in the universities is directed towards sewage treatment, production and conservation of food and energy, production of basic chemicals, and biomedicine. Some of this research involves genetic engineering. In this respect can be mentioned the Universities of Barcelona, Madrid, Valencia, Seville, and Cordoba, especially in the Departments of Chemistry, Medicine, Pharmacy, Veterinary Science, and Biology. As far as biotechnology courses are concerned, mainly only partial courses in the biological

sciences, pharmacy, and chemistry are given in the Departments of Microbiology and Chemical Technology at 15 universities. However, biotechnology training is now being greatly expanded, as will be discussed below.

Institutes

The National Research Council of Spain (CSIC) has a number of Institutes, one of which deals directly with industrial biotechnological research on topics which include alcoholic beverages and single-cell protein (SCP) production. This institute is located in Arganda del Rey (near Madrid), close to the National School for Brewing and Malting. Recently, a closer collaboration between the brewing industries and this CSIC Institute for Industrial Fermentation has been established. Some other CSIC Institutes in Seville and Valencia are working in other fields of applied biotechnology, including the anaerobic digestion of waste and food technology. The CSIC Institutes for Molecular Biology and for Enzymology and Molecular Pathology are located in Madrid.

Government

Three ministries are interested in biotechnology: the Ministry of Education and Science, the Ministry of Agriculture, and the Ministry of Industry and Energy. The latter Ministry manages the Center of Technological Development of Spain, which aims at improving cooperation between industry, research institutes, and universities.

In order to redress some of the deficiencies in various areas of biotechnology, the National Plan for Research (NPR) was finally approved a few months ago by the Spanish government. The plan covers the period 1988 to 1991 and is intended to coordinate the programs of the various ministries involved in research, and to increase expenditure on research from 0.7 percent of the gross national product to 1.2 percent by 1991. It also proposed to increase by about 50 percent the number of researchers.

The NPR requires the expenditure of more than \$5 billion in 4 years—though only a third of this represents actual funding of research in Spanish government and industrial laboratories. The budget also has to cover Spanish participation in international programs and administrative expenses. The plan includes programs aimed at encouraging high-quality basic research and at stimulating international cooperation.

The most important element is a group of 23 programs in which efforts will be concentrated in defined areas. Production technology (microelectronics, robotics, new materials, etc.) and telecommunications account for half the total spending. The natural resources and agrobiotechnology programs include food technology, agriculture, and geological resources. Another important program is biotechnology, in which most of the funding

will go to the new Center for Biotechnology in Madrid. In the opinion of the Secretary General of the NPR, Dr. Emilio Munoz, the plan provides insufficient funds for social and human sciences and for health research, but annual revisions of the plan will make it possible to better define and finance the weakest areas. Another imponderable is the response of private industry. Few Spanish companies have so far shown an interest in adopting new technologies, and unless things change, both the results of research and the trained personnel may be wasted.

In addition to a substantial increase in training of personnel in biotechnology and acquisition of equipment and instrumentation, the National Biotechnology Center has set up priority research areas. These are:

- Development of systems for genetic manipulation in microorganisms—cultures of plant and animal cells in relation to their potential application in biotechnology and biochemical and enzyme technology processes with potential application in biotechnology
- Agriculture and nutrition—genetic improvement of plant species, nitrogen binding, improvement of fermentation processes (wines, dairy, fermented beverages), improvement of starter microbiological cultures, bioconversion of lignocellulose materials, biomass, and pesticides.

The following paragraphs deal with a limited number of projects and scientists involved in biotechnology-related projects in Spain. The "limited number" is due in part to the fact that, as apparent from the above, Spain has lagged far behind other European countries in getting into the mainstream of the new biotechnology research and also due to Spain's previously insufficient funding of biotechnology.

Center of Molecular Biology, Cantoblanco (Madrid). This center is located on the campus of the University Autonomous of Madrid. Although the Center is affiliated with the university, its primary function is research. It was organized in 1975 with the aim of providing an interdisciplinary research center. (For further information see *ESN* 40-4:117.)

A. Machado and coworkers are studying the regulatory role of the NADPH/NADP ratio in modulating metabolic processes. Their studies have shown that NADP isocitrate dehydrogenase inhibition and glyoxylic acid-cycle function are modulated by the NADPH/NADP ratio. These investigators have used *Tetrahymena pyriformis* and *E. coli* for their studies. Machado and his group have also investigated the age-dependent behavior of a number of enzymes linked to energy metabolism during the lifetime of the rat in three organs: liver, brain, and heart.

C. Alonso and his group are investigating the induction and distribution of chromosomal transcripts in the

polytene chromosomes of *Drosophila melanogaster* and *Drosophila hydei* by indirect immunofluorescence using an antiserum directed against DNA/RNA hybrids.

J. Modolell and coworkers are studying various aspects of development in molecular terms, using *Drosophila melanogaster* (fruit fly) as a model system.

E. Vinuela and colleagues have been carrying out studies of the African Swine Fever (ASF) virus.

G. Ramirez and his group have been studying neurotransmission in the developing chick visual system. Another study by this group is the characterization of the general properties and developmental profiles of specific binding sites for excitatory (putative) amino acid transmitters (L-glutamate, L-aspartate, kainic acid, and N-methyl-D-aspartate) in the chick optic tectum. These researchers are also involved in a similar project involving inhibitory amino acid transmitter receptors. Their ultimate goal is to establish the possible existence of some kind of developmental coordination between excitatory (permissive) and inhibitory (signal-blocking) synaptic mechanisms. Ramirez and coworkers have also made monoclonal antibodies against the larval nervous system and used the antibodies to identify the genes that code for specific antigens in the larval nervous system. They have also recently found the presence of enkaphalin in the fruit fly which makes it possible to study peptide neurobiology in a relatively simple model system and to study the regulation of the expression of genes coding for these neuropeptides.

G. Morata and coworkers are involved in studies to determine the genetic components of the mechanisms governing the developmental processes of *Drosophila*.

J. Jiminez and colleagues are studying the expression of the Tn 601 (903) in the yeast *Saccharomyces cerevisiae*. This transposable element determines bacterial resistance to G148 and other aminoglycoside antibiotics.

L. Carrasco and coworkers are investigating the biology of animal virus infection. The infection of an animal cell by a virus normally leads to interference with cellular metabolism. For picornavirus (EMC virus and polio virus), these researchers have analyzed the effect of viral infection on a number of cellular parameters. The Carrasco group has developed new systems for the assay and study of compounds with antiviral activity. The use of these systems has led to the identification of several new molecules with antiherpes activity and almost devoid of toxicity both *in vitro* and *in vivo*.

M.A.R. Marcos and colleagues are investigating mutual cell interactions and the selection of immune repertoire which may play a role in the development of autoimmunity.

Some of the other research projects at the Center of Molecular Biology are:

- Energetic homeostasis during the perinatal period and metabolic relationships during the lactogenic process (J.M. Medina)
- Regulation of aerobic glycolysis in normal and tumor cells (J. Carrascosa)
- Molecular pathology of mammalian amino acid etiology and pathogenesis of hyperglycemia (P. Garcia)
- Post-translational modification of mammalian brain proteins (R. Manso)
- Ribosomal structure and function (F. Juan)
- Structure and function of proteins (M. Fernandez-Puentes)
- Replication and morphogenesis of bacteriophage O 29 from *Bacillus subtilis* (J.M. Hermosa)
- Regulation of gene expression at the translational level in eukaryotic cells (J.M. Sierra)
- Hormonal regulation of gene expression (A. Niets)
- Microtubules (J. Avila)
- Genetic variability of RNA viruses (E. Domingo).

Work at Other Research Organizations. C. De La Torre and coworkers (Center for Investigative Biology, CSIS, Madrid) are studying methods for altering the pattern of gene expression in the cell cycle of root meristem cells of *Allium cepa* L. bulbs.

J. Mata-Alvarez, P. Liabres, and P. Clapes (Department of Chemical Engineering and Metallurgy, University of Barcelona) are studying the use of spreadsheet programs in biotechnology. According to these investigators, spreadsheets provide a convenient way of archiving data, organizing medium-size databases, and performing mathematical operations. They do not require any special programming expertise and are very easy to use. Neat reports containing text, tables, and graphs can be produced and, importantly, spreadsheets make quick work of mathematical model building and testing. The most advanced of them can perform iterated calculations and, through the macro facilities, can perform tasks which previously required programming in FORTRAN or BASIC.

F. Valera, F. Ayata, J. Lopez-Sartin, and M. Poch (Unit of Chemical Engineering, Department of Chemistry, University Autonoma of Barcelona) are studying extracellular lipase production by *Candida rugosa* growth. The main growth parameters, and the lipase activity in the culture broth were determined in order to identify the maximum of enzymatic activity. The effect of lipid material and size and growth phase of the inoculum on enzymatic production were studied. It was found that maximum extracellular lipase activity was associated with an increase in enzyme production when the number of viable cells started to decrease. Interest in lipase enzymes has increased greatly in the past few years due to their potential application in fat splitting as well as in the synthesis of glycerides. The advantages of the enzymatic hy-

drolisis over the chemical process are lower energy requirements and higher quality of the obtained product.

M. Diaz (Department of Chemical Engineering, University of Oviedo) and coworkers are investigating three-phase extractive fermentation. According to Diaz, fermentation with simultaneous extraction of a product inside the fermentor is an attractive alternative where substrates or products otherwise inhibit processes.

F.G. Sanchez and coworkers (Department of Analytical Chemistry, Faculty of Science, University of Malaga) are studying the fluorimetric determination of procaine in pharmaceutical preparations. Procaine is an amino ester used as a local anesthetic. Due to its wide medical application, several methods for the quantitative determination of this compound and its salts in pharmaceutical preparations are available. The present work was done by Sanchez and coworkers to elucidate the luminescence behavior of procaine when modifying the environment, both by changing the solvent used or by using surfactants or beta-cyclodextrin in order to improve the sensitivity of the fluorimetric assay. (See ESN 41-10:544.)

J.F. Martin and his group (Department of Genetic Ecology and Microbiology, University of Leon) are carrying out studies of the cloning of genes involved in cephalosporin biosynthesis. According to Martin, fermentations for the production of antibiotics have provided one of the cornerstones of biotechnology in the twentieth century. However, despite tremendous improvements in fermentation yields, the molecular mech-

anisms of antibiotic synthesis are poorly understood. Martin thinks that the isolation of genes coding for enzymes involved in antibiotic pathways is an important step towards understanding of these molecular mechanisms. Martin and his group are also investigating cloning systems in amino acid-producing *Cornybacteria*. Members of the genera *Cornybacterium* and *Brevibacterium* are widely used in the production of amino acids and nucleotides, as well as in the bioconversion of steroids and in the cheese industry. In the last few years, cloning vectors have been developed in *Cornybacteria* using replicons from endogenous plasmids and antibiotic resistance genes as selectable makers.

Promoter-probe plasmids, high-expression vectors, transposon mutagenesis, and *in vitro* systems for RNA and protein synthesis are now being developed. Martin thinks that the availability of cloned genes and transformation and transfection systems in *Cornybacteria* will facilitate gene amplification studies, and the removal of bottlenecks in the amino acid biosynthetic pathways, thus leading to increased production of amino acids.

M.A. Murado and coworkers (Institute of Marine Investigation, CSIC, Vego) are studying mixed microfungus-yeast cultures in the degradation of amylaceous wastes and interactions affecting amylolytic activity. These researchers are investigating criteria in the selection of amylolytic microorganisms for the mixed culture with nonamylolytic yeasts and the growth of several mixed cultures on mussel-processing wastes.

Portugal

Industry

Traditional biotechnology products from the pre-antibiotic era such as wine, beer, and other alcoholic beverages have been produced in Portugal for a very long time. Its Port wine and Madeira wine were appreciated internationally. Dairy products including cheese and yogurt are produced chiefly for internal consumption. One traditional cheese (Serra) is still made with plant proteases. Other food products are also produced by fermentation.

The fermentation industry in Portugal is best represented by the private Portuguese companies CIPAN and Soc. Prod. Levedures Seleccionadas. CIPAN produces tetracycline and erythromycin on the full industrial scale and, at a pilot-plant level, cephalosporin C, penicillin G, and gentamicin. This company also produces penicillin-derived antibiotics and is now operating its own enzymatic

6APA process, using immobilized penicillin amidase. Soc. Prod. Levedures Seleccionadas, a subsidiary of Gist-brocades in the Netherlands, produces penicillin G and baker's yeast. The latter is also produced by PROPAM, a Portuguese-owned company.

Other Portuguese companies are now operating some biotechnological processes. COPAM, in the field of industrial starch produces high-fructose corn syrup using immobilized glucose isomerase. Amylolytic enzymes are also used by this company. QUATRAM, a steroid producing company is starting the microbiological modification of steroid compounds, based on their own research.

Environmental Biotechnology. Most of the recently built sewage treatment plants use either trickling filter or lagoon processes, in an attempt to reduce energy consumption. Of particular interest is a photosynthetic pool system operating for the treatment of sewage from a town of 15,000 inhabitants.

Government

Government involvement in biotechnology has so far been negligible. However, the Ministry of Industry is now promoting the formation of bio R&D companies, under the guidelines of a new national technology plan. JNICT – the Portuguese Science Research Council – is also supporting some research projects in the area of biotechnology.

Universities

Biotechnology research is mainly concentrated, with different emphases, at four universities – three in Lisbon and one in Oporto. At the Technical University of Lisbon the main interests concern immobilization of biocatalysts as well as plant cell cultures – this in cooperation with the Science Faculty of Lisbon. At the Technical University of Lisbon (IST) a branch of the chemical engineering course with an emphasis on biotechnology subjects was started in 1983. The New University of Lisbon is working on biological effluent treatment and on hydrogen and methane production. This university, with the support of the Gulbenkian Institute of Science, provides M.Sc. courses on biotechnology.

At Oporto University, the fields of microbial leaching and bioreactor design are being covered. A new School of Biotechnology is being organized at the Catholic University of Oporto: the first course, which was started in 1984, is in the area of food biotechnology.

Institutes

The Institute Gulbenkian de Ciencia, located in Oeiras, has a department of microbiology and another of cell biology which have research projects in fundamental fields of the life sciences. However, several projects are of interest for biotechnology, such as ethanol tolerance in yeasts, the study of the African Swine Fever Virus, genetic improvement of wheat, genetic engineering of *Bacillus*

subtilis, etc. This institute, which is mainly financed by the Gulbenkian Foundation, also offers several postgraduate courses.

Laborio Nacional de Engenharia e Tecnologia Industrial (LNETI) at Lisbon, is another institute, financed by the Ministry of Industry and Energy. It develops research projects with an intended industrial and economic impact. It is divided into two institutes, one concerned with energy and the other with industrial technology. In the Energy Institute, biotechnology research is mainly concerned with the development of processes for energy production from biomass. In the Technology Institute, there are biotechnology research projects in the departments of food industries (DTIA) and Chemical Industries (DTIQ).

J.M.S. Cabral and coworkers (Laboratory of Biochemical Engineering, Technical University of Lisbon) are engaged in studies of the esterification of alkanols in multiphase biocatalytic systems. (See *ESNIB* 88-02:5.) These investigators are also carrying out studies on the immobilization of microbial cells on transition metal-activated supports.

In the same department, J.P. Cardoso and his group are carrying out studies on the enzymatic conversion of Cephalosporin G to 7-amino-deacetoxycephalosporanic acid (7-ADCA) both at laboratory and pilot-plant levels using a novel type of enzymatic reactor to deal with a compressible immobilized preparation of Penicillin Amidase.

A.V. Xavier and J.J.G. Moura (Center for Chemical Structure and New University of Lisbon) are engaged in studies of the role of electron transfer proteins in the metabolism of reducing and methane-forming bacteria. Another line of investigation is concerned with the role of metal ions (heme iron, iron-sulfur, cobalt, molybdenum, and nickel) in biocatalysis. The work involves spectroscopic characterization of metal centers in proteins and bioproduction of H_2 and CH_4 -inorganic systems as model systems for biocatalysis.

Eastern European Countries

USSR

Soviet biotechnology is relatively little known to the West. This is partly due to the lack of mobility of Russian scientists and also to the relative infrequency of publication of their work in non-Russian literature and the infrequency of participation by Russians in Western conferences. However, under glasnost and Gorbachev, the access to news about Western research is improving

and more Soviet researchers are making visits out of the country since it is now easier to obtain approval to travel abroad. Several layers of red tape have been reduced and the main constraint on travel now, according to Soviet scientists, is lack of travel funds (i.e., hard currency). Next year, for the first time, Soviet biologists may be able to enjoy a convenience that American scientists have long been accustomed to. They will be able to obtain restriction enzymes, a fundamental research tool in biotechnol-

ogy, within days or weeks after ordering them from a new Soviet scientific association, instead of waiting up to a year to obtain them from foreign suppliers.

This modest, but significant development, essential if the Soviets are to catch up with Western biotechnology, is part of a larger experiment under way in Soviet science to spur industrial innovation and invigorate the country's ailing economy.

As part of General Secretary Mikhail Gorbachev's drive for economic reform, the Soviet Academy of Sciences and the government ministries in charge of manufacturing have teamed up to form 21 different enterprises to collaborate on research and development and the manufacture of a large variety of items, including biotechnology products for medicine and agriculture, industrial robots, industrial chemicals, personal computers, and machine tools. These enterprises, known generically by their Russian acronym as MNTK's, will do everything from research to production of products.

In recent years, Soviet authorities have established a variety of collaborative programs, including the MNTK plan, in an attempt to bridge the gap between researchers and industry. Apparently, these programs have had varying degrees of success. However, under the MNTK plan, unlike other programs, profit is the stimulus to improvement. In a major reform, the MNTK enterprises can keep the money made from sales to develop other products rather than funnel the profits back into the general government treasury. One of the ultimate aims of this change is to make research self-financing. Before, researchers have depended on the government for virtually all their support.

Under the MNTK's, the research institutes of the Soviet Academy for the first time control several of the enterprises. One of the most ambitious of the MNTK's enterprises is the Biotech Association. It is a collaborative enterprise that includes about 20 academic institutes and the Ministries of Health, Microbiology, and Agriculture and is headed by the Shemyakin Institute, the country's leading research facility in bioorganic chemistry.

The Biotech Association plans to produce not only restriction enzymes, but also a wide range of recombinant DNA products for laboratory and industrial production. The Biotech Association also hopes to set up joint ventures with foreign firms and to compete eventually in the international market. It just completed preliminary field trials of bovine growth hormone in cooperation, for example, with the Monsanto Company (St. Louis, Missouri). Academician Vadim Ivanov, director of both the Shemyakin Institute and the Biotech Association, has acknowledged that the Biotech Association faces many difficulties and that Soviet biological research and industrial production are far behind Western standards in many ways. However, he notes that the successful pro-

duction of restriction enzymes, a relatively simple product, is an indication that the Biotech Association can do to the job. According to Ivanov, about 100 different enzymes are now being produced and some are being exported to Japan. Ivanov has also secured new funding for the Biotech Association. The program was recently promised about \$80 million for next year. About 70 percent of these funds will come directly from the state budget for the first time. Until now, the Biotech Association has been funded mainly by member institutes and ministries from their own budgets. The money will go in part toward the development of 32 products — 24 in medicine and 8 in agriculture. These include hepatitis B vaccine, which is in clinical trial; alpha-interferon and human growth hormone, which are close to clinical trial; hepatitis A vaccine; amino acids; peptides; and even diagnostics for the AIDS virus.

While many of the pharmaceuticals under development are commonly available in the West, they are in short supply in the Soviet Union. Foreign trade is extremely complicated by the fact that the ruble is not an exchangeable currency. For example, the country needs 600 kilograms of insulin annually, but Soviet ministries can currently manufacture only 200 kilograms. The Biotech Association plans to supplement insulin production because the number one priority is to supply products for the Soviet people.

The Shemyakin and the Biotech Association are tightly linked. Researchers at the Shemyakin can divide their time between institute work and the Biotech Association. At present, according to Ivanov, one-third of the brainpower at the Shemyakin is devoted to projects related to the Biotech Association. The other two-thirds focus on fundamental research.

Despite the adoption of many reforms, the Biotech Association faces enormous hurdles. Reducing red tape in purchasing will not compensate for the fact that laboratory supplies and machinery, from the simple to the sophisticated, are in short supply. Even the Shemyakin, which is one of the best equipped biological laboratories in the country, must cope with chronic scarcity.

Institutes. According to a report of a few years ago, The Academy of Sciences Bulletin gave the following examples of advanced biotechnology and gene cloning research in Soviet institutes:

- Synthetic insulin production by "modern methods of nucleotide synthesis" at Shemyakin Institute of Bioorganic Chemistry, with biological trials in progress
- Chemical synthesis of interferon at the Institute of Bio-organic Chemistry, the (Siberian) Institute of Cytology and Genetics, and other institutes of Glavmikrobiopram (the main administration of microbiological industry)

- Production of somatotropin produced in *E. coli* at the the Institute of Molecular Biology, immunologically indistinguishable from the hormone isolated from the human pituitary
- Monoclonal antibodies against a widespread influenza virus obtained by collaboration between the Institute of Molecular Biology and the Institute of Virology
- In collaboration with the biology faculty at Moscow State University, production of monoclonals to the most important viruses of cultivated plants
- Focus by the All-Union Cardiological Research Center on finding useful monoclonal antibodies to detect atherosclerosis, and for targeted drug delivery
- Development by the Institute of Plant Physiology of a strain of plant cells in culture for direct extraction of ginseng which has been scaled up for production
- Reports that scientists at the All-Union Academy of Agricultural Sciences and Moscow State University have fertilized bovine ova *in vitro*, cleaved them, and transferred the embryos to surrogate mothers.

The following section deals with a limited number of specific projects and scientists involved.

A.B. Chetverin and colleagues (Institute of Protein Research, USSR Academy of Sciences, Pushchino [Moscow]) are investigating the mechanism by which the replicating RNA recombinants are produced *in vivo*. They have recently reported on an *in vivo* recombinant RNA capable of autocatalytic synthesis by QB replicase.

At the same institute, A.S. Girshovich and coworkers are studying the transient association of newly synthesized proteins with the heat-shock GroEL protein. They think that the unfolded state of pre- β -lactamase, for example, is maintained by the transient interaction with GroEL and may be essential for the secretion of this protein.

A.G. Ryazanov, E.A. Shestakova, and P.G. Natapov (also at the Institute of Protein Research), are studying how phosphorylation of elongation factor 2 by EF-2 kinase affects the rate of translation. They found that the phosphorylation of EF-2 by the EF-2 kinase results in a drastic inhibition of polyphenylalanine synthesis in poly (U)-directed translation. Phosphorylated EF-2 is completely inactive in translation and, moreover, inhibits the activity of nonphosphorylated EF-2. Dephosphorylation of EF-2 by phosphatase restores its activity. Thus, these investigators think that the phosphorylation of EF-2 directly affects the elongation stage of translation and so represents a novel mechanism of translational control.

G.K. Skryabin and K.A. Koshchlenko (Department of Microbiological Transformation of Organic Compounds, Institute of Biochemistry and Physiology of Microorganisms, USSR Academy of Sciences, Pushchino [Moscow]) are studying the influence of conditions on

immobilization and incubation of immobilized cells in a nutrient medium on the viability and enzymatic activity of cultures capable of transformation of steroids and other organic compounds.

I.V. Berezin (Institute of Biochemistry, USSR Academy of Sciences, Moscow) in collaboration with V.V. Mozhaev (Chemistry Department, Moscow State University) and K. Martinek (Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague) are investigating the reactivation of immobilized enzymes.

Z.G. Fetisova and colleagues (A.N. Belozersky Laboratory of Molecular Biology and Bioorganic Chemistry, Moscow State University) are studying long-range molecular order as an efficient strategy for light harvesting in photosynthesis.

O.N. Voloshin (M.M. Shemyakin Institute of Bioorganic Chemistry, Moscow) in collaboration with S.M. Mirkin, V.I. Lyamichev, B.P. Belotserkovskii and M.D. Frank-Kamenetskii (Institute of Molecular Genetics, USSR Academy of Sciences, Moscow) are investigating the chemical probing of homopurine-homopyrimidine mirror repeats in supercoiled DNA.

G.Kvesitadze, L. Kvachadaze, T. Aleksidze, and T. Buachidze (Institute of Plant Biochemistry, Georgian Academy of Sciences, Tbilisi) are working on thermophilic micromicetes which are producers of cellulases. They found 12 strains that were considered to be thermotolerant with optimal growing temperatures of 40°C to 50°C. The most active cellulase producers were selected from the thermotolerant cultures. These investigators found that endoglucanase from the thermotolerant micromicetes always exceeded the thermostability of the mesophilic analogues. The preparations, isolated from the thermotolerant micromicetes, were able to hydrolyze substrates for a long time at 60°C to 65°C. (See ONRL Report C-1-85.)

A.P. Demchenko and colleagues (Palladin Institute of Biochemistry, Ukrainian Academy of Sciences, Kiev) are studying the dependence of spectral, kinetic, and polarization parameters of fluorescence on excitation wave lengths and suggest a new trend in spectroscopic studies of protein and membrane dynamics.

M. Prokofyev (Director, USSR Embryogenetic and Livestock Reproduction Section of the All-Union Science and Research Institute of Agricultural Biochemistry) has reported that new methods have been developed to increase livestock productivity by programing insemination periods for cows and treating reproductive disorders with hormones. Hormones have been developed to increase impregnation in cows and reduce embryo loss. A single injection of an analogue of gonadotropic-releasing hormone (called Surfagon) has increased the fertility of cows by 10 to 15 percent. Prostaglandin F2 alpha or its analogues (such as Estofan and

Enzaprost), progesterone and other progestagens, gonadotropic preparations (synthetic fatty acids or hypophysal gonadotropins), and the gonadotropin-releasing hormone or its analogues are four basic types of compounds applied to regulate reproduction in livestock. These compounds are all produced in the USSR.

East Germany

I obtained the information on biotechnology research in East Germany from presentations organized by the East German government which took place at various biotechnology conferences held in Western Europe; I was unable to make a liaison trip to East German institutes. General information about biotechnology was obtained primarily at a seminar on East German research held at the 1986 Biotechnology Conference in Hannover, West Germany.

The 1986 meeting was under the auspices of Professor Manfred Ringpfeil (East German Academy of Sciences), Professor Rolf Schulze (Martin Luther University, Halle-Wittenberg) and Professor Robert Kunze (Chemical Plant Construction Combine, Leipzig). A detailed report on the conference is available in ESN 41-3:121. The program was designed to acquaint West European scientists and industry representatives with the biotechnological programs and developments in the areas of medicine, agriculture, and environmental protection in East Germany.

R. Schulze said that East Germany is emphasizing training in biotechnology at all universities, targeting interdisciplinary research and development areas, supporting collaborative projects between academic and industrial entities, expanding and updating laboratory facilities, and building new laboratories with modern equipment. East Germany's overall program at that time was to achieve a threefold increase in biotechnological application by 1990, according to Schulze.

Research in the application of microorganisms as well as cell and tissue cultures in production processes for the food industry and raw substances for use in pharmaceuticals, medicine, agriculture, and ecology are being carried out at the Technical University (Dresden and Freiberg), the Technical University "Carl Scharlemmer" (Leuna-Merseburg), and the University of Engineering (Köthen).

The targeted centers for interdisciplinary research and development are Humboldt University (East Berlin), Karl-Marx University (Leipzig), Martin Luther University (Halle-Wittenberg) and Friedrich Schiller University (Jena). At Humboldt University, a new method for destruction-proof analysis called electrorotation has been developed. Scientists at Martin Luther University have developed a new method for the fractionation of macromolecules (electrokinetic ultrafiltration).

Optimization of on-line regulation of continuous fermentation has been achieved in a cooperative study of the Technical University, Leipzig, and East Germany's Institute for Biotechnology. Methods developed for accelerated fermentation and maturation of beer at Humboldt University are already in use by industry. Methods and equipment for continuous hydrolysis of saccharin using immobilized enzymes have been developed at Martin Luther University.

Schulze also pointed out some of the contributions of the scientific institutions and the chemical industry combines to the accelerated development and broader utilization of products of biotechnical methods. For example, the biotechnical production at VEB Pharmaceutical Combine, GERMED (Dresden-Radebeul) has increased 20 percent in the production of antibiotics, enzymes for diagnosis and therapy, alkaloids, blood substitutes, and peptides. AT VEB Agrochemical Combine (Piesterize), VEB Fotochemical Combine (Wolfen), and VEB Petrochemical Combine (Schwedt), modern biotechnological plants are producing valuable feed proteins for animal feed from sugar, molasses, and petroleum distillates. With the development of new procedures for the improvement of technical enzymes, of ethanol, and of beer and their transformation into products, the VEB Chemical Plant Combine (Leipzig-Grimma) is increasing production in the traditional area of the biotechnology-foodstuff industry. This company is leading in the transfer of new biotechnological information to the area of environmental protection.

Already in operation, according to Schulze, are efficient bioreactors for biological wastewater purification and plants for the use of agricultural and communal by-products for biogas production.

East Germany has set up, according to Schulze, the following biotechnology goals to be reached by 1990:

- Development and production of highly effective diagnostics and pharmaceuticals for medicine
- Utilization of enzymes and taste substances for increasing effectiveness and quality of foodstuff production
- Utilization of genetic engineering and tissue culture methods for increasing effectiveness in animal and plant production
- Improvement in the quality of native raw materials
- Increased production of valuable substances from byproducts, including reduction of environmental damage.

Schulze stated that additional advantages are to be gained by concentrating research potential and utilizing modern techniques in biotechnology. For example, East Germany is establishing a gene technology center at its Biotechnology Research Center in cooperation with the chemical industry. Furthermore, the necessary bases for

development and realization of modern laboratory and production techniques for biotechnology are being created by the expansion of the VEB Chemistry Combine. Additional innovations are anticipated in the future from the recently formed Science-Industry-Cooperation Biotechnology (Leipzig) in conjunction with various departments of the East German Academy of Sciences and the Karl-Marx University (Leipzig).

Some of the research projects mentioned at this seminar are:

- Development of a new antibiotic (Nourseothricin) for use in farm animals. It is produced by VEB.
- Development of a method for the production of Fermosin in feed-yeast. The procedure was developed by VEB Petrochemical Combine (Schwedt) in collaboration with the Institute for Biotechnology of the East German Academy of Sciences, the VEB Chemistry Combine, and the USSR's All-Union Research Institute for Protein Research (Moscow). K. Bauer of VEB Pharmaceutical Combine reported that this process allows for the production of high-grade feed-yeast on the basis of petroleum distillates.
- Microbiological recycling processes for heavy metals were developed as a collaborative project by the Academy of Sciences and VEB Chemistry Combine (Bitterfeld).
- Development of functional polymers as an aid in the synthesis and purification of biological substances for biotechnological application (VEB Chemistry Combine (Bitterfeld)).
- Development of an enzymatic process for obtaining high-value protein hydrolysates from collagen-containing waste products of the leather industry. A microbial alkaline protease with a high specificity even in the presence of chrome tanning substances is used in the process (VEB Pharmaceutical Combine, GERMED).
- Development of a new procedure for the production of gluconic acids. This work was a collaborative effort between VEB Chemistry Combine (Bitterfeld) and the Institute for Biotechnology of the East German Academy of Sciences.

At the Gatersleben Central Institute for Genetics and Cultivated Plant Research, in cooperation with a combine partner, scientists have developed a process for producing the alpha amylase enzyme using biotechnological methods. This enzyme converts barley starch directly into sugar and is one of the most heavily produced technological enzymes. By isolating and transferring a highly active gene for this enzyme into a selected host strain of bacteria, the performance of the latter in making enzymes was increased by two- to three-fold.

The pharmaceutical industry is very interested in the cloning successfully carried out at the Jena Central Institute for Microbiology and Experimental Therapy, as well as the successful sequence analysis of the gene for the protein streptokinase (used clinically to dissolve thromboembolisms).

Work in genetic engineering at the Berlin-Buch Central Institute for Molecular Biology has resulted in valuable progress in the area of prenatal diagnosis, as well as in the prevention of hereditary diseases, including Duchenne's muscular dystrophy, which strikes one in 2,500 newborns and results in death at an early age. In addition, there are several projects for cloning viral genes that cause economically significant animal diseases, the goal being to develop cheaper, better, and more effective diagnostics. In addition, attempts at gene transfers among animals are underway, in part aiming to transfer genes that will improve the immune systems of animals for breeding and production so that they will become more resistant to certain diseases. There are similar projects in plant cultivation, such as one involved with improving the quality of seed proteins, since these proteins have only one-half to two-thirds of the nutritional value of animal protein. Other projects include the desirable manipulation of plants through genetic engineering, such as in the area of resistance to fungal and other plant diseases, as well as resistance to stress factors (heat and cold). Transferring to nonleguminous plants the ability to use atmospheric nitrogen – as papilionaceae do, thanks to their coexistence with rhizobia – is one of the most difficult projects in terms of yielding results, but one for which breeders have solid plans for the future.

The following section deals with a very limited number of projects and the scientists involved.

A. Leuchtenberg, C. Wardsack, H. Hermersdörfer, and H. Ruttlof (Berghoz-Renbrucke, East Germany) are studying the production of pectinases by immobilized mycelium of *Aspergillus niger*. The basis for the research is that increased processing of fruits and vegetables requires new technological procedures, including the application of pectinolytic enzymes resulting in higher yields and improved quality of the products. (See ONRL Report C-1-85.)

F.W. Scheller and coworkers (Central Institute for Molecular Biology, East German Academy of Sciences, Berlin-Buch) have developed enzyme-based biosensors with wide applications and high sensitivity which apparently are being marketed commercially in East Germany.

The simple instrumentation and operation of amperometric electrodes offers the opportunity to substitute them for optical devices in the laboratory. Scheller and his group, starting from enzyme-electrode-based analyzers for glucose, uric acid, and lactate, have succeeded in the development and application of amperometric sensors for the determination of alanine aminopeptidase and

leucine aminopeptidase. Also, according to Scheller, an amperometric urea electrode has been tested in monitoring the dialysis treatment of kidney patients. These investigators have also been able to obtain the highly sensitive determination of pyruvate in the micromolar range by using a lactate monooxygenase-lactate dehydrogenase (LDH) electrode, which has opened up the way to the measurement of pyruvate-forming enzymes such as LDH, pyruvate kinase, and glutamate pyruvate transaminase (GPT). Nanomolar substrate concentrations (lactate or glutamate) have also been measured by self-amplifying lactate oxidase-LDH or GPT-glutamate dehydrogenase electrodes, thus almost reaching the sensitivity of biological receptors. (See *ESN* 40-9:301.)

D. Kirstein also of the Central Institute for Molecular Biology has collaborated with F.W. Scheller in biosensor development, particularly in the preparation of a multienzyme reactor by coimmobilization of enzymes of a cofactor or substrate recycling system and its combination. (See ONRL Report 8-001-C.)

At the same institute, T.V. Kurzchalia, M. Wiedmann, and T.A. Rapaport have found for the first time a direct interaction between the signal sequence of a secretory protein and a component of the signal recognition particle (SRP), the 54 kilodalton polypeptide. This was achieved by means of a new method of affinity labeling which involves the translational incorporation of an amino acid, carrying a photoreactive group, into nascent polypeptides. This work was a collaborative project with scientists from the Institute of Protein Research, USSR Academy of Sciences, Moscow.

Lastly, at the same institute, studies on monoclonal antibodies are being carried out by F. Noll, E. Eichmann, M. Gaestel, W. Handshack, V. Valeva, and F. Schneider. These researchers are specifically interested in monoclonals specific for subtypes of human α -interferon (HuIFN- α). Two hybridomas secreting monoclonal antibodies (Mabs) against HuIFN- α -1 and - α -2, respectively, were established by immunization of mice with human leukocyte interferon. Using these antibodies, these investigators developed a highly sensitive immunoassay for HuIFN- α -1. Moreover, by means of Mab-immunosorbents, the purification of HuIFN- α -1 and - α -2) to homogeneity either from natural or microbial sources was possible in one step. Synthetic peptides were used to produce additional Mabs against IFN molecules. (See ONRL Report C-10-86.)

R. Grafe (Central Institute for Genetics and Plant Culture Research, Gaterslaben) and coworkers have been engaged in studies of mutant selection from *Nicotiana plumbaginifolia* mesophyll protoplasts. *N. plumbaginifolia* is becoming a model species in plant cell genetics, and various types of mutants have been obtained. Valine resistance and nitrate reductase deficiency were used as genetic markers to develop efficient

conditions of mutant selection from *N. plumbaginifolia* protoplasts. Grafe and coworkers think that some of the mutants they have isolated will also be useful tools for analyzing the mechanisms involved in amino acid uptake and nitrate assimilation by higher plants.

The Institute of Clinical Immunology at East Berlin's Charité Hospital has produced monoclonal antibodies against the (HIV) human immunodeficiency virus responsible for AIDS. The Charité team sees this as a step towards developing drugs to combat the virus. The head of the research team is R. von Baehr.

Hungary

Industry. Various branches of the classical fermentation industry—wine, beer, alcohol, acetic acid, starch products, etc.—have a long tradition in Hungary. Foundation of the first alcohol distillery can be traced back to 1842. The first acetic acid plant dates back to 1870; lactic acid production started in 1934, and the first acetone-butanol plant working under aseptic conditions was set up in 1935.

The food industry has always been of great economic importance in Hungary. Food exports earn nearly 40 percent of the country's foreign exchange revenue.

Hungary's antibiotic era started with the production of penicillin. The technology was introduced and first applied by Hungarian researchers in 1949 at the CHINOIN Pharmaceutical Company. The experience gained in production was then used in the design and construction of the first major fermentation plant, the BIOGAL Pharmaceutical Company. The worldwide boom in the pharmaceutical industry has included Hungary. It led to the foundation of the Drug Research Institute in 1950, and the elaboration of further antibiotics and their industrial-scale production in various pharmaceutical plants. In this institute, several original antibiotic procedures as well as a method for the identification of antibiotics has been developed.

In the field of steroid research, significant results have been achieved by two Hungarian researchers Horvath and Kramli, who were first to describe the microbiological oxidation of steroid compounds in 1948. Further investigations led to the development of procedures for microbiological production of various steroids and ergot alkaloids. Important results and a major breakthrough were also attained in the large-scale fermentation of vitamin B₁₂, the only fermentation product currently produced under nonsterile conditions. There was a period when Hungary produced 20 percent of total world production of vitamin B₁₂, mainly as a feed-additive, which is an important product on the world-market.

The Phylaxia Company, founded in 1912, produces vaccines and sera. Various pharmaceutical products of

plant origin have been prepared and are produced in these laboratories today.

As a means of adding value to vegetable resources, the world's first procedure for making a leaf-protein, VEPEX, was developed and brought to industrial scale in Hungary in 1972.

Pharmaceutical companies using up-to-date biotechnology in Hungary are: BIOGAL Pharmaceutical Company, CHINGIN Pharmaceutical Company, GEDEON Richter Pharmaceutical Company, EGYT Pharmaceutical Company, PHYLAXIA Company, and the Human Research Institute and Company for the production of vaccines.

The main products of the Hungarian fermentation industry are: penicillin, oxytetracyclin, bacitracin, fungilin, gentamycin, neomycin, nebramycins, erythromycin, nystatin, ergot-alkaloids, dextran, cyclodextrins, gibberellins, steroids, and vitamins B12 and B2.

Developments in the food industry were attained by application of up-to-date methods of biotechnology. Hungary was the first country in Europe to introduce a method of brewing beer with assistance from microbial enzymes and to apply immobilized enzymes in the large-scale production of iso-glucose syrup. One of the main food processing industries is the Biotechnological Plant of Szabadegehaza.

Among the biotechnological products used in the sector of foods and alcoholic beverages are: gluconate, enzymes (for example, pectinase, cellulase), starter cultures for wine, lactic acid, meat, bread and *Rhisobium*, and also baker's yeast, fodder yeast, ethanol, beer, wine, and dairy products.

In the mechanical industry, the following equipment and instrument manufacturing companies are involved in biotechnology:

- Jaszbereny Chopping Machine (fermentors)
- Budapest Factory of Chemical Machinery (centrifuges)
- Radelkisz Electrochemical Instruments (devices for pH measurement, ion- and enzyme-electrodes)
- Labormim Laboratory Instrument and Equipment (HPLC, autoanalyzers)
- MOM Hungarian Optical Works
- Reanal (fine chemicals).

The Hungarian Academy of Sciences, like a number of institutions in the West has adopted the venture capital approach to molecular biology to increase the pace and profit of biotechnological ventures. Economic liberalization has been underway for a number of years in Hungary. Although the state-controlled economy is suffering, there is an openness which allows money to be made in capitalist-style ventures. Since the Hungarian market is limited, the duty of the biotechnology enterprise is to export products and expertise and earn

money for the country. The new biotechnology venture was launched in Hungary in 1984.

When the government became interested in developing a long-term biotechnology program, the Academy, using its own funds plus money from the State Bank for Development and the innovative fund of the National Bank of Hungary, purchased Vepex Ltd (a contract engineering firm). Vepex is bringing together basic research in molecular biology and industry. Scientists from the Biotechnology Center of the Academy of Sciences in Szeged contract to work for Vepex for a period of 2 to 3 years. They then have the option of returning to their basic research positions at the Academy. Vepex, which also collaborates with research institutes of several Hungarian medical schools and the Institute of Pharmacological Research in Budapest, already has an international staff. Since the company is not state-owned, it is free to hire the best scientists available to do applied research and develop particular products. In addition, contracts for joint ventures with biotechnology companies in Sweden (Pharmacia), England, France, Germany, and the US have been made.

Vepex researchers are currently studying the generation of biogas by the bacterial fermentation of manure. Since hydrogen is the limiting factor in the production of biogas they are trying to clone the purple bacteria that make hydrogen. They plan to sequence the gene, isolate the enzyme for hydrogen production, and add the enzyme to waste systems to stimulate the continuous production of methane gas for fuel. Another project is the immobilization of yeast to accelerate the process of making champagne by the classical methods.

Products currently being produced or investigated at Vepex Ltd include monoclonal antibodies, plasmids, and enzymes involved in molecular biology research. For example, a "protoplasting enzyme" for use in protoplast fusion has been prepared from snails. Vepex is contracting for custom synthesis and sequence analysis of long oligonucleotides as well as hybridoma development. Tritium labeling, synthesis of peptides and of hapten-protein complexes, biotinylation for immunohistochemistry, and ELISA (a strain improvement of bacteria and yeasts using molecular biological techniques), and HPLC scale-up for biotechnology are also available. HPLC scaleup is represented in the US by Interconcepts Inc., Concord, California.

Meriklon Research Laboratories Co. was established in 1980, with investments from a dozen research institutes, cooperatives, and other Hungarian companies, to commercialize some newly developed techniques in crop plant propagation. The company now has 100 employees and is located on the site of the Rozmaring Agricultural Cooperative, just outside Budapest. The research scientists at Meriklon work on nontraditional breeding processes for a variety of plants and crops. The

first of the three major projects they have undertaken is the mass propagation through tissue culture of plant varieties specific to Hungary and beyond. This has been highly successful. The company's second major biotechnology project is the development of nematodes as biological pesticides, which kill insects in the soil surrounding crop plants.

Perhaps the most interesting and important product from Meriklon is small seed potatoes. Hungary has had a problem with viability of seed potatoes and has had to import at great expense from the Netherlands the seed potatoes for its vast potato crop. In 1983, Meriklon developed "mini-tubers" for Hungarian potato varieties. These are now available in three sizes from 10 to 35 mm in diameter. They are virus-free, highly viable, and inexpensive to produce. They can also be planted by commercial seeding equipment. The higher viability of the mini-tubers means that less field space is needed for the same size potato crop. Meriklon claims that it can use the technique to produce seeds for 40 different varieties of potatoes and is now working on other types of crop plants. Meriklon has entered license agreements with Denmark and the UK. Negotiations and test sites are also underway to use the tuber technology in many other countries, including the US.

Another biotechnology project at Meriklon is the development of monoclonal antibodies as diagnostic tools for various plant diseases. This allows the production of virus- and disease-free propagation materials and also facilitates quality testing at various stages of production.

Hungary also has a few joint ventures with non-Eastern European biotechnology companies. The largest of these involves an agricultural cooperative in the east of Hungary and the Japanese chemical giant, Kyowa Hakko, to produce L-lysine by fermentation process techniques. Following a combined investment totalling \$45 million, the lysine production plant in Hungary is expected to be in operation in the coming year and should produce lysine both for Hungary and for export to Japan and, perhaps, other countries.

A second joint venture is the formation of a new company, Biotechnology International Ltd, set up in the UK with about \$200,000 total investment. The Hungarian firm Vepex Contractor Ltd of Budapest owns 40 percent, the Hungarian National Bank, 10 percent, and Cambridge Life Sciences (UK), 50 percent. The company will develop new animal and human diagnostics with Hungarian scientists contributing basic research know-how. The UK partner will contribute access to its facilities and technology development as well as its production and marketing experience. The new company has exclusive rights to seven Hungarian patents and technologies.

The Egis Pharmaceutical Company established its Blood Products Laboratory in 1982 as a joint venture between the Szeged Biological Research Center, the Blood

Transfusion Institute, and the state-owned Egis Pharmaceutical Company. Its first product, a natural leukocyte interferon isolated from blood, received approval from the Hungarian government for use in the treatment of hairy cell leukemia. Using a proprietary technology for protein stimulation from the blood, the scientists at Egis claim to be able to isolate three times as much product as their nearest international competitor. They also claim that the natural product has as many as 15 synergistically acting interferon components and has fewer problems than genetically engineered interferon. Scientists at Egis are also working on using their proprietary technologies for isolating natural interleukin-2 and other blood peptides.

A joint venture between a US technology transfer firm and a Hungarian cooperative has resulted in a new corporation that is trying to bring technology developed in the Eastern bloc to the West. The new firm, CompuDrug USA of Austin, Texas, specializes in expert systems software for pharmaceutical researchers and toxicologists. The US company is the progeny of CompuDrug Ltd of Budapest and Kise Research, a Washington D.C. company that seeks to identify Eastern bloc technology that promises to be useful in the West. The Hungarian cooperative is a group of more than 60 medicinal chemists, pharmacologists, computer scientists, and other researchers. Headed by Ferenc Darvas, who spends part of his time in the US at the University of Florida's Center for Drug Design and Delivery in Gainesville, the Budapest firm is concentrating on software that uses artificial intelligence as a predictive tool.

Universities. The teaching of modern biotechnology, as of 1984, was introduced in two universities, with emphasis, however, on two different aspects. Microbiology and genetics are taught at the Joseph Attila University, Szeged, with high-level protoplast fusion research conducted at the Department of Microbiology. The education in biotechnology at the Technical University, Budapest, Faculty of Chemical Engineering is focused on bioengineering, including graduate and postgraduate courses for biotechnologies.

The activities of the Department of Agricultural Chemical Technology have gained recognition in the field of fermentor-computer coupling, fermentation instrumentation and on-line control, mathematical optimization, and enzyme engineering research.

A Department of Biotechnology has been organized at the University of Agriculture in Gödollo. Biotechnological activities are also carried out at the Department of Microbiology of the University of Horticulture as well as at the Biological Institute of the Medical University of Debrecen.

Institutes. The Biological Research Center of the Hungarian Academy of Sciences in Szeged was founded in 1970. The present director is Dr. Lajos Keszthelyi.

The Center (BRC) consists of five institutes: biophysics, biochemistry, genetics, and plant physiology. These are located in Szeged. The BRC in Budapest emphasizes enzymology. Research money is divided equally among the institutes. The BRC in Szeged is a self-contained enclave. The building contains rooms for overnight guests, and has dining facilities, a library, and several floors of laboratories filled with sophisticated modern equipment, much of it purchased in the West. The center makes its own restriction enzymes because of the limited availability of foreign currency. Several research groups work within each institute on various topics. All interact scientifically and have established a network of international ties so there are many exchanges of information and personnel with the West. Although the major emphasis is on basic research, consideration is also given to the solving of problems in agriculture and the food and pharmaceutical industries, all of which are of vital importance to the Hungarian economy. BRC scientists are currently producing or investigating products involving monoclonal antibodies, plasmids, and enzymes used in molecular biology research. The scientists are also studying the generation of biogas by the bacterial fermentation of manure. Another project is the immobilization of yeast to accelerate the champagne making process.

The World Bank has recently contributed funds to develop another biotechnology complex near Budapest in Gödölo. Under the auspices of the Ministry of Agriculture, the complex will focus on animal breeding and the molecular biology of animal viruses.

At the Institute of Plant Physiology, the Laboratory for Plant Gene Expression, under the directorship of Dr. Ferenc Solymosy, is investigating the molecular basis of viroid pathogenicity. They are also attempting to insert specific heat-inducible DNA sequences into the plant genome to examine stress-induced changes in nuclear gene expression. In the plant cell genetics laboratories, tissue culture is being used to select for herbicide resistance in wheat. Dr. Peter Medgyesy is using protoplast fusion to study the genetics of chloroplasts and mitochondria. During fusion, unlike the events occurring during a sexual cross, chloroplasts and mitochondria are inherited biparentally. The organelle transfer occurs without the transfer of nuclear genetic material. Genetic recombination between chloroplasts, a very rare event, was induced in two species of *Nicotiana*, after somatic cell fusion. In calli grown after fusion, six recombination sites were identified in the chloroplast genome. The cotransfer of mitochondria can result in the formation of sterile cybrids when there is an incompatible nuclear background. A method was therefore developed which transfers only chloroplasts. Restriction analysis showed that in both inter- and intra-specific crosses of *Nicotiana*, cell lines were obtained with paternal plastids in the offspring. The researchers reported that this was the first definite

proof of occasional parental transmission in species typically exhibiting strict maternal plastid inheritance. In addition, the discovery of conditions for the selection of plastids resistant to certain herbicides in tissue culture gives potential agronomic importance to the "sexual cybridization" technique.

Medgyesy has recently been able to achieve chloroplast recombination between tobacco (*Nicotiana*) and potato (*Salpiglossis*) plants. These cybrids possessed normal tobacco morphology and chromosome number, demonstrating that the nucleus was from the tobacco plant. The presence of potato plastids was verified by restriction analysis of the chloroplast DNA, which contained both tobacco and potato genes. The eventual goal of this research is to exchange entire chloroplasts between plant species with the concomitant transfer of plastid traits.

Overlapping projects involving molecular biology are underway in various institutes. For example, researchers at the Institute of Biochemistry are isolating and characterizing cDNA clones specific for corn tassel and studying mutants defective in tassel differentiation as well as determining DNA and gene transfer among higher plants. They are also investigating gene regulation in bacteria and *Drosophila*.

The Institute of Enzymology, in collaboration with other laboratories, is using the *dunce* mutant of *Drosophila* to clarify the molecular mechanisms underlying learning and memory. They are also studying the molecular basis of the immune response in order to determine how the binding of antigen by antibody triggers non-specific effector functions.

Research at the Institute of Genetics, directed by Dr. Lajos Alföldi, encompasses several areas. The laboratory of bacterial genetics is studying the genetic events occurring after protoplast fusion of *Bacillus megaterium* and is also developing a method for total gene synthesis in order to obtain genes that code for peptide hormones and their analogues.

The plant genetics laboratories are working with cultured alfalfa and carrot cells to isolate the genes involved in differentiation and to establish a system in which genes for morphologic alteration and viral and herbicide resistance can be introduced. A study of the bacterial and plant genes involved in symbiotic nitrogen fixation is underway in another laboratory.

The developmental genetics laboratories are using both *Drosophila melanogaster* and *Caenorhabditis elegans* (a nematode) in research designed to determine the role of chromatin in gene expression. They are also developing new insecticides and nematocides as well as screening procedures for mutagenicity.

The mammalian cell genetics laboratories are exploring three areas. One is the action of glucocorticoid hormones on the expression of individual genes in hepatoma

cells. Another group is studying gene expression in various differentiating eukaryotic systems such as teratocarcinoma cells and human hematopoietic and lymphoreticular cells and their tumors. They are also attempting to determine the morphological and biochemical characteristics of the isolated structural elements of eukaryotic chromosomes. A third laboratory is studying the mechanisms of the specific immune responses of the Epstein-Barr virus.

Even the Institute of Biophysics has a laboratory of nucleotide chemistry. It also boasts a laboratory for instrumental development which can make specialized equipment or modifications of complex apparatus. This ability to do sophisticated modern research is a characteristic of the various laboratories of the Hungarian National Academy of Sciences.

Studies on the use of chimeric genes and site-directed mutations to investigate structure/function relationships in the modification of methylases are being carried out by G. Posfai, P. Gal, A. Kiss, and P. Vnetianer at the Institute of Biochemistry, Biotechnology Research Center, Hungarian Academy of Sciences, Szeged. (See ONRL Report C-10-85.)

J. Ovadi (Institute of Enzymology, Biological Research Center, Hungarian Academy of Sciences, Budapest) and colleagues have developed a molecular model including the regulatory role of specific metabolites for the control of glycolysis by pairwise dynamic enzyme associations.

Radelkis Electrochemical Instruments, Budapest, has developed a commercial biosensor for clinical assays in which immobilized glucose oxidase is used with an oxygen electrode.

G. Langer and coworkers (Institute of Nuclear Research, Hungarian Academy of Sciences, Debrecen) have developed a procedure for mass spectrometric measurement in the wheat stalk. (See ONRL Report 8-001-C.)

An enzymatic method for the estimation of ornithine in tissue culture medium has been developed by A. Forgacs and T. Perenyi of the Department of Biochemistry Phylaxia, Budapest. (See ONRL Report C-10-86.)

Czechoslovakia

In October 1986, a long-term program for the development of biotechnology was carried out under the aegis of the State Committee for the Development of Science and Technology (SKVIRI). The Academy of Sciences (CsAV/SAV) has recently recommended that biotechnology should be an important development area for the country. Part of R&D is taking place within the framework of a Comecon agreement on a collaborative program in biotechnology, signed in March 1986. SKVIRI is

in charge of managing Czechoslovakia's contribution. A permanent Comecon committee has been set up for this purpose to which Minister M. Toman is a delegate.

Basic Research. Dependent on the Academy of Sciences, the Institute of Molecular Genetics carries out basic research along lines defined in 1982 (immobilized biological systems, gene manipulation technology, microbial processes, etc.). Other subjects are being studied in collaboration with the pharmaceutical industry (peptide regulators, new diagnostic techniques, and biopolymers).

Also dependent on CsAV/SAV, several institutes carry out more applied work: Institute of Microbiology (MBU), including a process engineering and automation department; Slovak Institute of Molecular Biology (biocatalysis, genetic engineering, nucleic acid metabolism); Czech Institute of Molecular Genetics (UMG), and Institute of Organic Chemistry and Biochemistry (UOCHB). The Institute of Nuclear Biology and Radiochemistry in Prague has developed a radioimmunoassay (RIA) for aflatoxin and ochratoxin. In addition there are microorganism collections. The Czech Collection of Microorganisms is specializing in species with an industrial interest.

Applied Research. As regards agro-food biotechnology, the main research organizations are: Institute for Food Research (VUP), Poultry Industry, Institute of Dairy Research, and the cannery and distillery industry. Six hundred tons per year of corn gluten is produced by the Boleraz starch processor. Technologies for biocatalysis of glucose-fructose syrup are being tested at the pilot-plant level. As in other East European countries, single-cell proteins (SCP) have been in the forefront for a few years. The cellulose factory in Paskov produces 24,000 tons of dry product per year and offers bacterial strains and know-how.

Food enzymes should become an important contribution of Czechoslovakia to the Comecon program. Industrial enzymes are under the responsibility of the State Committee for Development and Investment. The new Center for Food Biotechnology, opened 3 years ago in Modra, will carry out research along this line under the aegis of VUP.

As regards agriculture, improving crop varieties and animal stock is of major importance, as well as developing microbial crop protectors (*Beauveria bassiana* is produced on an industrial scale). A new biotechnology center for animal breeding (VUZV) has been operational since 1986 in Nitra, with the following goals: manipulating germ cells and embryos, regulating the digestive process by genetically modifying the microorganisms involved, biotransforming and producing feed-producing proteins by nonconventional species (insects), transferring embryos. This center coordinates for the Comecon program on Accelerated Reproduction of Cattle through Embryo Transplantation. The Ministry of Agriculture is

managing the national program on biotechnology, machinery, and equipment.

In human health care, most research is being undertaken with the USSR. At the industrial level, Czechoslovakia is engaged in alcaloid production; veterinary vaccines; therapeutic peptides; vitamin C, E, and A; and interferon. Antibiotics biocatalysis is being carried out on the pilot-plant scale.

Biotechnology in the Framework of Comecon

Generally speaking, the focus of the Comecon program is on proteic therapeutics, recombinant techniques, new antibiotics, new diagnostic tools (including monoclonal antibodies in infectious diseases, cancer, allergic and immunological dysfunctions, and somatic diseases). The main collaboration is with the USSR, East Germany, and Hungary.

With the USSR, the focus will be on large-scale microbial production and involves LIKO. Other subjects are: new devices for monitoring fermentation processes, amino acid production technology with Spofa (Institute of Pharmaceutical and Biochemical Research), Actinomyces selection with the MBU (Institute of Microbiology), and microorganism conservation.

With Hungary, research is being carried out on cattle reproduction, food enzymes, and fermenters. The following subjects are under discussion: data processing, culture, and separation of eukaryotic cells.

Regarding East Germany, Spofa and PKG (Dresden) are looking for new penicillins by genetic manipulation. Spofa also collaborates with a chemical concern in Leipzig on lysine production. Enzymes, recombinant chymosin, and genetic manipulation are important issues, and hybridoma culture is being studied with the Serological Institute in East Berlin.

In Czechoslovakia, new analogues of aminoglycoside antibiotics have been prepared by K. Barna and J. Kusnir (Department of Medical Chemistry, Safarika University, Kosice). (See ONRL Report C-10-86.)

The following is a list of the directors or contact persons of various research institutes in Czechoslovakia. The addresses are given in the list of scientists in Appendix B.

1. J. Zacker, Director, Center of Physiological Science SAV, CFS SAV, Bratislava.
2. M. Toman, Federal Ministry of Agriculture and Food (FMVZV), Prague.
3. Z. Hostalek, Vice-Manager, Institute of Microbiology (MBU), Prague.
4. J. Zelinka, Manager, SAV, Institute of Molecular Biology, Bratislava.
5. S. Zadrazil, Vice-Manager, UMG (CsAV Institute of Molecular Genetics), Prague.

6. L. Novotny, Vice-Manager, UOCHB (CsAV Institute of Organic Chemistry and Biochemistry), Prague.

7. O. Nemecek, Manager, Spofa (Institute of Pharmaceutical and Biochemical Research), Prague.

8. V. Hajko, President, SAV (Slovenska Akademie Ved, Slovak Academy of Science), Bratislava.

V. Jirku (Department of Fermentation Chemistry and Bioengineering, Institute of Chemical Technology, Prague) and J. Turkova (Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague) are working on cell immobilization by covalent linkage. They have reported on the preparation, properties, and the experimental application of different types of eukaryotic cells covalently bound to solid supports.

Bulgaria

One of the basic goals of the Bulgarian Academy of Sciences is to ensure from a scientific point of view the fulfillment of a national program for the development of biotechnology in the People's Republic of Bulgaria during a 5-year plan and up to the year 2000.

Bulgaria is one of the largest producers and exporters per capita of antibiotics for medical, veterinarian, and agricultural purposes. Future expansion of this production needs a solid scientific foundation. The Pharamkhin Company, with its scientific institutions and development bases, is a leading element in this activity. At the Elin Center for Biology at the Bulgarian Academy of Sciences, work is in progress to produce a certain number of antibiotics with antiviral and antifungal activity, and also antibiotics for crop protection.

The Institute of Microbiology, Sofia, plays a major role in the development of classical biotechnology for the production and use of bacterial enzymes. Considerable success has been achieved in isolating highly active bacterial, mold, and actinomycetes strains. On the basis of thorough basic and applied research, a series of biotechnological applications for the production of enzymes has been developed and introduced, or is being introduced.

According to the Bulgarian government, the achievements of the Institute of Molecular Biology in research on the structure and function of the nucleic acids in chromatin and the transfer mechanisms of genetic information have received worldwide acclaim. These achievements emphasize the leading role of the institute in the creation of genetic engineering biotechnologies in Bulgaria. Laboratories have been built for the processing and synthesis of DNA, for cell cultures and a large collection of bacterial strains, plasmid, and bacteriophage vectors. Characteristic of the research and applied work at the institute is the close tie between basic research and its practical

is the close tie between basic research and its practical application. An effective technology to produce human alpha-interferon has been developed from cell cultures. Supposedly, scientists at the institute have succeeded with a total chemical synthesis of human gamma-interferon.

With the aid of plant protoplasts and cell cultures, Bulgarian scientists are resolving a series of theoretical problems in genetics and the selection of plant species. The following institutes are participating in fulfillment of the general coordination program of the Bulgarian Academy of Sciences for plant tissue cell cultures: Institute of Molecular Biology, Institute of Plant Physiology, Institute of Botany, the Forestry Institute and the Institute of Physiology. The activity of the Laboratory of Plant Cell and Tissue Cultures is supported and expanded within the framework of the Institute of Kinetics, where, in addition to applied development, theoretical and methodological research is being done. Close cooperation has also been established between the Elin Center of Biology and the Agricultural Academy in the sphere of genetic engineering and plant and tissue cell cultures. In Bulgaria, the Institute of Biology and Immunology of the Reproduction and Development of Organisms is a pioneer in the processing of biotechnology for zygotic and embryonic transplants, in which animals reproduce in an accelerated fashion and select themselves.

According to Professor Stoyan Tsonkov, Director of the Central Laboratory of Bio-Tool Making and Automation, Bulgarian Academy of Sciences, the development of modern biotechnologies is impossible without the creation of modern bioreactor equipment and automation of biotechnological processes. In creating this, the specialists from the Elin Center for Biology have gradually directed work at the Central Laboratory for Bio-Tool Making and Automation. Tsonkov says that scientists in Bulgaria are now creating bioreactors with microprocessor regulation and are moving toward construction of bioreactors for biotechnological processes, and in the next few years, toward bioelectronics.

A.A. Hadjlov, Director of the Institute of Cell Biology and Morphology, Bulgarian Academy of Sciences has said that the institute has a long tradition in research. Recently, members of the institute have been investigating more and more successfully vertebrate and human cells. According to Hadjlov, its accomplishments in blood, reproductive, and nerve cell research are highly valued in scientific circles and have given the institute the opportunity to collaborate productively with scientific teams from the USSR and other countries. Hadjlov says that the institute is a pioneer in Bulgaria on implementation of hybridization methods for obtaining monoclonal antibodies. Some of them, such as those against viruses and rickettsias, as well as those against normal and cancer cells, are especially important for the

future of applied medicine. In the last few years the institute has been rapidly adopting the procedures and methods of modern cell biology. The most important part of Hadjlov's scientific work is dedicated to molecular mechanisms of cancerogenesis, structure, and transcription of genes in eukaryotic cells and regulatory mechanisms of gene translation in animal cells.

Bulgaria is specializing in the production of microbiological compounds for agriculture. A biochemical facility in Peshtera is manufacturing pesticides, bacterial fertilizers and plant growth regulators. The Peshtera facility is also producing feed additives and biologically active substances to increase livestock productivity. An unidentified combine in Peshtera is the only facility in Bulgaria with a joint production-plant/scientific-research institute for the manufacture of various antibiotics and veterinary compounds derived from bacteria. These compounds improve the vitality of livestock and compensate for nutrient deficiencies in forage. The compounds Tylosin, Monensin, Bacitracin, Flavofarm, and Biovit are being produced as feed additives to stimulate livestock growth. Their application has resulted in a 10- to 15-percent increase in meat, milk, and egg production in Bulgaria and a significant reduction in feed expenditure. A recent product of the Peshtera plant is Salinomycin, an antibiotic for poultry, which until recently, was purchased from abroad. Other high-quality products are Flavomycin and pure lysine (an essential amino acid for fattening livestock) which can be produced in the form of ampules, pellets, and powders for livestock needs. Antibiotics, growth stimulants and lysine (previously imported from Japan) are also priority production projects of the Peshtera combine. In addition, the Peshtera facility is producing Dipel (*Bacillus thuringiensis*) to protect plants against caterpillars. Plants are sprayed with a special protein crystal solution that destroys caterpillars but is nontoxic to humans, poultry, and bees. In addition, a local agroindustrial complex cooperates with the combine to supply lavender, from which an antibiotic with fungicide action is produced that protects plants from powdery mildew.

It has also been reported that three types of solid-phase fermenters have been constructed and tested: stationary, with an agitator, and with a rotating cylinder. Testing of these fermenters is in the initial stages and improvements are in progress.

M. Stoychev and coworkers, Bulgarian Academy of Sciences, Sofia, have developed a procedure for immobilized glucose isomerase. The enzyme catalyzes the conversion of D-glucose into D-fructose and is used in a continuous process of converting glucose syrups, obtained by starch enzymatic liquefaction and saccharification, into fructose syrups used as a substitute for sucrose in the food industry. The compound is called Bigizyme and is produced and marketed by BAN IMPEX, Sofia.

Israel

Only 40 years old, Israel has confidently asserted its claim to be taken seriously as a force in international science. Israeli scientists have certainly shown themselves capable of making valuable contributions across a wide spectrum.

Israel has grown up with a strong science community. Chaim Weizmann, Israel's first president, was also the first president of the scientific institute that bears his name. Weizmann believed that science would have to be one of the pillars upon which the state of Israel would rest, as there were and are few natural resources on which Israel can count for economic prosperity. From the first day of independence, Israel had three universities – two entirely devoted to science and engineering. Today, there are seven universities serving a population of just over 4 million.

Although fiercely independent, Israel has relied from the start on the generosity of wealthy patrons throughout the world to support all strata of society, especially science. There is scarcely a building in Israel that does not bear the name of some wealthy patron. But Israel is no longer in desperate need of buildings: it needs operational cash. US foreign aid has been particularly crucial, amounting to \$3 billion a year, or approximately 12 percent of Israel's gross domestic product. Researchers go abroad for the money to operate their laboratories. Domestically, the Binational Science Foundation is the largest source of funds for basic research (about \$8 million a year), but to qualify for a grant one must have a bona fide US collaborator. The Israeli National Council for Research and Development gets only about \$2.7 million from the Israeli government, although it does distribute other money, mostly from foreign sources.

In pushing towards economic independence – or what will pass for economic independence, given continued US support – Israel has concluded that it must put its resources into applied research; projects that will give Israel a market niche that it can profitably exploit.

Many of Israel's difficulties in the allocation of limited resources are the same as those now encountered elsewhere, but Israel has its own special problems. Money for basic research that is necessary also for advances in biotechnology, will probably always be tight in a country that spends nearly 60 percent of its research budget on defense. A solution of its political problems would give Israel the luxury of supporting its strong scientific community generously, but at the present time, this seems remote.

Government

Authority for setting policy and distributing money does not reside in one individual office of the Israeli government, but is spread throughout the various ministries. This decentralized organization results from the recommendation of a commission that was chaired by Ephraim Katchalski-Katzir, a professor at the Weizmann Institute of Science as well as head of Tel Aviv University's Biotechnology Center and also the fourth president of Israel.

Some ministries have come to play important roles in the pursuit of Israeli science. The chief scientist for the Ministry of Industry and Trade, for example, provides government support for start-up companies, and has been actively engaged in forming international cooperative agreements in industrial development and technology. In the Ministry of Agriculture, the Agriculture Research Organization (ARO) sets policy for agricultural research, both at the government-run Volcani Center and at academic institutions.

Energy's chief scientist also supports university and industrial research although recent policy has supported applied rather than basic research. The Defense Ministry conducts its research activities both through its wholly owned armament development authority (RAFAEL) and the Israel Military Industries, as well as supporting projects both in private industry and universities. Surprisingly, the chief scientist in the Ministry of Health has a tiny budget, and does not have a major role to play in biomedical research.

The prime minister's office has retained control of the Israel Atomic Energy Commission (IAEC), which in turn runs two experimental nuclear reactors at Dimona and Soreq. Also, under the prime minister is the Israel Institute for Biological Research (IIRB) in Ness-Ziona. In addition to conducting both basic and applied biological research, IIRB markets the fruits of the research that is performed there.

In 1982, the government created the science ministry and moved the NCRD into it. The new ministry has served mostly an advisory capacity, although it does have a small budget. The Israel Space Agency is also part of the science ministry.

Money for higher education goes to the Planning and Grants Committee (PCG) through the independent Council for Higher Education. PCG is nominally part of the education ministry, but for the most part acts independently.

Universities

The Weizmann Institute of Science ranks among the first-class science institutions in the world. The Weizmann has managed to produce some of the brightest stars in disciplines ranging from molecular biology to artificial intelligence. Although beset by the same financial burdens now plaguing all Israeli universities, the institute's problems are not nearly as severe, and scientists there continue to enjoy relative prosperity. But there is a growing fear that without some changes, even the Weizmann will feel the chill winds of financial neglect.

As a small institution devoted more to research than to teaching, unlike Israel's other universities (it has no undergraduates), the Weizmann has a flexibility not shared by other Israeli universities. Weizmann can concentrate its resources where they can make the greatest impact—as example, Hebrew University in Jerusalem cannot close a department if it begins to founder but the Weizmann can do so. The strengths of the institute are spread across many disciplines. There are strong faculties in molecular, cell and developmental biology, neurobiology, genetics, structural chemistry, theoretical physics, applied mathematics, and artificial intelligence to name a few. A detailed account of research activities at the Weizmann Institute is available in *ESN* 40-1:1.

The following section deals with some of the biotechnology-related projects and scientists involved at the Weizmann Institute.

Immunology. G. Berke (Department of Cell Biology) and colleagues are closely probing the way immune system cells attack and destroy foreign tissues, as is commonly observed in the rejection of organ transplants.

M. Sela and R. Arnon (Department of Chemical Immunology) are working on making vaccines easier to prepare. Using small, synthetically produced fragments of viruses or bacteria linked to special carriers, they have been able to induce immunity against disease without recourse to the weakened or dead viruses used in standard vaccines. They have already applied such "synthetic vaccines" to protect animals against influenza, diphtheria, and cholera.

I. Cohen and coworkers at the the Department of Cell Biology have, for the first time, isolated and grown in tissue culture the T-lymphocytes responsible for the appearance in animals of three autoimmune conditions, similar to multiple sclerosis, autoimmune thyroiditis, and arthritis in man. In all these cases, the researchers have been able to neutralize these cells and use them in a therapeutic program to lessen disease symptoms or prevent their appearance entirely.

I. Pecht (Department of Chemical Immunology) and his associates carried out the first mechanistic analysis of homogeneous antibody-hapten reactions. They were able to do a kinetic mapping of the antigen-binding site

of the examined Ig and to resolve the conformational transitions induced in the antibody upon hapten binding. (See ONRL Report R-6-85.)

Monoclonal antibodies against the *Torpedo* acetylcholine receptor (AChR) have been produced and analyzed by S. Fuchs, Head of the Department of Chemical Immunology, in her studies on experimental autoimmune myasthenia gravis (EAMG). These antibodies block AChR binding and sodium transport, accelerate the receptor turnover, and modify single channel properties. Antibodies to idiotypes on anti-AChR antibodies are being used to study the idiotypic repertoire of the immune response to AChR and to assess the potential of anti-idiotypes for immune regulation of EAMG. (See ONRL Report R-6-85.)

An important innovation in immunochemistry was the use of synthetic polypeptides to elucidate the genetic regulation of specific immune responses. Their use was pioneered by M. Sela and collaborators. For the first time, E. Mozes and coworkers showed that antibody specificity was genetically controlled in mice. They have recently demonstrated with synthetic T-cell replacing factors that immune response (Ir) genes may be expressed in different cell populations. Also in the Department of Chemical Immunology, P. Lonai and coworkers have studied the Ia-associated antigen complexes that are released by macrophages and that contain part of the antigen in conjunction with Ia gene products. At present, the immunogenicity, binding restrictions, and biochemical characteristics of these "processed" antigens are being studied. J. Puri and colleagues have analyzed the "immunogen" which is bound to T-cells responding to different species' insulin. They have found that the binding of radioactive antigen to these cells depends on the origin of MHC class II determinants of the antigen-presenting cells. (See ONRL Report R-6-85.)

The avidin-biotin complex is being used by I. Cohen and A. Friedman (Department of Cell Biology) and C. Gitler (Department of Membrane Research) as a tool to study the molecular mechanisms by which antigens under Ir gene control are processed and presented to lymphocytes. (See ONRL Report R-6-85.)

Genetics Research. At the Weizman Institute, researchers have long been occupied with finding out exactly how genetic information is selectively translated into the chemicals necessary for forming and sustaining body tissue. Basic work in this area is carried out in eight departments. Several years ago, Y. Aloni, S. Lavi, and Y. Groner (Department of Virology) demonstrated the existence of a "split gene," an important development that has helped in understanding the intricate workings of the genetic machinery. They are continuing to explore the complex molecular events that control the expression of genetic traits.

Other Institute scientists are closely examining the nature of genetic disease. In the Department of Genetics, L.Sach's early development of prenatal diagnosis via examination of amniotic fluid cells of a fetus has today been expanded by others to provide a standard method of screening for hereditary diseases, including Down's syndrome and Tay-Sachs disease.

D. Yaffe (Department of Cell Biology) is studying the hereditary disease of muscular dystrophy. He and his group have developed a system for isolating and growing pure cultures of muscle-forming cells taken from dystrophic mice. In cultures, these cells develop into muscle fibers able to contract and express other biochemical and physiological characteristics of muscle tissue. These researchers are using their system to identify the molecular basis of the biological defect responsible for this severe muscle-wasting disease.

Synthetic chemical research carried out at the Department of Organic Chemistry by D. Shapiro and colleagues in cooperation with US scientists has led to new information on three rare genetic afflictions: Gauchers, Niemann-Pick, and Fabry's diseases. Supplies of reagents available only from Shapiro's laboratories have already led to diagnostic tests for Niemann-Pick and Gauchers diseases, both debilitating illnesses characterized by faulty lipoprotein metabolism. These have also enabled isolation of an enzyme, the absence of which is responsible for Gauchers disease and that may eventually be used for treatment. Attempts are now underway to produce it in quantities large enough for therapeutic use.

Institute researchers N. Sharon, Head of the Department of Biophysics, and Y. Reisner have made an important contribution to the treatment of inborn immunodeficiency diseases, conditions characterized by failure of the bone marrow to produce the active white blood cells needed to combat infection. Using plant proteins known as lectins, these researchers, collaborating with US scientists, have designed a new way of preparing marrow transplants, making possible safe reconstitution of blood-forming tissue and immune function even with immunologically noncompatible donors.

Burn and Wound Healing. I. Schechter (Department of Chemical Immunology) has developed a special chemical treatment (glutaraldehyde-treated skin homografts) aimed at delaying the rejection of skin transplants (to cover burn surfaces) and thus allowing protective skin covering to remain in place longer. This technique, first tried successfully on animals has been used with promising results by the Israeli Defense Forces and is now being incorporated into routine treatment of chronically infected wounds and surgical procedures that involve the removal of large patches of skin.

In related work, scientists in the Department of Membrane Research study the process of wound healing, developing techniques to accelerate tissue repair. They

have found that by treating wounds with a carbohydrate called glucan, healing time in animals can be cut in half. Glucan is now being tried on patients, particularly for postoperative care of surgical incisions.

Brain Chemistry and Nervous Disorders. The Weizmann Institute has an extensive program concerned with the structure and function of the human brain and its interrelation with behavior, both normal and abnormal.

Recently, a newly formed Center for Neurosciences and Behavioral Research has been set up, headed by D. Samuel, to coordinate all neurobiological research. The aims of the projects in basic research are the elucidation – in molecular, cellular, and subcellular terms – of the structure, development, function, regeneration, and plasticity of the nervous system and its components. Among the properties studied are ionic channels, surface membrane components, enzymes specific to the nervous system, various receptors for neurotransmitters, and effects of neuropeptide growth factors and toxins. Molecular biology techniques are used in studies of gene expression and the cytoskeletal organization of differentiating nerve cells.

In the Department of Neurobiology, headed by U. Littauer, researchers seek to clarify the role of the surfaces of nerve cells in the development and maturation of the brain. He and his group have also been studying the structure and role of microtubule-associated proteins (MAPs) during nerve cell differentiation. This was one of the first groups to report on the importance of MAPs in nervous system function.

In the same department, I. Ginzburg and her group are studying the control of microtubule protein expression in the developing brain and are also cloning brain-specific genes.

H. Soreq and her group are engaged in several research projects: (1) molecular cloning of the human genes encoding nervous system acetylcholine esterase; (2) expression of brain messenger RNAs (mRNA) in *Xenopus* oocytes; (3) control of gene expression during the development of rodent cerebellum; and (4) selective alterations of gene expression in primary brain tumors.

M. Schwartz and her group (Department of Neurobiology) are trying to understand why the central nervous system in higher animals does not self-repair. They have some evidence that the body may be producing factors that prevent injured nerves from sprouting anew. Their goal is identification of these growth-suppression materials which may lead to ways of interfering with their function. Use of externally applied electric currents to stimulate repair of nerves is also under investigation.

I. Gozes and her group (Department of Hormone Research) are studying the molecular aspects of endocrinology, including gene cloning and control of expression of regulatory peptides which serve both as neurotransmitters and hormones. One of the research projects carried

out by this group is a study of the vasoactive intestinal peptide (VIP), which has been found to act both as a neurotransmitter and hormone. (See ESN 40-1:1.)

A. Patchornik and colleagues (Department of Organic Chemistry) have developed several novel approaches to the manufacture of fine biological and other organic chemicals with the aid of polymeric reagents – chemically reactive structures tethered to porous solid materials. Using these reactive solids, chemical interactions occur with ease between the insoluble polymer and soluble components taken up by its absorbent structure. According to Patchornik, solid reagents are particularly useful for large-scale manufacturing applications because they are suitable for mechanization and computer-control. Patchornik and coworkers have already designed various chemical strategies taking advantage of the special properties of polymeric reagents. Patchornik has already built a model machine for his solid-state approaches. A patent has been taken out by Yeda R&D, Ltd.

A Lapidot and her group (Department of Isotope Research) are developing novel microbial systems and matrix-bound microorganisms for industrial production of amino acids and biogenic amines tagged with nitrogen-15 and carbon-13 isotopes – or simultaneously with both.

S. Margel and coworkers (Department of Materials Research) have designed extremely uniform submicroscopic microspheres (which have been patented). These microspheres can be conveniently encapsulated in agarose (a polysaccharide element of agar) and easily modified for a specific task. The beads can be produced in sizes varying from 0.01 to 8 microns and be provided with fluorescent dyes for viewing under an optical microscope, magnetic particles for magnetic separation materials, and metal coatings for use as catalysts. Production of the beads is being scaled up in collaboration with Gailil Advanced Technologies Ltd of Tel Aviv. Safety trials for use of the agarose-encapsulated beads for detoxification of patients via hemoperfusion – similar to hemodialysis – are under investigation.

L. Addadi, Z. Berkovitch-Yellin, M. Lahav, and L. Leiserowitz (Department of Structural Chemistry) have developed a novel crystallization technique which makes possible improved yields of a wide range of industrially produced biochemicals and drugs. The new approach can be applied to the preparation of various biologically active materials and requires only minor modifications of currently used industrial and laboratory crystallization procedures. This technique has already been applied at the Weizmann Institute to syntheses of commercially valuable products, such as the amino acids threonine, lysine, and glutamic acid, and D-paraoxyphenylglycine, a starting material for the manufacture of

penicillin. Patents have been applied to protect some of these crystallization processes.

M. Revel (Department of Virology) and colleagues have carried out extensive research on understanding of the biological action of interferons and their production in the body. To carry out their studies, they developed a convenient method of preparing beta-interferon, an approach subsequently licensed to InterYeda. Institute investigators have also developed other methods for commercial production of interferon in each of its three forms – alpha, beta, and gamma. These utilize genetically engineered bacteria and DNA-altered hamster cells. Pilot plants for pure alpha-, beta-, and gamma-interferons, produced via recombinant DNA technology, are already on line, and clinical research is in progress.

Z. Bohak and A. Kadouri (Department of Biophysics) have designed a tissue culture system yielding tissue plasminogen activator (tPA) from human fibroblast cells. Research support for this project is being shared by Israeli, European, and Japanese industrial and governmental sources.

H. Eisenberg (Department of Polymer Research) and colleagues are carrying out studies on halophilic bacteria which thrive in the Dead Sea despite its extremely high salt concentration. In addition to gaining basic information about archaeobacteria (such as the halophilic bacteria) studies of these bacteria are aimed at the possible use of enzymes from them in industrial processes.

Tel Aviv University

This university is the largest in Israel. Under a new scheme initiated by Yehuda Ben-Shaul, Rector of Tel Aviv University, there will be two schools in the life sciences. One will focus on biotechnology and molecular, developmental, and cellular biology. The other will encompass ecology and physiology. Ben-Shaul says that the university will try to give a special push to biotechnology and cell and developmental biology.

Center for Biotechnology. This center at Tel Aviv University was started 4 years ago by Professor Ephraim Katchalski-Katzir, who is also the director. He has a joint appointment at the Weizmann Institute of Science. Katchalski-Katzir, who has an international reputation in biophysics/biochemistry, set up the biotechnology center in Israel in the rapidly expanding area of biotechnology research.

Although the center has been in existence for only a short time, the scientific staff has made important contributions in biotechnology research in several areas. The main fields of interest and some of the projects of the senior staff of the biotechnology center are presented in the following paragraphs.

Katchalski-Katzir and his group are engaged in research on biological macromolecules including enzymes, other proteins, and nucleic acids, as well as enzyme-polymer conjugates and immobilization of cells and enzymes. They have recently used a specific monoclonal antibody (Mab) for the preparation of a highly active immobilized carboxypeptidase A. Katchalski-Katzir has a patent pending on a reagent for the specific identification of enzymes and isoenzymes in clinical specimens using Mabs. A current research and development (R&D) project supported by the Israel Council for R&D is the influence of Mabs on the activity, conformation, and stability of an enzyme.

R. Lamed and coworkers are carrying out research on thermophilic methanol and ethanol fermentation, cellulose degradation, and reductive biotransformations as well as on the thermostable enzymes and their applications. They have recently used flow cytometry for rapid identification of *Streptococcus pyrogenes* and also characterized a cellulose-binding cellulase-containing complex in *Clostridium thermocellum*.

In another study, Lamed and his group found a discrete cell-surface organelle of *C. thermocellum* which exhibits separate antigenic, cellulase-binding, and various cellulolytic activities; it is termed "cellosome." These investigators are also studying enzyme diffusion and action on soluble and insoluble substrate biopolymers. Lamed has obtained a patent on the use of co-cultures in the production of ethanol by the fermentation of biomass. He and his group are also engaged in several R&D projects: (1) cellulase-containing structures in cellulolytic anaerobic bacteria, (2) synthetic applications of alcohol dehydrogenase from *Thermoanaerobium brockii*, (3) differential inhibition of methanogenesis from acetate by ionophores present in agricultural waste, and (4) applications of flow cytometry in bacteriology.

G. Fleminger and colleagues are engaged in studies of the intracellular activity of proteolytic enzymes, the biosynthesis and processing of bioactive peptides, and microprotein chemistry. These researchers are also studying soluble and immobilized clostridial aminopeptidase and aminopeptidase P which they have found to be a metal-requiring enzyme. They have also developed a method for the sequential hydrolysis of proline-containing peptides with immobilized aminopeptidases. Current R&D projects being carried out by Fleminger and his group include: (1) the purification and characterization of a lysosomal dipeptidyl carboxypeptidase and (2) studies of the interaction of lysosomes with anti-lysosome Mabs.

J. Rishpon and her group are carrying out studies in bioelectrochemistry, including modified electrodes, biosensors, and computerized electrochemical systems. They have recently completed a study on a combined system for automated ellipsometry and for network analysis

based on a microcomputer. A current R&D project is the development of a glucose sensor based on a computerized enzyme electrode.

Y. Shabtai and his group are engaged in studies on the development of computer-controlled fermentation and separation processes, and microbial and cell-culture bioprocesses. These researchers have been carrying out extensive studies on the production in *Acinetobacter* species such as *Acinetobacter calcoaceticus* of the bioemulsifier Emulsun. They have obtained a patent on the production of alpha-Emulsuns for industrial use. A current R&D project is the development of a combined fermentation-pervaporation system for the production of ethanol by immobilized yeasts.

A. Freeman and colleagues are carrying out various research projects such as: (1) immobilization of whole cells and enzymes, (2) enzyme and cell stabilization, and (3) controlled-release pesticides. They have developed a method for gel entrapment of enzymes in cross-linked prepolymerized polyacrylamide hydrazide. Freeman and his group are also investigating factors affecting cell attachments, spreading, and growth on derivatized microcarriers. Their objective is to develop new microcarriers for culturing mammalian cells. Current R&D projects are: (1) biotransformations with immobilized plant cells, (2) controlled release pesticides, and (3) immobilized whole-cell reactor coupled with membrane separation unit. Freeman has a patent pending on enzyme electrodes.

E. Sakar and his group are engaged in the following projects:

- Flow cytometry and cell sorting
- Drug uptake in cancer treatment
- Tumor immunology
- Early diagnosis of immune disorders
- Rapid bacterial identification
- Mutant selection by flow sorting.

Current R&D projects are:

- Rapid bacterial identification by flow cytometry (supported by Hy Laboratories Ltd.)
- Development of a flow cytometric method for strain improvement of microorganisms of industrial interest
- The use of flow cytometric techniques in the screening and selection of bacterial overproducers of cell-surface polymers and bioemulsifiers
- Development of methods for the rapid production of monoclonal antibodies of potential use in cancer diagnosis and therapy
- Drug targeting of human tumors using monoclonal antibodies
- Anthracycline drug uptake by blood and bone marrow cells in human leukemias.

A detailed account of the research at the Center for Biotechnology is available in ESN 40-3:79.

L. Goldstein and colleagues (Department of Biochemistry, The George S. Wise Center for Life Sciences, Tel Aviv University) are carrying out studies on polymers bearing isonitrile functional groups as supports for enzyme immobilization.

The Hebrew University, Jerusalem

The Hebrew University formally opened its doors in 1925 when A.J. Balfour (Lord Balfour) gave the inaugural speech. The university began with programs in chemistry, microbiology, and Jewish studies. The first campus was located on Mount Scopus, to the north of the Old City of Jerusalem and was rebuilt in 1981. Apart from clinical and public health research, all scientific disciplines are grouped in the faculty of science. There are about a dozen science research centers dedicated to research in a variety of scientific disciplines from lasers to computer science to aquatic biology. The Marine Sciences Research Center in Eilat on the Red Sea affords access to deep-ocean conditions just a few hundred meters offshore.

The Institute of Microbiology, within the Faculty of Medicine of The Hebrew University, was formally established in 1967 to unite a number of departments dealing with microbiology and related fields into a single teaching and research organization. The Institute currently comprises ten departments and two laboratories, and supervises the operation of a fermentation unit that is engaged, on a contract basis, in research and development for industrial applications. Members of the Institute offer research expertise in a wide range of disciplines within microbiology. Considerable endowments and legacies – such as the Lautenberg Center for General and Tumor Immunology, the Channock Center for Virology and the S.F. Kuvine Center for the Study of Tropical and Infectious Diseases – have established research centers within the Institute.

I. Goldberg and colleagues (Institute of Microbiology, Department of Applied Microbiology) are carrying out research on the metabolism of C1-compounds in microorganisms, submerged cultures of plant cells including biotransformation and biosynthesis of biochemicals, regulation of secondary metabolite production in microorganisms, and plant cells. These researchers have developed an extraction-fermentation method for ethanol production from sugar cane. They are also involved in projects on the microbial metabolism of methanol, fermentation of pentoses to ethanol and chemical feedstocks, production of diosgenin by plant cells in suspension cultures, and the production of secondary metabolites by plant cells. Another area of research is on single cell protein (SCP) production.

J.S. Rokem (also in the Department of Applied Microbiology) coworkers are involved in research on the production and regulation of secondary metabolites in *Streptomyces* species (antibiotics) and in plant cell suspension cultures (steroids).

R. Bar and colleagues (Biochemical Engineering Laboratory, Department of Applied Microbiology) are carrying out studies on fermentation calorimetry. They are concerned primarily with the study of microbial energetics for biotechnological purposes. Another project being investigated by Bar and his group is the use of liposomal solutions for microbial catalysis in organic solvents. They have recently demonstrated microbial conversion for the oxidation of cholesterol by *Rhodococcus erythropolis*.

B. Gavish (Department of Biomedical Engineering) and coworkers are involved in several projects including:

- Development of ultrasonic methods for high-precision determination of viscoelastic properties of liquids and soft tissues (ultrasound)
- Monitoring microcirculation dynamics by ultrasonic techniques
- Modeling the dynamic state of proteins.

D. Harmatz and colleagues, in the same department, are concerned with various projects such as:

- Spectroscopic methods in biochemical and biomedical research – light scattering of biological particles (for example, red blood cells and membranes) through absorption spectroscopy and circular dichroism
- Protein conformation and interaction
- Membrane-related biochemistry
- Nonsoluble iron detection and its possible pathological significance
- Research and development of biomedical diagnostic instrumentation for blood – sensitive methods for occult blood detection in the gastrointestinal tract.

U. Bachrach and coworkers, also in the Department of Molecular Biology, are involved in several lines of research such as:

- Biological function of naturally occurring polyamines – their role in regulating growth processes
- Use of polyamines as markers of malignancy in early detection of cancer
- Biology of tumor RNA viruses
- Biochemical properties of glioma and neuroblastoma cells grown *in vitro*
- Mode of action of opiates – *in vitro* studies
- Polyamines and growth of parasites (for example, *Leishmania* species and malaria)
- Transglutaminase and its role in the cell cycle.

N. Citri and colleagues, in the same department, are concerned with several research projects:

- Role of conformational response in function of enzymes
- Conformational aspects of secretion and cellular integration of bacterial enzymes
- Mode of action of beta-lactam antibiotics
- Alternative mechanisms of bacterial resistance to penicillins
- Immobilization of beta-lactamases.

A. Samuni and coworkers (Department of Molecular Biology) are carrying out a variety of studies such as:

- Kinetic aspects of penicillin hydrolysis
- Conformational patterns of penicillins and penicillinase as related to the dynamics of interaction in enzyme-substrate systems
- Role of oxygen and free radicals in radiodamage
- Effects of radiosensitizers and radioprotectants in biological systems.

In the Department of Molecular Genetics, Institute of Microbiology, A. Cohen and colleagues are engaged in several research projects:

- Mechanism of molecular recombination in bacteria
- Construction of chimera plasmids as substrate for study of interplasmidic and intraplasmidic recombination: involvement of different gene products in the recombination process
- Reconstruction of the recombination system *in vitro*
- Construction of plasmid cloning vehicles for industrial strains of *Streptomyces*
- Cloning of the Lac permease gene and investigation of its expression in *E. coli*.

In the same department, A. Honigman and coworkers are carrying out research on the following topics:

- Regulation of gene expression in prokaryotic and eukaryotic systems
- Molecular and genetic study of termination of transcription in bacteriophage lambda and Molony Murine Leukemia Virus
- Construction of expression plasmid vectors and shuttle vectors for expression of genetic signals in *E. coli* and eukaryotic cells
- Cloning and improved expression of *Bacillus thuringiensis* lepidopteran protein gene in *E. coli*.

M. Kotler (Department of Molecular Genetics) and colleagues are carrying out studies on retroviruses including genetic studies on the adaptation of avian sarcoma virus to mammalian cells. They are also introducing viral genes into prokaryotic and eukaryotic cell genomes to study their control of expression.

A.B. Oppenheim and his group (Department of Molecular Genetics) are studying regulatory elements in bacteria and bacteriophage lambda including transcription and translation signals. They are also engaged in research in applied genetic engineering – for example, in the expression of growth hormone and other proteins in bacteria.

The Department of Molecular Virology, Institute of Microbiology, deals with the molecular biology of cells and viruses. The department's Y. Becker and colleagues are studying the cloning and expression of herpes virus genes in *E. coli* and mammalian cells. They are also studying latency and neurovirulence of HSV-1 as well as carrying out molecular studies on ataxia-telangiectasia.

In the same department, R. Kaempfer and his group are involved in several research projects:

- Control of expression of the human gene encoding interleukin-2
- Control of expression of the human gene encoding immune interferon
- Erythropoietin – molecular biology and diagnostics
- Development of specialized eukaryotic gene screening and expression vector
- Translational control of eukaryotic gene expression
- Translational control of hemoglobin switching in man
- Development of a nontoxic interferon inducer.

Research in the Department of Membrane and Ultrastructure Research, Institute of Microbiology, deals mainly with the structure and function of biological membranes and with new approaches to improve the resolution of electron microscopy. Membranes of mycoplasmas, enveloped mycoplasma viruses, blood cells, and gram-negative bacteria are the major subjects of research.

I. Kahane and colleagues in this department are studying:

- The importance of the cell membrane glycoproteins in cell physiology and pathophysiology
- The interaction between the pathogenic mycoplasmas (which are membrane parasites) and the host cell membranes – characterization of those membrane components which are involved in the interaction
- The glycoporphins of normal and abnormal red blood cell membranes
- The formyl peptide chemotactic receptor of neutrophils
- The interactions of the contractile proteins and membrane components in mycoplasma and human platelets.

M. Kessel and coworkers are involved in the following projects

- Electron microscopy of periodic biological assemblies and of single molecules
- Special low-dose techniques in recording and computer image processing of the recorded data to achieve the highest possible resolution
- Studies of the enzyme glutamine synthetase
- Studies of the cell wall of halophilic bacteria under different physiological conditions
- Mycoplasma proteins and viruses
- Low-temperature electron microscopy.

S. Razin and his group are studying:

- Physiology and ultrastructure of mycoplasmas
- Molecular genetics of mycoplasmas
- Adherence of pathogenic mycoplasma to host cells
- Mycoplasma membranes, with particular emphasis on the role of cholesterol in membrane function.

S. Rottem and coworkers are involved in:

- Studies on the compositional distribution of lipids between the inner and outer leaflets of mycoplasma membranes and their rate of transbilayer movement
- Electrochemical gradients across the mycoplasma membrane and its influence on membrane structure and dynamics
- The structure of an enveloped mycoplasma virus and the mechanism of its interaction with the host cell.

Institute of Biochemistry. This is a newly established administrative body operating, since 1981, to bring together comprehensive research and the teaching of biochemistry at The Hebrew University-Hadassah Medical Center. Grouped within the Institute are the Departments of Cellular Biochemistry, Membrane Biochemistry and Neurochemistry, Physiological Chemistry, and Developmental Biochemistry.

H. Cedar and colleagues (Department of Cellular Biochemistry, Institute of Biochemistry) are concerned with the role of DNA methylation in the control of gene expression in eukaryotes – study of the metabolism and the mapping of changes in the methylated sites of specific genes that occur during differentiation. They are also interested in the role of chromatin proteins in the regulation of gene activity as well as the structure and function of chromatin and the localization of active genes. These researchers are also investigating the metabolism of methylation in eukaryotic DNA.

G. Glaser, in the same department, and coworkers are studying the control of prokaryotic ribosomal gene expression as well as cloning the promoter and terminator regions of the ribosomal gene. They are also studying the structure and control of ribosomal RNA genes in mycoplasma. In addition they are involved in research on the molecular basis and prenatal diagnosis of thalassemia.

Y. Pollack (Department of Cellular Biochemistry) and his group are involved in the following projects:

- Cloning of mitochondrial genes
- Studies in antimalarial drug resistance
- Basic properties of *Plasmodium falciparum* (malaria-causing agent) DNA
- Cloning of *P. falciparum* genes
- Role of DNA methylation in eukaryotes.

In the same department, A. Razin and coworkers are concerned with the following topics:

- Mode of methylation of DNA in microorganisms and in eukaryotic systems
- Role of DNA methylation in control of DNA replication and gene expression
- Use of restriction enzymes and molecular cloning in probing DNA methylation in prokaryotes and vertebrates
- Changing *in vitro* of biologically active sequences in DNA by the use of chemically synthesized deoxyribonucleotides.

Y. Barenholz (Department of Membrane Biochemistry and Neurochemistry) and colleagues are working on the following topics:

- Relationship between physical and biological properties of biological membranes
- Characterization of viral membranes
- Involvement of lipids in the aging process
- Application of liposomes in biomedical problems
- Relationship between lipid composition of cell membranes to membrane and cell functions.

H. Rahamimoff and her group, in the same department, are carrying out research on the following topics:

- Calcium fluxes in excitable membranes (nerve terminals and cardiac membranes)
- Investigation of calcium transport systems – ATP-dependent calcium transport systems; sodium-gradient-dependent calcium transport systems; membrane-potential-driven calcium transport systems
- Regulation of intracellular calcium ion concentration in nerve terminals
- Modulation of calcium transport by drugs and toxins.

S. Avramovici-Grisaru and colleagues (Department of Pharmaceutical Chemistry, School of Pharmacy) are carrying out studies on the synthesis of new drugs to combat iron overloads (chelation therapy) and pyridoxal-based siderophores as potential inhibitors of ribonucleoside-diphosphate reductase.

R. Ben-Shoshan and coworkers in the same department are engaged in the following studies:

- Bio-organic and organometallic chemistry
- Metal complexes of biological interest and their role in medicine

- Synthesis of coordination compounds of noble metal such as platinum and the evaluation of their potential antitumor properties
- Synthesis of oligonucleotides and the study of their interaction with metal complexes.

M. Chorev and his group (Department of Membrane and Ultrastructure Research) are involved in several projects:

- Bio-organic and medicinal chemistry of biologically active peptides – synthesis, conformational analysis, biology, and pharmacology of selective metabolically stable, semirigid, pseudopeptide analogues of substance P, enkephalin, and gastrin
- Topochemical approaches for transformation of peptides to either partially peptidic or fully nonpeptidic structures with retention of biological activities
- Synthesis of specific inhibitors of proteolytic enzymes and affinity labels for beta-adrenergic receptor
- Inhibitors for virus penetration into host cells.

In the same department, J. Deutsch and coworkers, are studying:

- Mass spectrometry – relation between structure and behavior of molecules in the mass spectrometer
- Biological and biochemical applications, genetic engineering, and synthesis of oligonucleotides and their characterization
- Structure elucidation of natural compounds.

Also in the same department, A. Goldblum and colleagues are involved in:

- Quantitative structure-activity relationships in biomedical chemistry
- Quantum mechanical calculations of structure, properties and interactions of drugs
- Electrostatic field and electrostatic forces between drugs and receptors
- Hydration of drug molecules
- Theoretical calculations of reaction kinetics.

S. Sarel and his group are studying:

- π -substituted cyclopropanes as building blocks for cyclic and polycyclic systems
- Nitrogen-centered free radical chemistry
- Reactive free radicals that can damage genetic material
- Total synthesis of antibiotics from sponges (Latrunculins A and B), resembling the activity displayed by the cytochalasins
- Chemotherapy of tropical diseases – drugs against Kalazar (*Leishmania donovani*) and against human malaria (*Plasmodium falciparum*)

- Pyridoxal-based siderophores as potential anticancer pro-drugs.

Industry

The promise of biotechnology has attracted interest in Israel just as it has in most countries. But Israel has some advantages to set it apart from the "me-too" players in the biotechnology game. The immobilized enzyme system used in bioreactors and bioanalyzers was developed by E. Katchalski-Katzir, and other scientists from Israel have done seminal work on synthetic peptides, synthetic antigens and, more recently, growth factors. But even with these advantages, turning a profit in biotechnology will not be easy, as older and better-situated companies have found.

The first biotechnology company in Israel was Miles-Yeda. Founded in 1967, Miles-Yeda was a joint venture between the large pharmaceutical company Miles, and the commercial holding company for the Weizmann Institute, Yeda. But after the West German company Bayer purchased Miles, Miles sold its share to Yeda, and the company became known as Bio-Yeda in 1983.

The arrangement with Miles had provided the Israeli company with the necessary international marketing force, but Bio-Yeda had to make its own arrangements. Since the Israeli market for biotechnology is small, international distribution is crucial. After struggling with this issue for 3 years, Yeda sold the company to Makor Chemicals, a subsidiary of the US chemical company Sigma, with a name change to BioMakor.

Charles Hexter, deputy managing director at Bio-Makor, says that the company works at a "basically scaled-up laboratory" size. Research immunochemicals were the first products, and remain BioMakor's main focus. The company's annual sales are about \$3 million – 90 percent from exports. Hexter says scientific talent in Israel is as good as anywhere, but market feedback is a problem. He believes that it would be "very difficult if not impossible" for an Israeli company to penetrate an international market without a US or European partner.

Despite the difficulties, more biotechnology companies are springing up in Israel, and biotechnology is frequently mentioned as a growth area for Israeli industry. Bio-Technology General and InterPharm Laboratories are, respectively, conducting clinical trials of human superoxide dismutase and developing a recombinant beta-interferon. Bio-Technology General is the first among Israel's companies and is backed by US investment. The company also offers an innovative range of recombinant DNA-based products. Proprietary vector and expression systems give BTG a competitive edge on many biotech companies. Other notable companies include BioHyTech, which has evolved an innovative and well-marketed range of probes for antinuclear anti-

bodies. Hy Labs was the first wholly Israeli-owned biotech firm. With a keen sense for exploiting niches in microbiology they intend to expand their export activities. They hope to find partners to develop equipment for automated clinical microbiology. This year, Bio-Technology General received Israel Ministry of Health approval to market its human growth hormone Bio-Tropin in Israel. This is the first approval the company has received to market a pharmaceutical.

Katchalski-Katzir believes the government must provide more money during the difficult intermediate stage between product development and marketing. However, even if the biotechnology industry thrives in Israel, its scale will be insignificant compared with the US and certainly much less than in the European countries, especially West Germany, France, and the UK.

APPENDIX A: ONREUR BIOTECHNOLOGY PUBLICATIONS BY C. ZOMZELY-NEURATH

The articles, reports, and notes listed below are in chronological order: ESN 39 (1985), ESN 40 (1986), ESN 41 and ESNIB 87 (1987), and ESNIB 88 (1988). The references, in order, indicate volume number (or year), issue number, and page number. Thus, 39-6:239 indicates volume 39, issue 6, page 239; and ESNIB 87-01:6 indicates 1987, issue 1, page 6. ONRL and ONREUR report numbers follow an equivalent scheme.

| | | |
|---|--------------|--|
| European Science Notes (ESN) | 40-4:117 | Center of Molecular Biology, Canto Blanco (Madrid), Spain |
| 39-6:239 Basel Institute for Immunology, Basel, Switzerland | 40-4:123 | Life Sciences Research at Trent Polytechnic, Nottingham, UK |
| 39-6:240 Neurobiology & Genetics at the Friedrich Miescher Institute, Basel | 40-5:151 | Plant Genetics Systems; University/Industry Collaboration |
| 39-7:293 Biology at ETH-Zurich: Institute for Biotechnology | 40-6:193 | Biological Science Under TNO – The Netherlands Organization for Applied Research |
| 39-7:298 Biology at ETH-Zurich: Molecular Biology and Biophysics | 40-6:197 | Center of Immunology, Marseille-Luminy, France |
| 39-7:304 Biology at ETH-Zurich: Institute for Molecular Biology II | 40-7:219 | Life Sciences Research at the Institute for Biochemistry, Free University of Berlin |
| 39-9:408 Research in the Life Sciences at the Universities of Uppsala, Stockholm, and Lund, Sweden | 40-7:223 | Research at the Institute for Biochemistry and Molecular Biology, Technical University of Berlin |
| 39-11:499 Biotechnology in France: Status and Prospects | 40-8:260 | Workshop-Conference on Growth Factors in the Nervous System |
| 39-11:501 Research at the FRG's Institute of Biotechnology | 40-9:301 | Biotechnology Conference on Biosensors Sponsored by the Royal Society London, UK |
| 40-1:7 Weizmann Institute of Science: Life Sciences Research | 40-10:333 | Life Sciences Conference: "From Enzymology to Cellular Biology" |
| 40-2:39 Biotechnology Research at GBF, West Germany | 40-11/12:405 | Second International Workshop on Immunomodulation |
| 40-2:39 Biotechnological Activities of the Institute of Technical Chemistry University of Hannover, West Germany | 41-2:60 | Gene Technology: 17th FEBS Meeting |
| 40-2:45 7th European Immunology Congress, Jerusalem, Israel | 41-2:63 | Biotechnology: 17th FEBS Meeting |
| 40-2:46 Biotechnica '85: First International Congress for Biotechnology | 41-3: 121 | Biotechnology in East Germany |
| 40-3:79 Center for Biotechnology, Tel-Aviv University, Israel | 41-3:124 | Regulatory Peptides in the Brain and Gastrointestinal Tract is Topic of Workshop |
| 40-3:81 Biotech '85 International Conference and Exhibition for Bio and Gene Technology, Düsseldorf, West Germany | 41-4:181 | Third European Seminar and Exhibition on Computer-Aided Molecular Design |
| 40-3:86 First International Conference on Protein Engineering, London, UK | 41-5: 230 | Molecular Biology: Eukaryotic Chromosome Replication |
| | 41-5:235 | Molecular Biology: Conference on Genetic Engineering Techniques |

| | | | |
|--------------------------------|--|-----------|--|
| 8-001-C | Fourth European Conference on Biotechnology (Amsterdam) | 39-11:537 | Industrial Production of Monoclonal Antibodies Underway at UK Firm |
| 8-002-C | Biotechnology Congress: Biotechnica '87 | 39-11:537 | Pilot Plant for Monoclonal Antibody Production |
| 8-003-C | International Conference on Separations for Biotechnology, Reading, UK | 39-11:537 | New Gene Technology Research Groups at MPI, West Germany |
| 8-006-C | Biotechnology Conference: Diagnostics '87 | 39-11:538 | United Kingdom Seeks Biotech Investments |
| 8-007-C | Biotechnology Conference: Drug Delivery and Drug Targeting Systems | 39-12:575 | Expansion of Swedish Biotechnology Center |
| 8-010-C | European Seminar on Neural Computing | 39-12:575 | New Biotechnology Research and Development Company Created in France |
| News and Notes (in ESN) | | | |
| 39-10:489 | Third World to Set Up Major Biotechnology Research Program | 39-12:575 | Academic-Industry Cooperative Programs in Biotechnology in The Netherlands |
| 39-10:490 | EEC Targets Biotechnology "Concertation" | 40-3:110 | Biotechnology Research and Development in Sweden |
| 39-10:491 | EEC Backs Biomass | 40-3:110 | UK Governmental Biotechnology Support |
| 39-10:491 | European Biotechnology Services | | |
| 39-10:492 | European Biotechnology Information Project | 40-3:111 | West German Government Program in Applied Biology and Biotechnology |
| 39-10:492 | Biotechnology Firms Back "Club" Named BIOSEP | 40-4:142 | New Laboratory Tool for Microbiological Research Developed by Israeli Scientists |
| 39-10:492 | New Biotechnology Centers in the UK | 40-5:185 | Emphasis on Biotechnology |
| 39-10:494 | GMIDC - A New Biotechnology Center in the UK Subsidized by Industry | 41-2:104 | EUREKA Proposals in Biotechnology |
| 39-10:495 | NOVO Plans Large-Scale DNA Human Insulin Production Plant in Denmark | 41-3:151 | Biotechnica '86: Second International Congress and Exhibition for Biotechnology |
| 39-11:536 | GBF and Industry Cooperate in West Germany | 41-8:451 | Update on Biotechnology Research in West Germany |

APPENDIX B: SCIENTISTS LISTED IN THIS REPORT

The following list of scientists is arranged alphabetically as a convenience for reference from the preceding text. For lists of these scientists by country, city, or institution, please contact Mrs. Sher Shroeder at ONREUR, Box 39, FPO New York 09510-0700. Phone: (44-1) 409-4131.

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APPENDIX C: BIOTECHNOLOGY INFORMATION FROM OTHER SOURCES

ONREUR has access to a wide variety of technical and administrative summaries, notes, report abstracts, and other items of interest that are generated by the European offices of US agencies.

These sources include: The European Office of Aerospace Research and Development (EOARD) and the US Army Research, Development, and Standardization Group (USARDSG) [both located in the same building with ONREUR]; US Embassies in the various countries; the Foreign Broadcast Information Service (FBIS) in both Antwerp and Milan; and others.

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