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UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

Genetic Engineering and Biotechnology Monitor

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1573/

Dear Reader,

This 14th issue of the Monitor, covering the three-month period from September to December of 1985, will hopefully again emphasize the importance of recent developments in this technology.

Many of our readers have been curious to hear news of the progress being made on the setting-up of the International Centre for Genetic Engineering and Biotechnology, and in this issue you will find a brief review of the meeting held in Havana (Cuba) at the end of November last year. Amongst the various items covered, considerable attention was devoted to the subject of appointing a Director and the heads of the two components at Trieste and New Delhi. It is hoped that by the next meeting of the Preparatory Committee a Director and the heads of components could be selected. More information on this matter will be brought in the next issue of the Monitor.

Another subject that will be receiving more attention in future will be the question of safety. UNIDO, together with the World Health Organization and the United Nations Environment Programme will hold the first meeting of an informal working group in January 1986 to review a number of safety related issues and to consider what elements are required for a set of minimal guidelines useful to developing countries wishing to regulate their bio-science based industries. Proposals may now be made by the informal working group to the International Centre for Genetic Engineering and Biotechnology for consideration and action.

In early March it is intended to hold a Workshop on Biotechnology and Industrial Commodities at Trieste (Italy) which will make recommendations for the Trieste components of the ICGEB to provide a sharper definition of the research needs in specified areas of industrial biotechnology, particularly those germane to the needs of developing countries, such as enzymes (including protein engineering); pharmaceuticals; vaccines, hormones and other synthetic polypeptides; bioprocessing and polysaccharides and hydrocarbon microbiology. A report on this workshop will also be made in the next Monitor.

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A. POLICY, NEWS AND OTHER EVENTS

UNIDO news

International Centre for Genetic Engineering and Biotechology

The Preparatory Committee on the Establishment of the International Centre for Genetic Engineering and Biotechnology (ICGEB) held its seventh session in Havana, Cuba, from 26-28 November 1985 and arrived at the following conclusions and decisions:

(a) Provisional application of the Statutes;

(b) Ratification of the Statutes;

(c) Headquarters agreements;

(d) Recruitment of scientists;

(e) Missions for securing additional financial resources;

(f) Installation of infrastructure in the components;

(g) Reports of specialized workshops;

(h) Report of the work of the Project Leader.

The Committee further agreed on the usefulness of the idea of drawing upon the expertise of high-level scientists on an ad hoc basis for specific purposes. It decided to request the Director, once appointed, to submit proposals to the Committee for the implementation of this concept, keeping in mind that a permanent group of senior consulting scientists should be established and that the financial implications of this proposal should be kept as moderate as possible.

The Committee took note of the observations of the Panel of Scientific Advisers in regard to a balanced programme of work between the two components of the ICGEB and emphasised the value of complementarity and interaction between the two components as well as between the components and affiliated centres in the implementation of research programmes and other activities.

The Committee also agreed with the report of the Panel of Scientific Advisers on the necessity and convenience of establishing computer conference facilities as soon as possible and expressed the hope that resources will soon be made available to UNIDO for this purpose so as to accelerate interaction with members of the Panel.

While noting that the five-year work programme will have to be approved by the Board of Governors after the Statutes have entered into force, the Committee emphasised the importance of continuing to elaborate a draft five-year work programme and decided to keep the matter under review in its future sessions. It agreed on the paramount need for ascertaining, in broad terms, the priorities and requirements of member coutries which would be a key input to the elaboration of the programme. This would also result in the involvement of developing country scientists in the articulation of needs and priorities in the field of genetic engineering and biotechnology.

The Committee took note of the recommendations of the Panel of Scientific Advisers in regard to training activities. Information was provided by representatives of the host countries on the training programmes available in their countries. The Committee requested the host countries to provide additional information to the UNIDO Secretariat, particularly on the qualifications required for participation in their various training courses so that all relevant information could be disseminated to member countries. The Committee further requested the member countries to indicate their specific training needs. Based on such information, a programme of training should be defined by the Director/the Heads of components and placed before the Committee for approval.

The Committee endorsed the recommendation of the Panel of Scientific Advisers on granting the status of affiliated centre to institutions mentioned in the proposals submitted by the Governments of Bulgaria, Cuba, Egypt, Nigeria and Yugoslavia and requested UNIDO to inform the countries mentioned above of this decision and further request proposals for co-operation between the components of the Centre and affiliated centres within the framework of the ICGEB in the following areas: training, studies and research, information, advisory and consulting services, etc. They are requested to provide information on the services they could provide and on their own needs. While the overall programme of the Centre may be kept in mind when making such proposals, they may also consider the kind of activities that could be initiated between the two components of the ICGEB and the affiliated centres as a part of the interim programme. Such an approach will not only enlarge the stock of experience but also the areas of co-operation, to the benefit of all participating institutions. In this co-operative activity, a suggestion was made to contact those countries which had earlier offered to host the Centre with a view to their possible participation in the Centre's activities.

UN and other organizations' news

Opposition to UN system for collecting and storing endangered genetic resources

A plan was tentatively agreed to at a United Nations conference in Rome, to establish a new global system for collecting and storing endangered genetic resources of plants, including rootstocks, seeds and tissues.

The plan, offered by delegates from more than 100 countries at a conference of the UN Food and Agriculture Organization, called on industrialized nations to provide up to $100 million annually to Third World countries interested in collecting and storing rare plant varieties that have valuable genetic characteristics. Most of the plant and animal genes useful to agriculture have been found in the less-developed nations of the Southern Hemisphere.

While the United States is the primary opponent of the proposal, the U.S. stance is supported by Canada, New Zealand, Australia, Japan and Britain.

U.S. officials maintained that a new system for storing genes was not needed; that an adequate, though less extensive programme existed; that the proposed UN control could lead to undesirable restrictions; and that seed producers that have developed elite strains of plants would unfairly lose the results of their labours.

Third World delegates insisted that their nations should be compensated for the seeds and plants found within their borders. For decades, these delegates contended, seed companies from the industrialized world have transplanted the genetic

traits of wild and primitive varieties found only in Third World nations into hybrid varieties that are worth fortunes.

The U.S. seed industry, according to the American Seed Trade Association, has annual sales exceeding $7 billion.

As genetic engineering becomes more prevalent, the control of access to genes is shaping up as a primary environmental and geopolitical issue. Genes, scientists say, are likely to be as important to the 21st century as oil has been to the 20th century and preserving a stock of genes is essential to modern agriculture.

Scientists estimate that up to a million species of plants and animals, nearly 10 per cent of the known number of living organisms, may become extinct in the next 20 years. (Extracted from International Herald Tribune, 29 November 1985)

Social issues

OECD proposes general biotechnology guidelines

The Organization for Economic Co-operation and Development's (OECD) working group on biotechnology has agreed on general guidelines for regulation of the fledgling industry. Ideally, biotechnology regulations now will be similar in each country and will not pose a trade barrier for gene-spliced products. The document produced at an OECD meeting in December is a compromise between European wishes for strict controls on industrial applications of biotechnology and the U.S. industry's desire for more relaxed regulation. The final document, which will apply to industry and agriculture, specifies the kinds of altered microbes and plants that might pose hazards to human health, either in the workplace or outside, and to the environment. The document also contains guidelines for good industrial large-scale practice, including containment criteria and protection of intellectual property rights. Agreement by the working group should now lead to quick approval of the document by OECD's approving body, the Committee on Science and Technology Policy. (Extracted from Chemical Week, 18 December 1985)

Members needed for new ASTM biotechnology committee

Members are needed for the new ASTM (American Society for Testing and Materials) Committee E-48 on Biotechnology. The committee will promote knowledge and develop voluntary standards for biotechnology. Its work will be co-ordinated with other organizations and ASTM committees with mutual interests. Subcommittees include: E48.01 on Materials for Biotechnology; E48.02 on Characterization and Identification of Biological Systems; E48.03 on Unit Processes and Their Control; and E48.04 on Environmental Issues.

E-48 will meet on 7-8 May 1986 at the Hyatt Regency in New Orleans, Louisiana. For more information, contact Ken Pearson, ASTM, 1916 Race Street, Philadelphia, Pennsylvania 19103, 215/299-5520. (Source: ASTM News Release, 10 December 1985)

Regulatory issues

RAC sets gene-therapy rules

At the September meeting of the National Institute of Health's Recombinant-DNA Advisory Committee (RAC), the deputy to President Reagan's Science Advisor said that plans for a powerful Biotechnology Sciences Board in the Department of Health and Human Services - also known as 'Super-Rac' - had been scrapped in favour of a clearing-house committee in the Science Advisor's office. Unlike the stillborn 'Super-RAC', the new committee, to be established in OSTP's Federal Co-ordinating Council for Science, Engineering and Technology, will exercise functions of co-operation, not control. It will meet behind closed doors, because deliberations open to the public are the function of the various agencies.

The various federal agencies have already formed RAC-like outside advisory panels of their own:

- RAC itself, reporting to NIH, was the first such biotechnology review committee, and will remain first among equals.
- The U.S. Department of Agriculture has a non-statutory Agricultural Recombinant-DNA Research Committee, consisting mainly of its own staff members.
- The Environmental Protection Agency is currently trying to construct a RAC-like science advisory group.
- The Food and Drug Administration has general advisory committees of outside medical experts that review all its new-drug approvals.

Unanimously, RAC adopted a long-awaited guideline to govern its future case-by-case approval of gene therapy. The document, entitled "Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy Protocols", spells out the approvals and evidence a clinical researcher must submit for each intended patient. The new rules apply only to recipients of NIH grants - which means, in effect, all prospective gene therapists in the U.S.A. And they limit molecular genetic intervention to attempts at correcting somatic-cell defects, expressly excluding experiments in altering the genomes of heritable, germline cells. Genetic-engineering aspects of the proposal must describe the structure and gene-regulation elements of the cloned DNA to be inserted in the patient.

Submissions - as complex as a major grant proposal - must initially be published in the Federal Register, then reviewed by RAC's gene-therapy working group, but only after primary approval by the applicant's local Institutional Biosafety and Review Boards.

RAC, the document says, "would prefer that the first proposals submitted for [its] review contain no proprietary information or trade secrets, enabling all aspects of the review to be open to the public". (Extracted from McGraw-Hill's Biotechnology Newswatch, 7 October 1985)

Field-testing of 'ice-minus' bacterium authorized

Last November, the Environmental Protection Agency formally approved the first deliberate release of a gene-spliced living organism beyond the laboratory. This allowed Advanced Genetic Sciences, Inc. (AGS), Oakland, Calif., to spray a strawberry patch with a genetically engineered strain of Pseudomonas syringae bacteria that lack the gene that the natural species carries for making the ice-nucleation protein. If all goes well, the strawberries will not suffer frost damage when exposed to sub-zero temperatures.

If any lawsuit is filed to stop the ice-minus field trial, it will most likely allege that EPA has not set up a predictive science base to assess the

actual effects of releasing living micro-organisms into the environment.

US genetic engineering critic, Jeremy Rifkin, is taking legal action to stop Advanced Genetic Sciences releasing gene-spliced bacteria into the environment. He accuses the EPA of caving in to political and commercial pressures and claims that the modified bacteria could have "a dramatic impact on global weather patterns and in the long term may even cause drought." Moreover he wants to know why the EPA is allowing AGS to conduct vertical transmission tests, investigating the effect of the bacteria on clouds, using the gene-spliced bacteria without first using the naturally occurring organism as a model.

Crops expected to benefit by the release of gene-altered microorganisms include potatoes, beans, rice, corn, wheat, grapes, lettuce, forest, fruit and ornamental trees. (Extracted from McGraw-Hill's Biotechnology Newswatch, 18 November 1985 and European Chemical News, 25 November 1985)

General

Biotechnology consortium calls for research

A process that could accelerate technology transfer between universities and agribusiness was launched last week by the Midwest Plant Biotechnology Consortium. The group consists of 14 universities and 31 companies organized by Argonne National Laboratory (Argonne, Ill.). At an inaugural workshop in Chicago - attended by more than 100 representatives of government, academia and industry - the consortium sought to identify industrial problems in the production of food, fuel, seeds, pharmaceuticals and chemicals.

Researchers are calling for increased basic research in plant sciences and more training in plant biochemistry. Proposals put forth include:

- Development of new assays to identify pharmaceuticals;
- Identification of basic control mechanisms in plant cells to increase understanding of secretion and extrusion;
- Development of herbicide resistance in plants and techniques for screening for such resistance;
- Improved methods of handling agricultural and agrichemical wastes;
- Improved soil stabilization techniques and better information about groundwater contamination;
- Technology to deliver the necessary quantity of pesticide to crops;
- Development of effective gene transformation systems for single genes and polygenic traits by DNA mapping, gene identification and other techniques;
- Generation of exotic germ plasms by cross-breeding with ancestral species and remote species.

(Extracted from Chemical Week, 18 December 1985)

Industrial Biotechnology Association

The Industrial Biotechnology Association (IBA) was founded in 1981 by seven U.S. companies concerned with establishing an industry presence and a centre for ongoing co-operation among firms engaged in commercial biotechnology. The association has now expanded its membership to include major Canadian and European corporations. IBA members are involved in applying biotechnology to a wide range of industrial uses, and they understand the value of working together to promote a climate in which issues of concern to the industry can be addressed in an informed manner. IBA has proven to be an energetic and visible centre for activities designed to meet the needs and concerns of its members. Through its diverse seminar and publication programmes, IBA serves as an effective forum wherein industry leaders can come together to exchange views, identify areas for co-operation, and combine talents to assist commercial biotechnology in achieving its fullest potential.

IBA objectives:

- Identifying industry consensus and communicating them to public policy decision makers.
- Assisting in educating the public about the goals and uses of commercial biotechnology.
- Informing members about current activities, trends, and views of government and public opinion makers and analyzing their impact on the development of commercial biotechnology.
- Affording leaders in related areas, such as the academic, financial, and legal communities, the opportunity to share their expertise and experiences.
- Providing a neutral territory where companies with differing viewpoints on regulation, public policy, and technical issues can interact comfortably and to mutual benefit.

For further information contact: Harvey S. Price, Executive Director, IBA, Industrial Biotechnology Association, 2115 East Jefferson Street, Rockville, Maryland 20852, Telephone: (301) 984-9598.

Prospects for small biotechnology firms

Small genetic engineering and hybridoma companies face changes prior to technology commercialization. Some of these firms, which received seed money from venture capitalists and stock market investors, will become integrated manufacturers and marketers of medical or agricultural products, or do contract research or production work for clients with greater resources, or be acquired or merged to survive, or disappear. Previously, evaluation of biotechnology firms has involved determining the firm's market value, business plan, progress in product development, quality of management and cash reserves. Now firms can be evaluated by product commercialization.

Hybritech was acquired for over $300 million by Eli Lilly while Genetic Systems was bought by Bristol-Myers for $294 million. Both are visible biotechnology firms currently producing in-vitro diagnostic tests using hybridoma technology. Analysts speculate that monoclonal antibody contract producers like Damon Biotech and Bio-Response may be the next takeover targets, but probably not until the 1990s, when therapeutic agents using monoclonals reach commercialization.

Monsanto's broad commitment to biotechnology encompasses human health, animal nutrition and plant agricultural products. It has medical tie-ups with Washington University, Oxford, Harvard, Tufts and other universities, which with its internal efforts, is considered adequate. Its massive restructuring programme will shift emphasis to value-added

products, many of which will result from biotechnology research. PPG Industries' $120 million, 15-year biotechnology R & D deal with Scripps Clinic's Research Institute will focus on agricultural biotechnology to take advantage of its large R & D, manufacturing and marketing infrastructure. (Extracted from Chemical & Engineering News, 18 November 1985)

B. COUNTRY NEWS

Australia

Government support for biotechnology

Australia's developing biotechnology industry was given a boost by the Canberra government. Six research projects were awarded funds totalling $2 million under the government's three-year-old national biotechnology programme. The Canberra government has now committed more than $7.8 million since the establishment of the scheme. Although only two years old the scheme appears to be achieving certain goals. Scientists at the University of Adelaide, in collaboration with Faulding, the South Australia-based drug firm, are now developing oral live vaccines against enteric diseases in man and animals. Field trials with a hybrid live vaccine protecting pigs from Scours disease have produced promising results. (Extracted from European Chemical News, 2 December 1985)

American groups offer site to Queensland company

Three U.S. groups have offered Queensland Science and Technology Ltd. (QSTL) a site, probably at Peoria, Illinois, to install its 'Sucrotech' process for converting sucrose to fuel alcohol in a single stream, but, licensing agreements in the U.S.A. will not be decided until QSTL has set up a subsidiary there, perhaps in early 1986. The proposed U.S. subsidiary would look for opportunities to apply its ethanol-from-corn technology and for potential expansion of sugar-based ethanol production in the Caribbean and Central and South America. The Sucrotech process uses the bacterium Zymomonas mobilis, and "offers significant advantages over existing methods." These include higher substrate concentration, increased throughput and reduced effluent volumes, 24-hour fermentations yielding up to 12 per cent ethanol concentration, and single-stage production of ethanol and fructose.

The process, which can convert either corn or beet-sugar, was developed by Queensland University microbiologist Horst W. Doelle. The University holds patents on the technology and sold QSTL world licenses. (Extracted from McGraw-Hill's biotechnology Newswatch, 18 November 1985)

Austria

Chemie Linz begins biotechnology R & D

Chemie Linz AG, a large, state-owned chemical plant, is initiating two biotechnology projects: transferring genes for herbicide and pesticide resistance into crop plants, and using biological catalysts to produce plant-protection components and pharmaceuticals.

Protests and public outrage recently forced Chemie Linz to abandon production of the herbicide trichlorophenoxyacetic acid (2,4,5-T). The compound is not degraded after field use, so it can contaminate the environment. Biodegradable plant-protection substances do exist, but they come with another serious disadvantage: they tend to kill many of the plants they are designed to protect. Genetic engineers at Chemie Linz hope to introduce genes for tolerance to these substances into sensitive crop plants.

Two recent research developments could help. The host range of the Ti plasmid from Agrobacterium tumefaciens has been extended to include some monocot species. Perhaps in the near future it will be adapted to transfer genes to agriculturally valuable monocots. Also, a locus-specific gene transfer is now possible with this system, albeit with low efficiencies.

Chemie Linz's second project involves developing biological catalysts that can be used to produce various organic substances. Often they enable a cheap and efficient separation of optical isomers - not possible with classical procedures. (Extracted from Bio/Technology Vol. 3., October 1985)

Brazil

Biotechnology in Brazil

Brazil has chosen to focus major resources on agricultural biotechnology. Brazil has actively committed itself to biotechnology and found it easy to develop various aspects of this research. The ethanol project, for example, which produces more than 10 million litres of fuel alcohol a year has provided Brazil with tremendous fermentation expertise. And as in Mexico, useful tissue culture research for coffee, cocoa, sugar cane, coconuts, and other crops is already underway.

The Brazilian government through its agricultural research arm, the Brazilian Agricultural Research Enterprise (EMBRAPA), has invested millions of dollars in a biotechnology centre in Brasilia. The National Genetic Materials Center (CENARGEN) is undertaking a number of tasks including: germplasm preservation, genetic engineering, tissue culture, and biological pest control research. The most impressive investment is CENARGEN's new germplasm repository. The repository stores traditional crop material and botanical materials collected from Amazon river areas soon to be flooded by hydroelectric projects. To ease recordkeeping, essential data on the genetic potential of the seed is being transferred onto a computer. However, research at CENARGEN is hindered by a lack of qualified doctoral-level personnel and government funding.

Throughout Brazil university biologists are mobilizing to adapt newly developed biological techniques to Brazil's needs. Companies, such as Biomatrix and Bioplanta, expect to soon be selling virus free strawberries and potatoes to Brazilian farmers. These companies will focus on displacing foreign companies that now provide germplasm to Brazil at the cost of precious foreign exchange. Some biotechnology firms have also been founded to encourage professors to adapt their inventions to economic purposes and university-industry linkages continue to grow. (Source: Genewatch, September-October 1985)

Bulgaria

Bulgaria signs contract with John Brown (UK)

Following an earlier contract with APV International, which has set up a joint venture company with Bioinvest, the state investment organisation, Bulgaria has now signed an agreement with John Brown Engineers and Constructors of the U.K. This covers the "preliminary engineering" of a factory to produce enzymes for food processing and medical applications. The plant, to be built near

Plovdiv, could ultimately cost between £20m and £50m. Bulgaria has also been conducting negotiations with Celltech covering some of that company's proprietary technology. (Source: Biotechnology Bulletin, Vol. 4, No. 11, December 1985)

Canada

Quebec Science and Technology Council calls for assistance

The Quebec Science & Technology Council feels that not enough biotechnologists are active in agriculture and forestry, as against health fields. The Council made 21 recommendations to the government to maximize profit from biotechnology in Quebec. The government was encouraged to regard development of biotechnology as a long-term investment, not as a political issue. The Council recommends that government aid be directed more toward development of diagnostic drugs than toward therapeutic drugs. Private research organizations should be encouraged to better respond to the needs of private industry, especially in relatively neglected fields. (Extracted from Canadian Chemical News, September 1985)

Monoclonal antibodies developed for tumour diagnosis

Monoclonal antibodies have been developed for diagnosis of multidrug-resistant tumours by researchers at the Ontario Cancer Institute. The binding of the monoclonal antibodies to plasma membranes of different multidrug-resistant mammalian tumour cells correlates with the drug resistors, and the antibodies may serve as diagnostic reagents for clinically unresponsive tumours. The expression of P-glycoprotein on the surface of the tumour cell is the main alternation of the multidrug-resistant cell surface. High levels of P-glycoprotein can be detected early by use of the monoclonal antibodies. (Extracted from Clinica, 13 September 1985)

China

Shanghai Centre of Biotechnology

The Chinese Academy of Sciences has decided to establish the Shanghai Centre of Biotechnology. The Academy's decision is based on the fact that in Shanghai there are a number of high-level research institutes in experimental biology with long histories, such as Shanghai Institute of Biochemistry, Shanghai Institute of Cell Biology, Shanghai Institute of Plant Physiology, Shanghai Institute of Materia Medica, Shanghai Institute of Physiology, Shanghai Institute of Brain Research and Shanghai Institute of Entomology. Most of these institutes were established in the early 1950's. Since then, extensive research has been carried out in the fields of molecular biology, cell biology, microbiology, pharmaceutics, virology and immunology, and a strong competent scientific and technical team has emerged, which has produced excellent work in basic and applied research on biotechnology over the past few years and will no doubt make even greater progress in the future. In addition, Shanghai is one of the well-developed, modern industrial bases in China.

The main purpose of the Centre is to concentrate on research and development in biotechnology, to co-ordinate research and production, to provide new products in biotechnology, and new techniques for the expansion of production through applied research, development and pilot scale production.

The Chinese Academy of Sciences officially made an investment of 57 million Yuan in July 1984. The Shanghai Municipal Government has also approved of the site, south of No. 3 Bridge, Caobao Lu in a suburb, with an area of 46,620m^2. The laboratory building and pilot plants with a total building area of about 32,000m^2 is expected to be completed by 1987.

The policy of opening up to the outside world is a fixed policy of the Chinese government. The Chinese Academy of Sciences has decided that the Centre will be conducted as a open institution, not only to domestic counterparts but also to overseas counterparts and is ready to co-operate with foreign research institutions and companies to the benefit of both parties by various ways and means, such as joint ventures, accepting investment, joint projects, transfer of technology, development and marketing.

Denmark

Novo plans large-scale DNA human insulin production plant

Novo has applied to the Danish Environmental Authorities for approval to build commercial-scale plants for the production of human insulin from genetically engineered micro-organisms. The company has indicated that pilot plant upscaling of its fermentation and purification processes are in progress. However, the new plant's targeted completion and start-up have not been specified.

The planned facilities have been designed to the specification of the US National Institutes of Health and will also be usable for the production of other peptide hormones and enzymes based on micro-organisms classified as suitable for industrial applications of genetic engineering.

In 1982, Novo was the first company in the world to market a human insulin identical to that produced by the human body, based on an enzymatic conversion of porcine insulin. (Source: European Science News, 39-10 (1985))

European Economic Community

AIDS research hampered

Lack of funds in the EEC countries could hinder efforts to prevent the spread of AIDS, according to researchers. Some 1,200 AIDS victims have been diagnosed in the EEC. The Pasteur Institute (France) is a leader in AIDS research in the EEC, which has also designated other centres to study the disease, but it is having trouble acquiring the necessary research funds. Western European governments provided only $8 million in special AIDS research funds in 1984 and funding has not increased significantly in 1985, according to the Common Market's working group on AIDS. In contrast the US Congress approved $200 million in funds for AIDS research in Fiscal Year 1986 beginning October 1985, versus $109 million in Fiscal Year 1985. The relatively limited number of AIDS patients in Europe should make it more important for doctors to co-ordinate their clinical tests. (Extracted from New York Times, 11 November 1985)

EEC targets biotechnology "concertation"

The Council of Ministers of the member states of the European Economic Community (EEC) has agreed on a 4-year research programme in biotechnology for 1985-89. The budget of $35 million, is bout half of what the EEC Committee asked for in its six-point

proposal of April 1984. The money covers just two projects: a programme for research and training, and a "concertation" of policies and actions. It is not yet clear how the funding reduction will affect the plan.

The proposal's other points, not yet approved, are: (1) a plea for new regimes on agricultural outputs for industrial use, (2) an agreement on regulation, (3) a programme to achieve agreement on intellectual property rights (harmonizations of patent law), and (4) a programme to start demonstration projects.

The new research programme follows a 1982-86 initiative on biomolecular engineering, which emphasized research on enzyme technology and plant genetic engineering. The recent programme has a wider scope. In addition to research projects, it aims to promote transnational co-operation among the members of the EEC and the transfer of biotechnology from universities to industry and agriculture.

The official document underlying the Council of Ministers' decision states that a co-operative European home market is needed for the EEC to be competitive. The report leans heavily on the US Office of Science and Technology Policy and OTA strategic information to describe Europe's position.

Under the EEC programme, the staff will monitor developments in biotechnology and related fields such as environmental affairs and Europe's co-operation with developing countries. It will also assess the social dimensions of biotechnology - at a cost of about $4 million over the next four years.

The research and training programme is divided into two subprogrammes called "contextual" and "basic". The basic subprogramme will receive the main part of the money, $27 million; the contextual subprogramme gets $4 million. Both have begun, following the official go-ahead in March. Some other programme points (regulation, patent harmonization, and demonstration projects) have made a small start.

The basic subprogramme is to a large extent a continuation of the biomolecular engineering programme. Later, attention (and money) will be paid to research and training in cell and tissue culture, and developments of test methods and scientific assessment of the risks associated with certain modern biotechnologies - e.g., recombinant DNA.

The contextual subprogramme is meant to build up a European infrastructure in bio-information (programmes, databases) and culture collections. This infrastructure, partly based on already existing institutes, must be accessible to European industries and research institutes.

An important aim of the EEC programme is to keep young researchers from relocating to the US. In support of this goal, apart from grants for contract research, much of the funding will be put into long- and short-term training grants for scientists. Researchers will work for varying periods - a few weeks to a few years - in institutions outside their home countries.

One of the main problem areas remains the new regime on agricultural products for industrial use. Europe sets the prices of agricultural commodities - higher than world levels. These products are then too expensive to serve as feedstocks for the biotechnology industry. Proposals for new regimes for sugar and starch have met with resistance from growers. A European strategic forecasting group is studying this problem - whatever it recommends is bound to be met with more dispute.

As for the two approved points of the programme, one question overshadows all others: will $35 million prove enough to strengthen the EEC's position in world biotechnology? The general view is that Europe plays an important role in the scientific aspect of biotechnology, but that it lacks an infrastructure for commercialization and, historically, a mechanism for harmonization. However, it is hoped that the relatively small amount of funds will be enough to serve as a catalyst. (Extracted from European Science News, 39-10 (1985))

European biotechnology services

Europe is setting up new services to improve information exchange in biotechnology:

CUBE, the Commission of the European Communities' Concertation Unit for Biotechnology in Europe, provides a focal point for European activity in biotechnology. It comes under DGXII, the commission's directorate general for science, research, and development. Its role is to monitor strategic developments in biotechnology worldwide and to make recommendations in community strategy, to promote collaboration and the exchange of information between member countries, and to facilitate the co-ordination of activities within the commission itself. Some of CUBE's specific activities include providing the secretariat for the commission's task force on biotechnology information, providing representation and advice in international fora and for conferences and commissioning study contracts. CUBE can be contacted at DBXII, rue de la Loi, 200, 1049 Brussels, Belgium. A particular interest of CUBE has been the application of computing to biotechnology. Together with the commission's information technologies and telecommunications task force a programme of work on bio-information has been set up. Ten contacts have been arranged so far. (Extracted from European Science News, 39-10 (1985))

Data banks in Europe

A move to co-ordinate European activities in nucleic acids and protein sequence data was made at a European Economic Community (EEC)-sponsored workshop held in Italy, last May, with participants from all EEC member states, the US, and Japan. It seems that the future lies with networks of national systems, rather than large central facilities. Attention will also have to be given to software portability, user training, and easy communication via electronic bulletin boards.

CODATA, the EEC's commission on data banks, has already established a task force to stimulate international collaboration in the use of protein data banks.

The European Biotechnology Information Project (EBIP) offers an information service in biotechnology to industry and research workers. EBIP has been set up with the help of funds from the Commission of the European Communities and will be collaborating with other European information centres. Information is vital for the progress of industry and research, but in biotechnology it is often fragmented and difficult to find. EBIP draws together and exploits the publications, on-line

computer services, and other sources that cover biotechnology, including scientific and technical information, business, news, patents, culture collections, and regulatory affairs.

The following are information services provided by EBIP:

1. Enquiry service - the EBIP staff uses the resources of the British Science Reference Library to deal with queries on all aspects of biotechnology.

2. Publications - information guides to key sources and topics appear regularly; new publications are announced in the EBIP newsletter sent to all members of the mailing list.

3. Seminars - 1-day courses for business users and research workers are held several times a year.

The EBIP newsletter and information about EBIP guides and services can be obtained by writing to the following address: EBIP, British Library Science Reference Library (Aldwych), 9 Kean Street, London SC2B 4AT, England. (Extracted from European Science News, 39-10 (1985))

France

French INRA, CEA sign accord

At the beginning of July 1985, the National Institute for Agronomic Research and the Atomic Energy Commission signed a global agreement for a three year period to pursue joint research programmes. This co-operation is mainly focused on three themes: plant biotechnologies, radiobiology applied to animal production and separative techniques for basic products in agriculture. (Extracted from BIOFUTUR, September 1985, p. 25)

Somatostatin production unit

French pharmaceuticals producer Sanofi, plans construction of a unit at Mêtre Dame de Boudeville near Rouen in northern France for production of the growth hormone somatostatin. The technology was developed by Sanofi at its Labège laboratory near Toulouse. Start-up is scheduled for the first quarter of 1986. (Source: European Chemical News, 4 November 1985)

New biotechnology R & D company created

Rousel-Uclaf, one of the three major French pharmaceutical firms, and Sucre Union (which controls 30 per cent of French sugar production) have recently created Bio Europe, a biotechnology research and development company. Bio Europe's goal is to work on biocatalysts and on purification and extraction techniques with emphasis on enzymes and fermentation. The Bio Europe investment is for the purpose of gaining a better knowledge of plant treatment possibilities, providing plant protection, and obtaining greater yield and quality. Sucre Union's interest in Bio Europe is diversification, because the drop in sugar prices and competition have motivated the company to become involved in new products which can be fabricated with enzymes starting from agricultural raw materials. (Extracted from European Science News, 39-12 (1985))

Germany, Federal Republic of

Pilot plant for monoclonal antibody production

Boehringer Mannheim Co., West Germany, plans a pilot plant for industrial production of monoclonal antibodies for therapeutic use. The 5-year research project using hybridoma techniques will receive government support from the Federal Ministry of Research and Technology to the amount of DM5.8 million (about $1.7 million).

Boehringer will be co-operating in this project with the universities of Munich and Heidelberg. The company will use a patented process to obtain hybrid cells which produce antibodies in permanent cultures. For production, Boehringer will use a capillary modular bioreactor with hollow fibres. (Source: European Science News, 39-11 (1985))

Protein and fat from lupins

The German scientist Dr. Peter Hussman considers the lupin to be a new weapon in the fight against hunger in the world: The plant, it is claimed, can provide protein and fat, in particular for the Third World. It has long been known that this hardy plant contains more protein than, for example, the soya bean, but up to now the flower has been inedible as the alkaloid it contains makes it very bitter. Dr. Hussmann, in collaboration with the Society for Technical Co-operation in Eschborn near Frankfurt-am-Main has now developed an apparatus for washing the alkaloid out of lupin seeds making the plant edible. It can also be used in the manufacture of foodstuffs. The results give rise to hopes: 39 to 42 per cent of a lupin is protein, and 18 to 21 per cent fat. Also, it thrives almost anywhere: it grows at an altitude of 4,000 metres as well as it does in extremely dry areas or in humid jungles. (Source: Scala, October 1985)

New gene technology research groups at Max Planck Institute

Three independent gene technological research groups are being established in the following areas at the Max Planck Institute in Martinsreid, Munich.

1. Microsequencing of proteins and biologically active peptides with emphasis on gas phase sequencing.

2. Molecular embryology, emphasizing early mammalian development.

3. Transcription (gene expression) in eucaryotes - mechanisms and controls, emphasizing differentiation.

The Max Planck Institutes for Bio-chemistry and Psychiatry - together with the gene centre at the University of Munich, supported by industry - are setting up new research divisions in gene technology research. Each group will have about 150 m^2 of laboratory space, positions for scientific and technical assistance, and appropriate financial support for equipment and running costs. (Source: European Science News, 39-11 (1985))

Jülich Nuclear Research Center, Institutes of Biotechnology

The Institute of Biotechnology (IBT), which emerged in 1977 from the former Institute of Botany and Microbiology, consists of three units which share the general tasks of developing biotechnological processes and contribute to the treatment of solid and liquid wastes. Current research and development activities are focussed on the following areas:

- Microbial degradation of biopolymers
- Conversion of substrates with biocatalysts
- Biological treatment of wastewaters

The studies of 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 (e.g. 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 micro-organisms capable of metabolizing plant residues. Of special interest are the enzymes cellulases and hemicellulases, which cleave the polysaccarides cellulose and hemicellulose into oligosaccharides or monosaccharides. Attempts are being made to increase the enzyme yields by mutant selection and by gene manipulation.

Once biocatalysts are isolated and characterized, they should be used in the most economical way. For this purpose processes known from chemical engineering are adopted and specifically improved for the proper handling of microbes or of purified enzymes.

Enzyme membrane reactors are operated continuously not only with individual enzymes but also with coenzyme dependent multi-enzyme systems. Target products are, for example, optically active organic acids like amino acids. In membrane reactors the products of the reaction are continuously withdrawn, while the larger enzyme molecules are retained within the system by ultrafiltration membranes. Thus a continuing homogenous catalysis is ensured.

For the exploitation of metabolic routes which lead from the substrate to the end product (e.g. an amino acid) in more than one step, whole cells can be used as the catalysts. They are held back in the reactor by membranes with larger pores than those described above, i.e. microfiltration membranes. The feed solution contains precursors of the target product that are available via chemical synthesis.

Product formation can not always be uncoupled from microbial growth. For instance, in the case of ethanol production from glucose the growing microbial 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. For calculating the dimensions of bioreactors with a precision comparable to that obtainable with conventional chemical reactors, the quantitative determination of all decisive reaction parameters has to be as precise as possible.

As an alternative to entirely bacterial processes, photosynthesizing planktonic algae can be used for biogenic aeration of flat pondlike containers in which bacteria oxidise sewage compounds. In 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 co-operation between algae and bacteria also facilitates the degradation of relatively persistent chemicals, e.g. of naphthalene sulfonic acids. Under the same aspect the treatment of residues of anaerobic fermentations is under study. The tests are carried out in the laboratory as well as at the pilot plant scale.

Since the biological treatment of wastewaters can also proceed without a supply of oxygen, strains of anaerobic bacteria which participate in the conversion of dissolved organics into methane are being isolated and investigated with respect to their metabolic reactions. Besides the work on pure cultures, the conversion of various substrates by defined mixed populations is being tested. After laying the microbiological groundwork for increasing the catalyst concentration in the anaerobic fermentation of wastewaters with high organic loads, research on process technology becomes necessary. It concerns, for example, the uncoupling of solids (catalyst) retention time from liquid retention time. In this connection it is of interest to know how the formation of cell aggregates can be favoured, because the latter facilitates the retaining of bacterial biomass and its partial recycle to the process.

Recent research highlights are:

- The scale-up to the industrial level of an enzyme membrane reactor developed by IBT for the production of pure L-amino acids (industrial production began in 1981).

- Development of a technique for co-enzyme regeneration in the continuous operation of reactor systems based on coenzyme dependent enzymes. Successful industrial test runs have been made for reductive amination of L-keto acids to yield the respective L-amino acids at a level of 0.5 kg of product per day.

- The scale-up to the industrial level of a process for ethanol production by the bacterium Zymomonas mobilis. Production was started in April 1983.

- Planning, construction and running of a pilot plant for microalgae production in Egypt.

- Degradation of naphthalin sulfonic acid with algae bacteria mixed cultures.

- Continuous treatment of a highly loaded wastewater from a cellulose factory by means of a mixed culture of bacteria. The dissolved organics are acetic acid and furfurol. At a retention time of 6 hours the removal of COD is 90 per cent and the production of biogas 0.73 m^3 per kg of substrate. (Source: Bio/Technica 1985 Journal No.3)

India

Bioconversion plant

The Indian government is financing construction of a major new bioconversion facility in New Delhi. Now being erected in the Biochemical Engineering Research Centre at the Indian Institute of Technology, it is designed to carry out an integrated process of solvent delignification of lignocellulosic residues and simultaneous saccharification and fermentation. The 450-litre fermentor is designed to handle about 200 kg of rice straw per day and yield 50 litres of ethanol (95 per cent v/v), 100 kg of single cell protein for use as an animal feed supplement, and 23 kg of lignin as a by-product.

Pretreatment will separate nearly 80 per cent of the lignin and 90 per cent of the hemicellulose from the straw. (Extracted from Bio/Technology, Vol. 3, October 1985)

Integrated pest management for plant protection

Delegates at a recent plant protection conference in India agreed that the country should work towards an integrated pest management approach for plant protection which would avoid the side effects of chemical pesticides as well as maintaining ecological balance. The two-day conference stressed the need to develop biological agents and regulate their application and use. Delegates were also advised to publicise the use of

pest and disease-resistant varieties of crops. The conference urged the pesticides industry to introduce voluntary price control, in-house quality control and screening systems. (Source: European Chemical News, 21 October 1985)

Israel

Cost of protein reduced

Scientists in Israel say they have come up with a cheaper, industrial-scale method for building polypeptides.

The traditional way to build polypeptides is time consuming and some peptide is lost at each stage. An attempt to improve this process was made in the 1960s with the introduction of the "solid-state" method, but unfortunately, after the last stage of building the polypeptide, incomplete peptides also remain bound to the polymer, giving an impure product.

Abraham Patchornik at the Weizmann Institute in Rehovot, Israel, has introduced modifications to the solid-state method that overcome the problems of the technique. Patchornik says that he gets successful amino acid additions on more that 95 per cent of the peptides in the first tank. Other methods yield only 80 per cent.

Patchornik has applied the method to make the neurotransmitter, encephalin, which is 30 amino acids long. He has also patented a "matchmaker" machine. His team of researchers has come up with donor polymers and matchmakers suitable for producing short chains of DNA and RNA. (Extracted from New Scientist, 24 October 1985)

Israeli-Japanese joint venture in biotechnology

Orgenics Ltd. (Yavne, Israel) has formed a joint venture with Takara-Shuzo (Kyoto, Japan) for the development, production and marketing of genetic probes for clinical diagnostics. Orgenics representatives estimate that the market in the U.S. alone for such probes will reach $200 million by 1990. The new company - Orgenics-Takara (Kyoto) - will launch its first products in 1986. (Source: Chemical Week, 4 December 1985)

Italy

Biodegradable plastic bags

International Plastics Italiana is launching a new biodegradable polyethylene-based plastic bag on the Italian market. The bags are said to decompose under natural atmospheric agents, that is the sun, rain and wind. The company is based at Scarperia near Florence, and has two other plants at Sant' Agata de Mugello and Cesenatico. (Source: European Chemical News, 11 November 1985)

Japan

Ministry to launch protein engineering project

The Ministry of International Trade and Industry (MITI) will launch an eight-year, 30 billion yen (125 million dollar) project next year to develop protein engineering. MITI initially plans to improve analysing devices such as X-ray spectroscopic analysers and nuclear magnetic resonance computerised tomography (NMR-CT) units. In the second step, new varieties of protein will be designed with the aid of computer graphics after relations between protein structure and performance are made known. Eventually, MITI plans to establish a technique for mass production. (Extracted from Kyodo, 5 August 1985)

Crop testing guidelines

The Ministry of Agriculture, Forestry & Fisheries will formulate guidelines on the testing of crops modified by recombinant DNA technology. The Ministry's research council will examine applications to field test genetically engineered crops. Private firms will be required to conduct such tests in conjunction with a research institute equipped to the Ministry's standards. Preliminary tests on plant genetic engineering must now be conducted in a completely closed environment. (Source: Technology Update, 11 November 1985)

Plans for gene bank

The Ministry for Agriculture, Forestry and Fisheries has formulated a plan to utilize a gene bank system, which will start within the current fiscal year. According to the plan, the bank, aimed at securing biologically important genetic resources, envisages collecting plant seeds and seedlings from Europe, South America and Asia, and supplying the nation's various research institutions with 34,000 species of plant seeds and seedlings. (Source: Mainichi Daily News, 20 July 1985)

Hepatitis antigen sequenced

Tohoku University professor Makoo Iwmida has purified and sequenced a previously unknown hepatitis non-A, non-B antigen. The 16-amino-acid "SO" peptide, isolated from patients' urine, is thought to be part of the viral protein coat. The antigen does not correspond to known protein sequences of the virus. (Extracted from McGraw-Hill's Biotechnology Newswatch, 16 December 1985)

Lactose-converter isolated

Nisshin Sugar Co. Ltd., Tokyo, has isolated a new bacterium, Cryptococcus laurentii var. laurentii OKN-4, which converts lactose to 4'-galactosyllactose. Efficiency of the process is currently only 50 per cent conversion of a 10 per cent lactose solution after five days at 30°C. Nisshin is testing the novel sugar for food safety and plans commercial production within two years. (Extracted from McGraw-Hill's Biotechnology Newswatch, 16 December 1985)

IPCR screens soil 'Super Bugs'

Institute of Physical and Chemical Research (IPCR), Wako City, reported on four strains of soil bacteria with commercial potential:

- A high-pH-loving bacterium resembling Bacillus licheniformis produces an invertase enzyme with optimal activity between 55°C and 60°C at mildly acidic conditions.
- Two Bacillus species survive environments with 1 per cent selenium, a concentration ten-times higher than most bacteria can tolerate.
- A Corynebacterium makes an extracellular trehalase that yields an anti-freeze carbohydrate. (Extracted from McGraw-Hill's Biotechnology Newswatch, 16 December 1985)

TPA fermenters scaled up

At least six companies are competing to bring tissue plasminogen activator (TPA) to market in Japan. Mitsui Toatsu Chemicals, Inc., has completed construction of a 1,000-litre production plant for TPA at its Yokahama research laboratory. Mitsui, which is co-operating with the Beckman Research Institute, City of Hope, Duarte, California, plans

to produce TPA in animal host cells other than Chinese hamster ovary cultures - the route Genetech has taken.

Others in the contest include Kyowa Hakko Kogyo/Mitsubishi Chemical Industries, using TPA from Genentech, S. San Francisco, California, and Toyobo Co. Ltd., employing technology from Integrated Genetics, Inc., Framingham, Mass. Asahi Chemical Industry Co. Ltd., Osaka, has completed Phase I human studies with a non-recombinant form of TPA extracted from mammalian embryonic renal cells.

Sumitomo Pharmaceuticals Co. Ltd., Tokyo, recently signed an agreement to use production technology from the Wellcome Foundation Ltd., Kent, U.K., for mass production of TPA from genetically engineered animal cells. Its subsidiary, Sumitomo Chemical Co. Ltd., Osaka, has already begun construction of an 8,000-litre fermenter for the process. (Source: McGraw-Hill's Biotechnology Newswatch, 16 December 1985)

E. coli secretes enzyme products

Genetic recombination technology has successfully been used to make E. coli secrete enzyme products, according to researchers at the University of Tokyo's Agriculture Department. They transplanted the gene for the protein-degrading enzyme protease into the E. coli cell. The particular bacilli chosen by the Tokyo University researchers as a donor is also a member of the gram-negative group as E. coli but is unique in that its protease is transported across the cell wall. It was decided to implant the secreting-type protease gene into the E. coli by means of a plasmid vector to determine if this property would also show up in the host. Protease was successfully secreted into the culture. The enzyme was also of a form characteristic of the host, with the amino acid serine at its activation centre instead of the zinc of the donor cell's metal protease. (Extracted from Japan Economic Journal, 7 September 1985)

Hemostatic paper from alginic acid

An inexpensive way to produce hemostatic paper from alginic acid in seaweed has been developed by the Industrial Research Institute (Shikoku). Since alginic acid can stop bleeding, paper made from it will have applications in bandages. The substance can also fix enzymes and microbes firmly, which will make it an excellent immobilising agent for bioreactors and biosensors. The papermaking process begins with the extrusion of sodium alginate in agar form from a small hole into a solution of calcium chloride to produce thin calcium alginate fibres. The fibres are then cut into 3 mm strands and floated on water. The water is drained and the fibres formed into paper by pressure from above. The paper is difficult to burn, is an excellent hemostatic and is insoluble in water. (Extracted from Japan Economic Journal, 14 September 1985)

Biosensors

Japan's electronics giants are pouring research money into the development of biosensors. Their attraction is that they can detect minute quantities of substances, such as glucose in blood, quickly and reliably.

All biosensors consist of two sections: a biological receptor, which could be enzymes, antibodies or microbes immobilised in a membrane, and an electronic transducer. The receptor covers the transducer. The biosensor reacts with the chemical it is designed to detect, and the transducer converts this chemical activity into a measurable electrical signal. In Japan, between 30 and 40 companies are developing biosensors.

The man leading Japanese industry's research efforts in biosensors is Isao Karube from the Tokyo Institute of Technology. Most company groups working on biosensors include researchers who have spent time in his laboratory.

Karube's work on biosensors began in 1970, when he developed a new type of casing using collagen as the raw material. The casing was a membrane that was strong and thin and Karube was sure that immobilising enzymes in his membrane (by chemical bonding) might make it useful for industrial purposes.

He realised he could apply his membrane to build an electrode that would be robust and sensitive enough to respond quickly to electrochemical changes in the environment. By 1974 Karube and his group had developed their first sensor for the determination of hydrogen peroxide in food. The group went on to make many kinds of enzyme electrode.

Today, as a direct result of this work, seven or eight Japanese companies are selling biosensors, which are made from electrodes coated by enzymes. One, Fuji Electric, sells three systems, for measuring glucose, uric acid and amylase. The glucose sensor is popular with sake brewers, who use it during fermentation. It can detect the concentration of glucose in a 20 microlitre sample within a minute. Such a fast response means the sensor can be incorporated in a production process, allowing on-line analysis.

But enzymes, in addition to being expensive to extract and purify, are notoriously unstable. Karube reasoned that, instead of using enzymes, it would be cheaper and more effective to use the microorganism from which the enzymes were extracted.

In the microbial biosensor developed by Karube, whole cells are immobilised in the membrane, which is then fixed on top of an electrode and suspended in a liquid containing an organic compound. As the living cells assimilate the oxygen in the compound, their respiration activity increases. By measuring this change, in the form of an electric signal from the electrode, Karube determined the concentration of the organic compound in the liquid.

Work on making biosensors as small as possible began in 1980, when Toyosaka Moriizumi, a specialist on silicon process technology, joined Karube's group. Together, they have worked on integrating several sensors on the same chip.

Integration is the great advantage of the biochip. Using pattern masks, scientists can deposit as many electrodes on a substrate as necessary, hundreds in theory, then fix an enzyme to each.

Karube has already developed an integrated sensor for the food industry. It detects compounds in fish, then displays the result as a pattern on a screen. The pattern shows whether the fish is fresh enough to be eaten raw - a problem of considerable interest to the Japanese.

In future, an array of small, disposable biosensors, each detecting different parameters, might determine body condition from a drop of blood or urine. The devices could plug into a microcomputer to give an instant readout. The patient could then phone in any abnormalities for

remote diagnosis by expert computer systems in hospitals.

Several problems remain to be solved, however, before biosensors detecting more than one parameter hit the market. The most difficult, according to Karube, is how to immobilise active enzymes in the right place and in sufficient numbers. The other main problem is producing a batch of biosensors that are the same. Karube reckons these problems are surmountable. His view is shared by NEC.

The working life of the new multisensor is more than 30 days. Having demonstrated the device's feasibility, NEC says it plans to develop a range of multi-function biosensors capable of measuring many other substances (including cholesterol) in the next two or three years. (Extracted from New Scientist, 21 November 1985)

Laser beams in microbiology

Ishikawajima-Harima Heavy Industries and Nippon Zeon have developed a way to extract useful substances from microbes by irradiating them with laser beams. The new process will make it possible to extract 80 per cent of the insulin, DNA, amino acid, oxidation-reducing enzyme cytochrome, S-adenosilmentionin and other substances 10 minutes. It can be used with colon bacillus, fungi, the aspergillus family, yeast and saccharomyces genus. (Extracted from Japan Economic Journal, 14 September 1985)

Mexico

Biotechnology in Mexico

In Mexico the Center for Genetic Engineering and Biotechnology was opened in Cuernavaca to do basic research in molecular biology. The centre, which cost over $3 million to build and equip, is currently pursuing microbial insulin production. The aim of this Center and its sister, the Center for Investigacion into Nitrogen Fixation, is to produce world-class research. The leading scientists in both institutions were trained in prestigious research laboratories.

The University of Chapingo, where scientists are engaged in agricultural research, houses projects which offer tangible benefits to Mexican citizens. Researchers are using plant tissue culture to improve agriculture. Dr. Victor Villa-Lobos is preserving in vitro rare and commercially valuable pines. This project is important because Mexico contains approximately 50 per cent of the world's pine genetic diversity and many of the species are in danger of extinction. Dr. Villa-Lobos hopes his work will preserve some of these materials. Another project is the micropropagation of the edible Opuntia cactus. The researchers' objective is to produce clones of elite varieties to be planted commercially. A number of other agricultural projects are underway at Chapingo, and other Mexican research institutions, though funding for this work is scarce.

The level of sophistication of Mexican scientists is high, but large obstacles constrain the conduct of science and the translation of that science into benefits for Mexicans. The primary obstacle in Mexico is disinterest among Mexican industries in commercialising the results of scientific research. Scientists perceive Mexican industry as content to import technology from the developed countries rather than to use the results of its scientists. Few Mexican companies find it necessary to invest in research and development. (Source: Copewatch September/October 1985)

Netherlands

Dutch biotechnology

The Dutch government is taking an active role in stimulating the development of the biotechnology industry in the Netherlands. The government offers tax and other financial incentives to emerging biotechnology companies, including its $400 million NIP Equity Fund. These incentives have already attracted some US companies to establish operations in the Netherlands.

Other government initiatives include the Biotechnology Research and Feasibility Studies, in which companies can qualify for subsidies of up to 50 per cent of their investments in basic research projects. The Innovation Stimulation Scheme enables firms to apply for subsidization of R & D wage costs. Businesses can obtain government loans to support the development of new products, technologies, or services through the Technological Development Credits programme. High Technology Grants can total 20 per cent of a firm's investments in fixed assets.

Biotechnological research in the Netherlands emphasises human and veterinary health care, the food and beverage industry, and agricultural applications. Dutch companies active in these fields include Gist Brocades, Heineken, Akzo-Pharma, Avebe, DSM, Duphar and Unilever.

The biotechnology Innovation Research Programme, a joint effort of the Dutch government, industry and academia, seeks to promote the application of research projects in academic institutions to aid the Dutch economy.

New Zealand

Fungi can improve crop grasses

Endophytic fungi can produce beneficial effects on host crop grasses, according to G. Latch of the Department of Scientific & Industrial Research. Acremonium loliae can confer resistance to the Argentine stem weevil and the sod wewworm. Moreover, ryegrass grows 40 per cent faster when infected with A. loliae. Some endophytes hinder crop growth, and some adversely affect animals grazing in treated pastures. Strains of fungus might be developed to maintain the beneficial effects while eliminating the animal toxins. (Extracted from New Scientist, 12 September 1985)

United Kingdom

Plan to attract biotechnology groups to Great Britain

The Department of Trade and Industry (DTI) has launched a campaign to attract biotechnology companies wishing to make genetically-engineered products in Britain. The Biotechnology Unit of the DTI in London is in charge of the campaign which will enable companies to receive departmental grants for innovation.

Genetics International Inc. of USA has already been aided to start manufacture of advanced sensors and bio-sensors in Britain, the company having strong links with researchers at the Cranfield Institute of Technology.

The Unit hopes to attract many firms currently wishing to expand their enterprises into Europe and Dr. Ron Coleman, Chief Government Chemist and its main adviser on biotechnology, believes Britain is able to make a strong case for siting such enterprises, partly because it has a fairly national

regulatory system for new health products compared with other European countries. And precedent has been set by G. D. Searle and Eli Lilly who are already manufacturing genetically engineered products in the U.K.

In addition, there is the attraction of the strong scientific base which universities and government laboratories are able to provide.

Investment of £9.1m has already been approved for 67 proposed projects in the U.K., of which £3.4m was expended in 1984/85 with this figure likely to be exceeded in the current year. (Source: Industrial Biotechnology August/September 1985)

Biological methods to reclaim a waste site

The first known application of novel biotechnological methods to decontaminate a major toxic waste site in the U.K. will be undertaken by BioTechnica, the affiliate of BioTechnica International (Cardiff, Wales). The Blackburn Borough Council has awarded a contract worth more than $1 million to a joint venture between BioTechnica and Miller Buckley Projects to decontaminate the 25-acre Greenbank Gas Works site in Blackburn. The cleanup technique is based on the enhancement of the natural biodegradation process. Contaminated samples from the site will be analysed in the laboratory to isolate suitable microbial communities. They will be treated by appropriate nutrients and other physical or chemical processes to make them more stable, then returned to the waste site. Decontamination should be completed within two years, says BioTechnica. (Source: Chemical Week, 30 October 1985)

Biotechnology firms back "club" named BIOSEP

BIOSEP, the new "technology-transfer club" for biotechnology industries, was launched recently by the Harwell and Warren Spring Laboratories, UK. BIOSEP has been set up to develop the large-scale biotechnology separation technology (downstream processing) which is essential for the industrial application of major advances in biotechnology.

BIOSEP already has 38 members, including some of the world's largest biotechnology, food, and chemical engineering companies. The club provides the mechanism for transferring the results of downstream processing research and development. Its aim is to provide information rapidly and in a form which can be easily used.

BIOSEP's services include design studies, design data, and state-of-the-art reports which can be used immediately in the design, construction, and operation of separation plants. The club's activities are based on major research and development programmes funded by the Department of Trade and Industry and carried out at Harwell and Warren Spring. Both laboratories have been designated by the Department of Trade and Industry as UK centres of expertise in biotechnology.

Research priorities for the technology transfer programme have been agreed upon by the members of the club. Key BIOSEP research topics include membrane separation processes, absorption and chromatography, and primary solid-liquid separation, including a downstream processing database. This will be used to provide specialist literature searches for members and to produce a regular BIOSEP information bulletin.

BIOSEP membership fees are linked to company turnover, with overseas-based companies paying a surcharge determined by the degree of their involvement in the UK economy.

For further information, contact Mr. Martin Lewis, Commercial Manager BIOSEP, Bldg. 329, Harwell Laboratory, Didcot, Oxon OX11 ORA, UK. (Source: European Science News, 39-10 (1985))

New biotechnology centres

Work at the Leicester Biocentre and Cranfield Biotechnology Centre is part of a recent initiative in the UK to stimulate biotechnology research.

Leicester Biocentre:

In response to an identified and growing need for co-operation between the industrial and academic sectors, Leicester University - with support from several industrial sponsors and the Biotechnology Directorate of the Science and Engineering Research Council - has recently established a unique type of research centre, the Leicester Biocentre. The Biocentre is seeking a rapid transfer of ideas and high technological developments in biology from university to industry. In addition, it aims to guide academic research into areas of commercial significance.

Taking advantage of the expertise available at Leicester University in recombinant DNA technology, the Biocentre is concentrating initially on a number of themes, such as studies on the mechanism of DNA replication and gene expression in yeast and higher plants. The research areas will be expanded to include surface protein biogenesis, mammalian virology, and the control of gene expression in mammals, including primates.

The Biocentre will also offer facilities for contract research which will be undertaken in areas where the expertise from the basic research programme - i.e., gene cloning, expression, and transfer - can be expected to make a significant contribution to the goals of contract projects. The Biocentre, which has close links with several university departments, intends to provide opportunities for the training of both industrial and academic personnel in the techniques of in vitro gene manipulation. The Biocentre will also provide consultancy services as well as courses and seminars.

Professor I.J. Higgins, Director of the Cranfield Biotechnology Center and Leverhulme Professor of Biotechnology, was appointed director of the Leicester Biocentre in December 1984. He is forming a new association to take full advantage of the strengths of Leicester Biocentre and Cranfield Biotechnology Centre in the development of biotechnology in Britain, and he is building on the strong links already established with industrial organization.

Cranfield Biotechnology Centre:

This centre was created in 1981 under the directorship of Britains's first Professor of Biotechnology, I.J. Higgins. This chair was established and financed by the Leverhulme Trust.

Cranfield Biotechnology Centre is a contract research organization which also provides advanced training facilities for post-doctoral fellows. It is housed in well-equipped modern laboratories attached to a suite of offices. The next phase of development will extend work in several key areas and entails provisions of accommodation for a staffing level of over 100. The centre has been developed with assistance from industry to relate its activities closely to industrial needs, and from academic and technological institutions to provide industrially oriented post-doctoral training in biotechnology. The centre has also adopted a

deliberate policy of collaborative research with both industry and academia.

The current research interests include:

1. Biofuel cells, electrocatalysis, biosensors for clinical research, environmental monitoring systems, fermentation and process monitoring, and biosensors for the food industry in the Bioelectrochemistry Division.

2. Investigation of microbial transformations to devise industrially viable biocatalytic processes for chemical conversions. In addition to specific transformations, they are also studying the fundamental physiology and biochemistry of carbon-one oxidizing bacteria. Bacterial strains with a high capacity for biosurfactant production for uses in oil recovery are being developed.

3. A contract research and testing service to industry and government as well as long-term fundamental studies in environmental microbiology are provided by the Biodeterioration Division.

4. Genetic manipulation techniques are being applied to improving industrially important microorganisms; and research into applied aspects, such as factors affecting plasmid stability, is in progress.

5. The Fermentation Technology Division is perfecting large-scale methods for producing a range of microorganisms, and projects include the development of computer control of fermentation processes. Novel techniques for separating particles and proteins applicable to downstream processing are being developed.

Cranfield Biotechnology Centre has the capacity to undertake all types of innovative industrial research programmes, ranging from long-term basic research to one-time projects. The work is carried out by key personnel with substantial specialist expertise.

The scope and effectiveness of the centre's operation has been strengthened considerably by the recent appointment of Higgins as joint director of the Cranfield Biotechnology Centre and Leicester Biocentre. This association extends the commitment to the multidisciplinary, collaborative approach, bringing together the world-leading expertise in genetic manipulation techniques of Leicester Biocentre and the many strengths, in particular those in fermentation technology and downstream processing, of the Cranfield Biotechnology Centre.

For further information about the two biotechnology centres, contact: Dr. Jennifer Jones, Cranfield Biotechnology Centre, Cranfield Institute of Technology, Cranfield, Bedford MK43 0AL, UK; Professor I.J. Higgins, Director, Leicester Biocentre, Medical Sciences Building, University Road, Leicester LE1 7RH, UK.

GMIDC - A new biotechnology centre subsidized by industry:

The Grand Metropolitan Innovation Development Centre (GMIDC) is a unique new venture which combines the extensive research and development facilities of the University of Surrey with the commercial and financial expertise of Grand Metropolitan PLC, one of Britain's largest companies. The primary aim of the Innovation Development Centre is to help inventions from British universities, research institutes, and other sources of original thinking to become marketable products which can form the basis of new British industries in the field of high technology.

Through the Innovation Development Centre, Grand Metropolitan Biotechnology Limited, a subsidiary of Grand Metropolitan PLC, will be providing successful applicants with space and technical and administrative services, supported by a full evaluation and business development service using the international resources and management strength of the Grand Metropolitan Group. In addition, the University of Surrey offers some of the best technical research and reference facilities in Britain, backed by top technological academic expertise within the university itself and a highly attractive location convenient to all types of transport.

With a consultancy agreement, the resources and commitment to assist in realizing the full market potential of any invention successfully developed at the Innovation Development Centre can be achieved with or without the full-time involvement of the inventor.

Grand Metropolitan PLC has been committed to the principle of research and development to create growth and employment. The company decided that a major seedbed of British inventiveness - the universities and technical research institutes - were not being provided with sufficient facilities to develop new ideas to the advantage of British industry. Unfortunately this has been true. This lack of co-ordination between academia and industry has also been recognized by the government.

The GMIDC development is located in a new 70-acre research park adjacent to the University of Surrey. All the resources and services of the university are available to the occupiers of the GMIDC through automatic membership in the Surrey Network for Industrial Collaboration. This network involves the entire university - no faculty or department is exempt - offering a formidable intellectual resource as well as superbly equipped research facilities.

There are many research groups, units, and departments whose services, facilities, and expertise will be available to companies and organisations at the research park (GMIDC). The following are a few examples: (1) biochemical engineering and downstream processing; (2) biotechnology unit; (3) computerized data bank on drug diagnostic test interaction; (4) computer-assisted learning; (5) environmental research groups; (6) microstructural studies unit; (7) nuclear magnetic resonance imaging in biological materials; (8) particle technology; (9) structural plastics unit; (10) surface analysis group; (11) facilities for mechanical testing of materials; (12) medical and environmental physics groups; and (13) Guildhay ancisers.

Additional information can be obtained from: Grand Metropolitan Innovation Development Centre, Research Park, University of Surrey, Guildford, Surrey, UK. (Source: European Science News, 39-10 (1985))

Services for the bioprocess industry

Part of the process-setting group Porton International, based in London and Washington DC, LH Bioprocessing has now established itself at the Kent Research and Development Centre, where it will develop process technology for licensing and carry out contract R & D.

Porton International, the biotechnology group which earlier this year won an exclusive 13-year contract covering the exploitation of research carried out at the PHLS Centre for Applied Microbiology and Research continues to expand.

Earlier in the year, for example, it announced that a £15m biotechnology production plant would be built at CAMR, Porton Down, near Salisbury. The plant will be funded and owned by Porton International, but up to a third of its capacity will be made available to CAMR for at least 50 years. The group also set up Porton Products to co-ordinate the development, production and marketing of diagnostic, research or therapeutic products from any of its companies. Porton's therapeutics and research products division, based at CAMR, covers work in such areas as frozen microbial cell pastes, microbial enzymes, cell products, therapeutic enzymes and vaccines. Its diagnostic products activity meanwhile operates from Speywood Laboratories, Wrexham, another member of the group.

Now a new Porton company is in business: LH Bioprocessing (LHB). Operating under the direction of Drs. Geoffrey Holt and Alan T. Bull, who have been associated with Porton International since 1982, LHB aims to apply its expertise to projects covering the biotechnology of yeasts and filamentous micro-organisms (e.g. the production of agricultural chemicals, antibiotics and steroids), industrial chemistry (e.g. generic pharmaceuticals), extended use of biocatalysts (e.g. food additives), marine and environmental biotechnology (e.g. biohydrometallurgy, water monitoring and treatment), and instrumentation and the control of bioreactors (e.g. the development of serial interfaces for networking fermenters, and of fermenters for teaching use).

Considerable attention has been devoted to ensuring that LHB's activities complement those of its sister companies in the Porton International group. For example, one of the first LHB products to reach the market is likely to be an interface for networking groups of fermenters - an interface which will suit the LH Fermentation range. LHB is also expected to work closely with CAMR on some projects. In offering a contract R & D service to industrial clients, LHB also provides an initial evaluation service for clients wishing to explore and define biotechnology's potential contribution to their current and planned future businesses.

In the field of bioprocess development, LHB's skills fall into four broad categories: (a) the search for and discovery of novel biological activities, including organism selection and targeting screens, gene transfer methods, and novel chemical design and synthesis; (b) product and process research, focusing on vector design and strain improvement, process optimization, and the development of analytical methods; (c) product and process development, with emphasis on immobilised biocatalysts and computer-linked bioprocessing and control; and (d) downstream processing, particularly the manipulation of organisms to improve the efficiency of downstream operations.

In its next round of recruitment, LHB will need project leaders and associated staff in a number of fields, including molecular biology, microbial physiology, biochemical engineering, and organic and analytical chemistry. Details from: Dr. Geoffrey Holt, managing director, LH Bioprocessing Ltd., Research & Development Centre, The University of Kent at Canterbury, Kent CT2 7PD. Porton International is at 29 Chesham Place, London SW1X 8HB or on 01-245 6144. In the US, Porton International Inc.'s offices are at 1128 Sixteenth Street NW, Washington DC 20036 or on (202) 833 4344/5/6. (Extracted from Biotechnology Bulletin, Vol. 4 No. 11, December 1985)

USA

Imminent environmental releases

Last November a briefing report prepared by the U.S. General Accounting Office (GAO) for the Committee on Science and Technology, identified 87 biotechnology research projects involving planned release of genetically altered organisms into the environment (see table, pages 44 and 45). The report, notes that USDA is supporting these and 691 other biotechnology projects with $40.5 million for fiscal 1984 and 1985. The table, pages 44 and 45, was prepared by Newswatch from the recent GAO report, and lists 87 deliberate-release projects planned by Agricultural Experiment Stations in 28 states. Enhanced characteristics are being developed, at least in part, by recombinant DNA, except where noted. Risk assessment is the opinion of each project researcher. Of the 87 experiments under development, 76 involve no foreseen hazard; 10, a "very minor" or slight danger. In only one project is the likely risk "unknown". (Source: McGraw-Hill's Biotechnology Newswatch, 2 December 1985)

Bill to permit export of non-US-approved drugs

A U.S. Senate committee has approved legislation that would allow American companies to export drugs not yet approved in the U.S.A. to at least 15 industrialized nations that license them first.

The Bill, S. 1848, now goes to the full Senate, where one predicts it will have no trouble passing. However, opponents of the bill, including the American Public Health Association, and the International Chemical Workers Union - which represents many pharmaceutical employees - call it "immoral". They say it sets up a double standard, which violates Americans' basic belief that the health and safety of consumers abroad is no less important than that of U.S. users. According to the pharmaceutical and biotechnology industries, which support the legislation, eventual passage would increase U.S. exports by $400 million to $500 million a year, and create 8,000 to 10,000 new jobs. (Extracted from McGraw-Hill's Biotechnology Newswatch, 2 December 1985)

Navy will fund 'focussed' Archaebacteria research

A five-year, $12 million US government research programme on Archaebacteria has just funded its first project. The Office of Naval Research (ONR) recently awarded $220,000 to Dr. John H. Baross, University of Washington Seattle, to study the exotic micro-organisms, which he reports can live at deep-sea temperatures above 250°C.

Archaebacteria produce enzymes capable of catalysing biochemical reactions at temperatures far higher than those of conventional organisms, notes Dr. Thomas D. Brock, University of Wisconsin, Madison. He points out that enzymes from thermophiles are more stable at conventional temperatures, hence can confer long shelf life on commercial products. Moreover, at high temperatures, the surface tension and viscosity of

water decrease, enhancing fermenter performance. And with no energy needed for cooling, the reaction can run faster and cheaper. Given such advantageous parameters, specific strains of Archaebacteria can be harnessed to such large-scale processes as waste treatment and metal-ore leaching. On the latter score, some research is already under way with one archaeorganism, Sulfolobus sp., which can scavenge metals at 90°C.

Eventually, according to its solicitation of grant proposals, the Navy sees possible payoffs in "applicability of the Archaebacteria to the biotechnology of biosensors, biodosimeters, bioreactors, biofouling, biocorrosion, and materials ..." Dr. Baross's project is entitled "Multi-disciplinary Studies of Archaebacteria from Submarine Hydrothermal Environments." He will dredge up the organisms from Pacific-ocean deep-sea vents off the coast of Washington, where they live in water that reaches 350°C to 400°C. The research submersible, Alvin, will aspirate the high-temperature, low-density water from the vents at bottom depths of some 2,500 m., where the extreme pressures keep the water fluid. (Source: McGraw Hill's Biotechnology Newswatch, 16 December 1985)

OTA to take another look at biotechnology

The U.S. Office of Technology Assessment (OTA) has initiated a project called "New Developments in Biotechnology." The 28-month assessment, which began officially on 1 October, will produce technical memoranda, background papers, and small reports, plus an overall assessment volume.

Throughout the assessment, OTA will examine technology with an eye to predicting its direction and importance. Although OTA has not yet selected definite topics, project leader Louise A. Williams notes that her office has received some specific requests from Congressional committees. Among the issues likely to be included are:

- Federal funding of basic, generic, applied, and risk assessment research;
- Patents (including, possibly, deposit requirements);
- International concerns, such as export control;
- Social relevance of products (such as a malaria vaccine) and how to facilitate technology use by the Third World;
- Patients' rights (to what extent should people retain ownership of products derived from their tissues or fluids, and what are the ethical and legal ramifications); and
- Ethical issues of gene therapy.

OTA might also assess the quality and accuracy of biotechnology information reaching the general public. This could include a case study of several representative high schools to determine what students are being taught about biotechnology.

OTA intends to produce a variety of comparatively short documents, each tailored to a particular topic. (Extracted from Bio/Technology, Vol. 3, December 1985)

Competition in biotechnology heats up - around the country and throughout the world

A variety of strategies to stimulate biotechnological R & D are attracting the attention of researchers, entrepreneurs, and venture capitalists. State governments are including in their budgets allocations to improve the faculty and facilities of science programmes in higher education institutions and to establish statewide advanced technology programmes. These programmes often include regional high technology centers that stress advanced research in biotechnology and other technology-oriented fields, incubator facilities for start-up companies, financial assistance to support basic and applied research efforts, technology transfer mechanisms, and other forms of technical and business assistance.

State and local officials hope that these initiatives will help prompt the development of products and technologies with commercial potential, resulting in entrepreneurial ventures as offshoots of university research projects and the establishment or relocation of high technology companies. To assist in the development of new industries, state governments throughout the country offer tax and other financial incentives, employment training programs, consulting services on regulatory and marketing considerations, and financial assistance.

Benefiting from regional resources

Companies searching for a site to set up shop or to relocate should evaluate a variety of factors. For example, the accessibility of research- or production- oriented corporations in related fields is an important consideration. Local corporations can prove valuable for technology transfer and as sources of licensing agreements to develop and market the technology and products of start-up companies. The presence of high technology research parks or industrial corridors is also an attractive attribute based on their technology transfer possibilities, support facilities such as incubator space and computer resources, and support services such as technical and business counseling, administrative assistance, and joint conferences and symposia.

Local academic institutions offer library resources, laboratory facilities, educational opportunities, employee training programmes, and consulting agreements. High technology companies commonly cluster around major research universities and medical centres.

In addition to evaluating the individual attributes and special features of a region, developing businesses should scrutinize the overall attractiveness of the region. For example, does the state and/or local government take an active interest in promoting the region to new industries and in nurturing their development? Has the government taken any specific initiatives to stimulate activity in biotechnological R & D or other high technology fields? Does the government adequately support existing businesses by maintaining the region's transportation networks?

In general, what is the business climate, and what is the cost of operating a business in a given region? In the "Sixth Annual Study of General Manufacturing Climates of the Forty-eight Contiguous States of America", prepared by Alexander Grant & Co., 48 states were compared and ranked based on 22 variables "considered by manufacturers as key measures of a state's ability to provide a productive environment in the future". The variables focused on "the cost of doing business and availability of selected resources".

Tax incentives offered by state and local governments vary, offering all or partial exemption on items such as corporate income, land costs,

capital improvements, foreign-source income, raw materials used in manufacturing, and inventory.

Louisiana:

The state of Louisiana is actively supporting biotechnological activities in an effort to strengthen and diversify the state's economy. The Louisiana Science and Technology Foundation is a public agency that seeks to enhance communication and foster technology transfer among technology-based industries. State officials hope to build on Louisiana's leadership in medicine and agriculture by attracting companies active in diagnosing and treating disease, increasing crop yields, and improving animal stocks.

State funding for biotechnological research programmes has been proposed at a level of $10 to $50 million annually. A planned Biotechnology Institute will emphasize vaccine production, gene selection and mutation to isolate organisms with commercial potential, and fermentation and product purification.

Louisiana State University has proposed the development of a centre for biotechnology research in Baton Rouge to pursue research in genetic engineering, fermentation, neurobiology, biomembranes, and food science. A $125 million endowment by the Pennington Medical Foundation will fund a biomedical research centre, also at LSU-Baton Rouge.

Maryland:

The Baltimore-Washington Common Market, including Maryland, Virgina, and the District of Columbia is home to 56 biotechnology companies and more that 220 biotechnology-related support and service firms. High technology companies that locate in the Baltimore-Washington area are often attracted by the extent and variety of research and information resources clustered in this region: the National Institutes of Health, including the National Cancer Institute; NASA; the Beltsville Agricultural Research Center; the Food and Drug Administration; the National Bureau of Standards; the Naval Medical Center and Research Institute, and the Army Medical Bioengineering Research and Development Laboratory at Fort Detrick.

Montgomery County sponsors the Shady Grove Life Sciences Center, a research park devoted to health care and other bio-medical-related activities. Located within the Shady Grove Center is the Center for Advanced Research in Biotechnology, a joint project of the University of Maryland, the National Bureau of Standards, and the county. The Corporation for Technology Training, a private organization in Montgomery County, will provide a labour force trained for specific jobs in high technology industries.

In addition to establishing the Center for Advanced Research in Biotechnology, the University of Maryland is creating a university-wide programme in biotechnology, which includes the Institute for Biotechnology, located on the College Park campus. The university's Institute for Marine Biotechnology, to be situated at the school's campus in downtown Baltimore, will co-operate on projects with Maryland's Sea Grant College and the National Aquarium. The Institute for Biotechnology's biomedical research activities will be performed in conjunction with the University of Maryland Medical School in Baltimore.

The Francis Scott Key Medical Center, being developed by the Baltimore Economic Development Corp. and Johns Hopkins University, will include a biomedical business park with incubator facilities for emerging companies. The Maryland Science and Technology Center, a planned 466-acre park in Bowie, is a joint venture of the University of Maryland Foundation and the Carly Capital Group.

Michigan:

The Michigan Biotechnology Institute was established in 1982 with funds from the Michigan Economic Development Authority and the W.K. Kellogg Foundation. It is dedicated to the commercialization of biotechnology in the state. In an effort to exploit the state's vast woodland resources, institute-sponsored projects stress research in agriculture, energy, chemical products, waste treatment, forest products, and pharmaceutical industries.

The institute is planning to build its own research centre near Michigan State University. It will also fund studies at the University of Michigan, Michigan Technological University, and Michigan State University.

A $1.5 million donation from Dow Chemical Co. will be used by the University of Michigan to upgrade its teaching and research facilities in chemistry and the life sciences. Union Carbide recently provided a $999,990 grant to the Michigan State University Pesticide Research Center.

Tennessee:

The Appalachian Regional Commission provided $1.2 million in funding to establish the Tennessee Technology Foundation in 1982. This private, non-profit corporation assists emerging technology companies obtain needed financial resources and locate a site for their business. The primary focus of the foundation has been the development of the Knoxville/Oak Ridge Technology Corridor, which draws its resources from the neighboring University of Tennessee, the Oak Ridge National Laboratory, and the Tennessee Valley Authority.

The foundation has expanded its efforts to include planned R & D facilities in Memphis and south central Tennessee. To aid in this expansion, the state legislature allocated an additional $2 million to the foundation in 1985.

A planned $65 million research complex to be located in the Biomedical Research Zone near downtown Memphis is scheduled for completion in 1986. The development will benefit from the nearby University of Tennessee Center for the Health Sciences. Nashville will be the home of a proposed 31 acre office and research park for health care industries.

USSR

New bacterial enzyme beneficial to livestock production

Production of dry bacteria enzymes has begun at a Turkestan Food antibiotics plant. This new production is intended for the ensilage of practically all types of coarse fodders; it improves their quality and extends their storage life.

"Retsept" is a highly effective compound developed by scientists at the Institute of Microbiology and Virology of the Kazakh SSR Academy of Sciences. It is prepared from lactic acid bacteria cultures and when it is introduced to a feed mass at designated doses it increases its nutrient properties.

Republic stock breeders have evaluated the merits of the bacterial enzymes, which promote

increased yields, weight gains and wool shearings. (Source: Izvestiya, 25 July 1985)

Hybrid cell production in USSR

Soviet biologists have succeeded in fusing yeast cells with animal cells so that the resultant unusual cells with two and sometimes more nuclei and merged protoplasm have lived for about a month in laboratory conditions.

Fused cells usually die within 24 hours, but the scientists are confident that their cells have kept living and functioning for just as long as they have been able to watch the processes of interaction between the ingredients of such cells that have a single membrane each.

It is the first time that genetic engineers have managed to produce cells from such evolutionary distant components as a microbian cell and an animal cell.

According to one of the researchers of the Institute of Molecular Biology of the USSR Academy of Sciences, such cells are not yet hybrids since they have different kinds of nuclei and cannot reproduce.

The scientists look at such cells as a model for studying the finest processes of interaction between elements that are evolutionarily far apart. The studies are important to solving the problem of tissue compatibility and breeding new varieties of agricultural crops.

The problem of cell reconstruction from individual molecules has long held the interest of researchers who are now making just the first steps to cracking it. But they have already been able to use the method to investigate the structure of many genes of plants, bacteria and animals. Such medicinal preparations as insulin, somatotropin and interferon are commercially produced from bacteria with in-built heterologous genes responsible for heredity. Plant selectionists have also been able to produce the interspecific hybrids of cultivated tobacco, potatoes, tomatoes and cabbage with their wild-growing kin. (Source: TASS, 24 July 1985)

Hydrogen-producing bacteria

A hydrogen-producing bacteria discovered on the Kamchatka peninsula forms the basis of a biological system developed by Soviet scientists at Moscow University for the continuous production of hydrogen and oxygen from water. The organisms utilise solar energy. The Soviet team, led by Professor Varfolomeyev, hopes to perfect the system to permit the biological production of fuel hydrogen. (Source: European Chemical News, 4 November 1985)

C. RESEARCH

Research on human genes

Gene mutations test

A technique that can determine if DNA contains any mutations is being developed by W. Thilly of Massachusetts Institute of Technology. The procedure requires only 10 ml of blood, and could be sensitive enough to detect point mutations and what caused the mutation. The test assumes that certain regions of the genome are more susceptible to attack by one mutagen than others. Each mutagen is also assumed to cause a characteristic mutation pattern. If a library of mutations caused by a given mutagen can be built up, it should be feasible to identify the mutagen responsible for any mutations observed in blood cells drawn from a person's fingertip. Details of how the mutation spectra are obtained have not been made public. At present, the test would be prohibitively expensive, about $5,000 per person. If the test can be perfected, however, it may have an impact on preventing birth defects and could identify damage done by mutagens that a worker was exposed to on the job. (Extracted from New Scientist, 31 October 1985)

Cystic fibrosis marker mapped

Genetic engineers are closing in on cystic fibrosis (CF) disease from two directions - diagnosis and therapy. Two U.S. R&D firms have independently located a chromosomal marker pointing to the still-unmapped CF gene, and a microbiologist has cloned one of the genes coding for one of the disease-related enzymes. Scientists working with Collaborative Research, Inc. (CR), Lexington, Mass., and Integrated Genetics, Inc. (IG), Framingham, Mass., reported separately that they have narrowed the location of the CF gene from anywhere on the human genome's three billion DNA bases to 30 million. IG's director of genetic disease research, Dr. Katherine W. Klinger, pinpointed the elusive CF gene to the short arm of chromosome 21.

Cystic fibrosis afflicts primarily Caucasians, such as sickle-cell anaemia singles out blacks and Lesch-Nyhan disease strikes Jewish children. One in 2,000 Caucasian infants is born with CF, and most victims die in their teens. Ten million Americans carry the CF gene, but as the disease is recessive, both parents must be carriers to pass on the lethal double-dose of DNA.

There is no cure for CF, and it cannot be diagnosed prenatally. Death is usually caused by progressive pulmonary destruction or infection by invading Pseudomonas aeruginosa bacteria. These pathogens secrete large build-ups of alginic acid, a viscous mucus, which must be expelled from the lungs by frequent painful bouts of heavy back-slapping.

In recent months, Dr. Ananda M. Chakrabarty, University of Illinois Medical Center, Chicago, has isolated and completely sequenced an enzyme involved in the bacterial synthesis of alginic acid. Chakrabarty's Pseudomonas enzyme, phosphomannose isomerase, is 1,440 base pairs long, and can be overproduced under "a very strong promoter". Presumably, this is what the bacterium does, lodged in the lungs of CF patients, secreting alginic acid non-stop. "We are now characterizing a number of genes that appear to map close together with phosphomannose, and hope to overproduce many other of the alginic enzymes", Chakrabarty says, explaining that alginic acid is commercially important as a thickener in the food industry. It is now extracted from sewage.

The two Massachusetts-based R&D firms both tracked inheritance of the CF gene marker by screening the DNA in blood samples taken from families with a strong incidence of CF children, and finding in them nucleotide sequences that matched cleavage-site patterns in random probes - restriction fragment length polymorphisms. Collaborative Research worked with Drs. Lap-Chee Tsui and Manuel Buchwald at The Hospital for Sick Children in Toronto, who studied two generations of 50 carrier families. Integrated Genetics analysed the genomes of some 250 individuals, 26 of them CF patients, in closely related family pedigrees among Amish, Mennonite and Hutterite communities in the U.S.A.

In CR's Canadian families, the marker DNA sequence was found to be co-inherited in 85 per cent of CF-afflicted offspring; in the IG sample, 94 per cent. Now both research groups will try to find another such sequence on the far side of the gene

and then narrow their "walk" down the chromosome until the lethal gene is located. This may take "several years", says CF's Dr. Helen Donis-Keller, after which pre-natal diagnosis and eventual treatment for CF should be possible. Meanwhile, both companies have applied for patents covering their identification of the CF locus and eventual approaches to diagnosis. (Source: McGraw-Hill's Biotechnology Newswatch, 4 November 1985)

Human hybridomas shed light on autoimmune diseases

Autoimmune diseases are mysterious ailments that cause the body literally to attack itself. Their cause is unknown, but recent research by a Tel Aviv University scientist has shown how an infecting agent, such as bacteria, may trigger the condition.

Found mainly in young women of childbearing age, autoimmune diseases break down the immune system. Instead of producing antibodies to fight infection, victims of autoimmune disease produce "autoantibodies", which attack healthy tissues - the skin, the joints, the central nervous system, or the kidneys. Hundreds of autoimmune diseases have been identified, but one of the most serious is systemic lupus erythematosus (SLE), which affects the kidneys and may lead to renal failure and death.

Dr. Yehuda Shoenfeld, professor of medicine at Tel Aviv University's Sackler Faculty of Medicine, working with Dr. Robert S. Schwartz and Dr. David Stollar of the New England Medical Center in Boston, has used the hybridoma technique to demonstrate the mechanism of binding of autoantibodies to normal tissues.

Hybridomas were first developed in the mid-1970s by Dr. Cesar Milstein and Dr. Georges Kohler, winners of this year's Nobel Prize in medicine. The technique involves three steps. A mouse is stimulated to produce a particular antibody. Then the mouse lymphocytes are fused with malignant mouse cells. The cells resulting from the fusion, called hybridomas, have the characteristics of both parent cells: the malignant cells make them capable of reproducing infinitely, and they are able to generate the specific antibody desired.

Shoenfeld and his colleagues were among the first to produce human hybridomas, using lymphocytes from patients with SLE, who are, so to speak, already immunized - against themselves. The two scientists used the MCAs produced by these hybridomas, as well as autoantibodies from the SLE patients, in experiments with tuberculosis bacteria.

Previous research had shown that tuberculosis was associated with autoimmune disease. Autoantibodies had been found in TB patients, and a vaccine used against TB caused autoimmune symptoms. Shoenfeld and his colleagues showed that the association was valid, and helped to define the mechanism used by invading agents to trigger autoimmune diseases.

Shoenfeld hopes these discoveries will one day lead to treatments for SLE and other autoimmune afflictions. He also wants to apply the hybridoma technique to cancer research. "We have succeeded in producing a hybridoma using cells from a woman with breast cancer, which secretes monoclonal antibodies against breast cancer antigens", he said. Working with Professor Iafa Keydar, dean of the George S. Wise Faculty of Life Sciences, and Dr. Amnon Hizi of the Sackler Faculty of Medicine Department of Histology and Cell Biology, Shoenfeld demonstrated that the antibodies from this hybridoma react with the antigen from a mammary tumor virus from mice. (Extracted from European Science News, 39-10 (1985))

Unlimited length genes for protein engineering developed

"Proteins nature never saw" - in any desired length - are the predicted product of an inside-out gene-assembly system under development at the California Institute of Technology. Last spring at the American Association for the Advancement of Science meeting, CalTech's John H. Richards described his strategy, which involves separately synthesizing short segments of the desired gene, cloning them in a vector, transforming a host organism for amplification of the sequences, then linking these up into long chains.

Since then, Richards' method has reached a point where he and his graduate students are putting together the 297-base-pair gene for plastocyanin, an electron-transfer protein that is a key player in plant photosynthesis. This protein, he explains, is serving as a demonstrator model, using known sequences to check out that the system "for making proteins without going back to the chromosome" really works.

They are inserting three 100-base fragments of the gene - which they synthesized by coding for its 99 amino acids - into plasmid pBR322, one stretch at a time, making multiple copies of the cloned vehicle in Escherichia coli, then joining the sequences to assemble the total gene.

After a segment has been cloned into the vector and amplified, Richards explains, the plasmid can be opened at built-in restriction sites, which in turn act as recipient ends between which subsequent add-on segments of the structural gene are inserted. (Extracted from McGraw-Hill's Biotechnology Newswatch, 2 December 1985)

Histones as hormones

Much of the DNA within the cells is coated with proteins known as histones. Although their existence has long been known, new studies suggest that they are much more versatile and influential than had been supposed.

Histones contain a high proportion of positively charged amino acids, allowing them to bind to the negatively charged groups studded along the "backbone" of DNA. They may act as a chromosomal "glue", wrapping up DNA that isn't being actively decoded into protein; and they probably protect their parcelled DNA molecules from damaging chemicals and radiation. In addition to accepted roles, a previously unrecognised activity of histones may now have been uncovered.

The evidence for histones as hormones has been gathered by Robert Reichhart and Hans Jornvall at the Karolinska Institute in Stockholm, together with Michael Zeppezauer of the University of Saarlandes in West Germany.

They report that a hormone produced by the thymus gland, known as homeostatic thymus hormone (HTH), seems to consist of two histones known as H2A and H2B.

The thymus gland is involved in the proper development of the immune system, and HTH is one of the hormones that allows it to perform this role. But what HTH does is not as important as the discovery that it seems to consist of two histones.

This suggests that other histones may also act as hormones in other ways and places.

The three scientists backed up their conclusion that HTH really is made of the two histones by looking at these proteins' amino acid sequences in detail. They identified various suggestive similarities between the histones' sequences and important parts of some well recognized protein hormones. (Extracted from New Scientist, 28 November 1985)

Human retroviruses and multiple sclerosis

Multiple sclerosis is a tragic disease of the nervous system which mostly surfaces when its victims are in their late teens or early twenties, causing progressive debilitation until death about 20 years later. Despite many years of intensive research, nobody knows exactly what causes multiple sclerosis (MS), and there is no cure. Infection by a virus is the prime suspected cause, although viruses are believed to be involved in a rather round-about way, and no single "MS virus" appears to exist. The presumed involvement of viruses in MS is in the news again thanks to a research team which includes Robert Gallo - co-discoverer of the virus that causes AIDS (Nature, vol. 318, p. 154).

Hilary Koprowski, Robert Gallo and eight other members of a team drawn from the US National Cancer Institute, the Wistar Institute in Philadelphia, and the Universities of Miami in Florida and Lund in Sweden, suggest that a virus similar to the AIDS virus may be involved in causing MS.

They have found raised levels of antibodies against the celebrated HTLV viruses in the blood and cerebrospinal fluid of people with MS. The HTLVs are responsible for some human cancers and also AIDS. (Whether the AIDS virus really does belong to the HTLV category is still a matter of some controversy.) The researchers also claim to have detected nucleic acid "related to but distinct from" that of the HTLV viruses in a few cells taken from the cerebrospinal fluid of MS sufferers, although the evidence backing up that claim is as yet rather weak.

The evidence suggesting that some sort of infection, or infections, are responsible for the disease has been convincing for a long time. In the Faroe Islands, for example, the disease was unknown until British troops arrived in 1940. A few years later the islanders began to fall victim to a small MS epidemic.

The incidence of the disease varies throughout the world, being more common in temperate regions than nearer the tropics; and migrants to warmer countries take their increased risk with them unless they leave before the age of about 15. This suggests that some childhood infection or infections are to blame.

The nervous system of MS sufferers is progressively damaged by a process known as "demyelination" and the resulting breaks in the insulation between axons produce the symptoms of the disease - such as problems with vision, poor co-ordination, lack of balance and, eventually, death.

The myelin does not seem to be destroyed by viral infection directly. Instead, it apparently falls victim to an "autoimmune" attack, in which the body's immune system begins to destroy its own myelin as if it were part of some foreign organism. Viral infection is believed to "trigger" this autoimmunity.

Some viruses might trigger autoimmunity by infecting the cells of the immune system directly, interfering with their proper functioning. Others might damage infected cells sufficiently to release components of the cells that are normally hidden from the immune system. These perfectly normal cell components would appear foreign to the immune system, so would be attacked.

Antibodies that bind to several viruses such as measles virus, Epstein-Barr virus and others, are found at higher levels in the cerebrospinal fluid of people with MS than in healthy people. Various viruses, or bits of them, such as their nucleic acid genomes, have been found in the brains of MS victims. The proteins of some of the suspect viruses have been shown to be similar in parts to a protein found in myelin. This might explain why such viruses should induce autoimmunity against myelin; but no single consistent candidate for the supposed MS virus has ever emerged.

With this in mind, scientists have turned away from the search for a specific MS virus and become increasingly convinced that a variety of different common viruses might be able to initiate the disease. According to this idea some people are genetically predisposed to contract MS when viruses such as measles virus, Epstein-Barr virus, herpes viruses, influenza virus and so on, infect them during childhood. The evidence implicating the HTLV viruses so far is really no stronger than some of the evidence already accumulated to incriminate various other types of virus. Until it is backed up with more convincing details it will be treated with great caution. (Extracted from New Scientist, 5 December 1985)

Interleukin-2 receptor gene structure

The structure of a gene important in regulating the body's response to infections and possibly cancer has been determined by a team of researchers at several institutions headed by Warren J. Leonard of the National Institute of Child Health & Human Development, Bethesda, Md. The gene encodes the receptor for interleukin-2. Both interleukin-2 and its receptor play key roles in stimulating the growth and activation of T-cells of the immune system. The gene consists of eight exons spanning more than 25 kilobases on chromosome 10. It is a complicated gene, with three different transcription sites, the possibility for alternative messenger RNA (mRNA) splicing, and at least three different polyadenylation signals. "We conclude that perhaps as many as 18 different mature mRNA forms can be produced by this single gene", the researchers say. "The events that regulate which of these mRNAs are made and when remain to be elucidated". (Source: Chemical and Engineering News, 4 November 1985)

Diphtheria toxin as possible anti-cancer drug

The diphtheria toxin could be used as an anticancer drug, according to research carried out at Boston University Medical Center. A modified diphtheria toxin has been produced by removing the binder for diphtheria-sensitive cells and replacing it with a hormone for alpha-melanocyte stimulating hormone (MSH). MSH receptors occur on the surfaces of melanocyte cells, which can grow uncontrollably to produce malignant melanoma. The modified toxin kills malignant melanoma cells grown in culture, but does not effect diphtheria-sensitive cells, which lack MSH receptors. No ill-effects were observed

when guinea pigs were injected with 1,000 times the lethal dose of modified diphtheria toxin. The toxin might also be modified to kill T cells responsible for organ rejection, some forms of leukemia and autoimmune diseases. (Extracted from Science News, 28 September 1985)

Trans splicing

RNA splicing of codons from different genes has been discovered by researchers at Yale University, Massachusetts Institute of Technology and the Polish Academy of Sciences. Such trans splicing may combine exons (coding segments of genes) from various genes even when there are no shared introns (noncoding segments of genes) segments. (Extracted from Science News, 14 September 1985)

Protein production switched-off at certain level

Higher organisms may switch off production of proteins when the amount of a control peptide reaches a certain level, binding to mRNA to block further transcription, according to Dr. Y. Aloni of the Weizmann Institute. Studies with simian virus (SV40) indicate that coat protein synthesis is regulated by the peptide agnoprotein that binds to mRNA when it reaches a certain concentration. In the nucleus, incomplete copies of mRNA are formed because the agnoprotein binds to it immediately, and this provides a feedback to switch off production of any more mRNA. (Extracted from New Scientist, 12 September 1985)

New method to label gene probes

A non-radioactive way to label gene probes has been developed by J. McGee of Oxford University. The technique is a refinement of biotin labeling of probes, developed in 1983 by D. Ward of Yale University. Researchers can bind proteins to the biotin to produce a colour change when the compound DAB is used. The colour change is too slight to be detected if only a few genes are present. The new technique adds hydrogen peroxide to bind to the DAB, and this allows a heavy metal such as gold to bind to the gene. Silver grains can then be made to precipitate at the site of the gold to make the gene probe readily visible. The procedure takes 24 hours. (Extracted from New Scientist, 17 October 1985)

Genes linked to heart attacks

California Biotechnology Inc. of the US has revealed that its scientists may have unravelled some clues as to why some people are more susceptible to heart attacks than others. The concern said it has discovered three genetic markers which have "a strong correlation" to susceptibility to a heart attack. These are being incorporated into prognostic tests for high risk patients.

The company, in collaboration with Dr. Gerd Assmann of the University of Westphalia in the Federal Republic of Germany, examined about 200 patients and found that 40 per cent of those who had previously suffered from a heart attack had at least one or two of the high-risk markers. In the "normal" population, only 16 per cent of people possess these two marker genes. The third marker was associated with a decreased risk of heart attack, according to researchers. (Extracted from European Chemical News, 21 October 1985)

Catalysis by RNA

The RNA molecule can act as an autocatalyst to connect short RNA molecules into longer chains, according to T. Cech and A. Zaug of the University of Colorado. Thus, RNA in early life could have acted both as genetic material and catalyst. The discovery of catalysis by RNA means that protein enzymes are not the only biological catalysts, and it indicates that RNA may play a variety of roles in modern cells. Heating RNA to disrupt its folded structure and allowing it to cool produces RNA chains. Similar results might be obtained by changing the ion content of the surrounding solution. Infectious RNAs known as viroids reproduce themselves as repetitive chains, and then break into smaller RNA molecules. (Extracted from New Scientist, 3 October 1985)

Biological membrane fusion

The fusion of biological membranes has been modelled by scientists at the University of Groningen, Netherlands. Fusion of membranes is essential for the transport of materials into and out of the cell, but the mechanism of fusion has so far remained unknown. Artificial surfactant vesicles fuse in much the same way as natural vesicles. The fusion of membranes in these artificial vesicles was studied by adding some molecules that absorb or emit fluorescent light. The vesicles only fused when dipicolinic acid was added to the mixture. Vesicles 220 nm in diameter formed aggregates, but did not fuse, whereas vesicles 320 nm in diameter fused to form vesicles 2-3 microns in diameter. All aspects of the two-step fusion process are not yet understood. (Extracted from New Scientist, 24 October 1985)

Protein to stimulate growth of human blood vessels

A protein that stimulates the growth of human blood vessels has been discovered and produced in pure form by researchers at Harvard Medical School, who have named it angiogenin. It is the first known organ-forming protein to be identified and analysed genetically and chemically. It was first isolated from human colon cancer and has also been detected in normal human liver tissue. In laboratory studies, it stimulated the growth of capillaries in fertilized hens' eggs and rabbit corneas. The researchers reconstructed the gene that directs the synthesis of angiogenin in the laboratory, making possible mass production of the protein via new rDNA techniques. Large quantities of angiogenin will now be available for further study. The protein consists of a single chain of 123 amino acids and is very similar in structure and chemistry to ribonuclease. The discovery of angiogenin may lead to a new way to fight cancer, which must generate new blood vessels to survive. A better understanding of the production of blood vessels may make it possible to inhibit the process and thereby starve the cancer. Angiogenin may help speed the healing of bones, tendons, wounds and intractable duodenal ulcers. (Extracted from New York Times, 27 September 1985 and Newsweek, 7 October 1985)

Technique to control gene expression

A new technique to control the expression of any single gene within a cell has been developed by researchers at Stony Brook, New York State. Antisense RNA is used to block expression of a gene. The use of promotors to enhance the production of a gene product has been possible for several years. Antisense RNA blocks the transcription of RNA into a protein. The expression of the gene ompF in E. coli is naturally regulated by production of the antisense RNA. It is not clear if this mechanism is at work in more advanced cells, but researchers have been able to suppress expression of the normal actin gene using antisense RNA. Experiments conducted by Herbert Jackie of

Tübingen, Federal Republic of Germany, with fruit fly embryos indicated that antisense RNA can prevent gene expression throughout a higher organism. Antisense RNA may be useful in treating cancer by blocking the actions of oncogenes. (Extracted from New Scientist, 10 October 1985)

Thrombi detection by radioactive MAs

Brookhaven National Laboratory has developed radioactive monoclonal antiplatelet antibodies to detect thrombi, which can cause heart attacks, impair limb circulation and contribute to the rejection of transplanted organs. Since thrombi contain many platelets, researchers decided to test the antibodies' thrombi-detecting abilities in dogs (human platelets cross-react with dogs'). The entire test took 24 hours, but when the researchers used a fragment (the active site) of the antibody, it cleared from the blood in two hours. As the antibody clears from the blood it causes a clearer picture of the clot because background radioactivity in the blood is looser. (Extracted from Industrial Chemical News, November 1985)

Oncogene linked to stomach cancer

Japanese researchers have discovered a new oncogene which they believe is associated with human cancer of the stomach.

The DNA used in the team's experiments was cloned directly from tissue surgically removed from the stomach tumours of patients at the National Cancer Centre in Tokyo. The team transfected NIH 3T3 cells - mouse cells which are used as an assay to detect "transforming" oncogenes. The transfected cells produced tumours when injected into mice with a DNA probe. Researchers identified human sequences expressed in cells taken from the tumours, and to demonstrate that the transforming sequence - the section of DNA which causes the cells to become cancerous - was of human origin.

The new oncogene's transforming sequence consists of nearly 60 kilobase pairs, making it the longest discovered in human DNA (the average length is about 50 kilobase pairs). A more significant difference is that the oncogene is not homologous to the ras gene family to which the majority of the naturally occurring transforming genes thus far discovered in human tumours belong. The researchers established, however, that it is closely related to v-raf, a retroviral oncogene which causes cancer in mice. (Extracted from New Scientist, 24 October 1985)

Pneumonias-related findings create new problems in growing AIDS epidemic

Certain AIDS patients, and others with conditions related to AIDS, are at risk for unusually severe respiratory infections and complications, due to S. pneumoniae and H. influenzae, according to a study just reported in AIDS Research. The article entitled "Community-Acquired Bacterial Pneumonias in Homosexual Men: Presumptive Evidence for a Defect in Host Resistance" is written by Glen A. Murata, Mark J. Ault, and Richard D. Meyer, from the Divisions of General Internal Medicine and Infectious Diseases, Department of Medicine, Cedars-Sinai Medical Center-UCLA School of Medicine, Los Angeles, CA.

The study, which took over three years, was based on 16 male patients admitted to the Cedars-Sinai Medical Center. All had documented pneumococcal or H. influenzae pneumonia - none had any conditions known to increase the risk of complications. Seven of these patients were homosexuals. When compared to heterosexual controls, the homosexual group had a much higher complication rate, including a much higher frequency of acteremia, complicated primary infections, multilobar involvement, longer antibiotic therapy, and a longer defervescence period.

AIDS is presently defined by "clinical criteria reflecting a defect in cell-mediated immunity occurring in the absence of a known cause for diminished response". However, the Centers for Disease Control (CDC) states that "this case definition may not include the full spectrum of AIDS manifestations." This study explores this unknown dimension, in an attempt for further definition.

The results of this study are significant - this is the first analysis attempted that associates AIDS or "pre-AIDS" and a defect in host resistance to certain pyogenic infections, in this case specifically S. pneumoniae and H. influenzae. Although the vast majority of AIDS research to date show opportunistic infections associated with T-cell dysfunction, recent studies have increasingly shown abnormalities in the B-cell function as well. According to the authors of this article, "further studies of B-cell function and phagocytosis should be done to elucidate the defects in host resistance."

For further information contact the publisher of AIDS RESEARCH: Mary Ann Liebert, Inc., 157 East 86th Street, New York, NY 10028. (212) 289-2300. (Source: News Release, October 1985)

Lipids may prevent infection by HTLV-III virus

A combination of lipids could prevent infection of human cells by HTLV-III virus, which is implicated in the development of AIDS. Researchers from the National Cancer Institute, Yale University, the University of Florida and Praxis Pharmaceuticals incubated human peripheral-blood lymphocytes, HTLV-III virus and the lipid combination AL 721 for 90 per cent plus cell protection. AL 721 contains neutral glycerides, phosphatidycholine and phosphatidylethanolamine in a 7:2:1 ratio, and can extract cholesterol from cell membranes.

A test to detect antibodies to the HTLV-III virus has apparently been developed at Cambridge University. The test uses an isolate of the HTLV-III virus replicated in the Karpas T-cell line. Serum samples are incubated with acetone-fixed HTLV-III connected T-cells. These cells have been lysed by the action of the virus. The antibody-virus complex which results is detectable by peroxidase or fluorescent staining. (Extracted from Clinica, 11 October 1985 and Chemical and Engineering News, 18 November 1985)

Clinical trials for AIDS treatment

ICN Pharmaceuticals and Eastman Kodak have started large-scale human clinical trials for a drug to treat AIDS at New York University/Cornell Medical Center, MD Anderson Hospital, the University of Southern California (Los Angeles), the University of California (San Diego) and the University of Miami. The firms will test the effectiveness of ribavirin on 350 patients with AIDS-related complexes. Ribavirin was developed by ICN as a broad-spectrum antiviral, and has applications against various virally induced diseases. ICN and Kodak jointly operate the nucleic acid research institute, which is researching a wide range of antiviral compounds. (Extracted from Chemical Marketing Reporter, 7 October 1985)

AIDS source

The existence of AIDS in Africa is still the source of great controversy. Estimates of the

prevalence of the disease are made by random testing of blood for antibodies to the AIDS virus. They suggest that the disease is spreading from central Africa to western and southern parts of the continent. Some scientists believe that the tests lead to an overestimation of the problem. There is controversy, too, about how the virus is transmitted in Africa. A third key question is whether AIDS in Africa and AIDS elsewhere are the same or different.

The majority of cases of AIDS in the US and Europe are still among homosexual men, but in Central Africa, especially the capitals of Zaire, Rwanda and Uganda, the disease affects men and women almost equally. This fact alone makes it vitally important that scientists know for certain exactly how the AIDS virus is transmitted in Africa. According to Dr. Anne Bayley of the University of Zambia in Lusaka, AIDS in Africa is the same as AIDS anywhere else, but given its prevalence among women, others have doubts.

Many researchers believe that the AIDS virus originated in Africa. Myron Essex, of the Harvard School of Public Health in Boston, has isolated a virus that infects captive macaques and produces a disease in the monkeys that resembles AIDS in humans. The virus, which he has called simian T-lymphotropic virus type III (STLV-III mac), resembles the human AIDS virus which Robert Gallo of the US's National Cancer Institute in Bathesda, Maryland, labelled human T-lymphotropic virus type III (HTLV-III). It resembles it both in appearance and behaviour. STLV-III too has a preference for T cells, hence the term T-lymphotropic.

According to Essex, various regions of the genes making up HTLV-III and STLV-III are chemically very close, having similar genetic codes. Essex hypothesized that the AIDS virus might have first affected monkeys, before being transmitted to a human being in what he refers to as a "rare" evolutionary event.

Essex looked for antibodies to STLV-III in the blood of African green monkeys, the species most prevalent in those regions of central Africa in which AIDS is found. He found that 40 per cent of the wild monkeys tested were positive for the simian-virus antibody. Essex has since shown that the virus infecting African green monkeys (which he calls STLV-III AGM) is very similar to STLV-III mac.

To take this story to its logical conclusion, Essex looked for a relationship between STLV-III AGM and HTLV-III. He found the antibodies of about half of the people he tested in the US, who had at some time acquired AIDS antibodies, reacted with STLV-III from African green monkeys. Of the Africans he tested, 97-100 per cent had antibodies that reacted with STLV-III AGM.

These experiments have convinced many that the AIDS virus that is wreaking death in the West is a mutated form of the virus that is apparently endemic in African green monkeys. A related piece of evidence is that HTLV-1, a leukaemia virus which Essex says is another member of the human T-lymphotropic virus family is also thought to have originated in Africa.

What African scientists cannot understand is why this "rare" evolutionary event should have been confined so long to Zaire.

Another major piece of evidence linking AIDS to Africa is that antibodies to the AIDS virus have been found in blood that has been stored for some years. The stored serum samples predate the emergence of the disease in the US. Richard Tedder of the Middlesex Hospital in London, however, believes that the tests used to detect antibodies in the stored sera were more primitive than those available now. (Extracted from New Scientist, 28 November 1985)

Promising drug against sleeping sickness

One recent object of adulation is a chemical called alpha difluoromethylornithine (DFMO); the disease it cures is sleeping sickness, but it could be effective against other tropical parasitic diseases, some virus infections and even bowel cancer.

DFMO is made by Merrell Dow Pharmaceutical, who developed it with New York University and Pace University in New York. Like many cancer drugs, it inhibits the growth of all fast-dividing cells. DFMO's secret is that it is only slowly absorbed by normal cells, while the trypanosome parasites ("tryps") which cause sleeping sickness absorb it rapidly. Tryps change their antigens to evade the body's immune system. DFMO stops that. It prevents the tryps building new antigens and allows the immune system to catch up.

In the Sudan, one WHO-sponsored trial cured 97 out of 100 sleeping-sickness patients, in some of whom the parasites had become resistant to other drugs. In some, also, the parasites had invaded the central nervous system, making the condition difficult or impossible to treat by other means and sending the patients into comas (hence the new drug's nickname - resurrection drug).

Preliminary tests suggest that DFMO is also promising against more than one stage of the life cycle of the malarial parasite, and against the different kinds of tryps which cause Chagas' disease in Central and South America and leishmaniasis in the Middle East. DFMO might work against some human virus infections, notably cytomegalovirus (CMV), which can kill transplant patients. Dr. Stan Tyms, working in the virology department of St. Mary's Hospital in London, has shown that it can arrest the growth of CMV in laboratory cultures without damaging the human cells in which the virus replicates. (Extracted from The Economist, 19 October 1985)

Treatment in sight for tropical diseases

Malaria, the most important parasitic disease of the tropics, has benefited from some dramatic strides in research in the past two years. Among the breakthroughs has been the cloning of surface coatings of the sporozoite stage of Plasmodium falciparum, the organism responsible for the severest forms of malaria. Experiments with animals have shown that an inoculation with the synthetic sporozoite coat triggers the body's immune system into action. The latest report of the World Health Organisation's Special Programme for Research and Training in Tropical Diseases predicts that a vaccine "should soon be ready for initial toxicity, tolerance and efficacy testing".

Other research has identified antigens on the surface of different parasites in their asexual stages that may offer some protection. This work could provide another approach to making a vaccine. Meanwhile, monoclonal antibodies have been used to develop a simple, species-specific assay, called the Zavala test, which identifies sporozoites in infected mosquitoes. This test could become a powerful tool for monitoring the spread of different types of parasites.

The "mapping" of the immune system's response to malaria is also promising. Researchers,

supported by the special programme, have identified an antigen of P. falciparum, exhibited when the parasite leaves its host, the red blood cell, in the human liver. Researchers are also analysing and identifying the sequences of amino acids in the so-called S-antigens, which the schizont stage releases.

New drugs against malaria - the first for 30 years - are coming out of work that the special programme is supporting on the treatment of malaria with drugs. One novel drug is ginghaosu, the active ingredient in a Chinese medicinal herb, Artemisia annua. Chinese scientists have studied the compound and some of its derivatives. They show that the compounds work quickly against malaria caused by P. falciparum parasites that are resistant to chloroquine, the drug most commonly taken to prevent and treat malaria. Meanwhile, the special programme is trying to interest five pharmaceutical companies in developing compounds to destroy the parasite's schizontal phase in the blood.

In other potentially important research, scientists have cultivated the extra-erythrocytic (outside the red blood cell) stages of Plasmodium vivax, paving the way for the development of screening techniques for compounds suspected of being active against the parasite in the tissue.

Schistosomiasis is another disease whose mysteries are gradually being solved. One hopeful sign is that scientists have induced immunity in rats by inoculating them with particles of parasites. They now hope to test the response to antigens embedded in liposomes. Antibodies from rats infected with Schistosoma mansoni kill the parasite in the test tube, but so far there is no evidence that the same thing happens in live animals. However, mice vaccinated with a high dose of irradiated parasites seemed to become more resistant to subsequent infection. Research strongly suggests that humans do develop immunity, but attempts to pin down the type of immune response responsible have been unsuccessful. Any vaccine against schistosomiasis remains a long way away.

Leprosy is the disease for which research on a vaccine has made the most progress. Tests on human volunteers have shown that inoculations of killed Mycobacterium leprae are safe and effective. In Venezuela, authorities have begun testing a vaccine consisting of killed M. leprae and BCG against 60,000 people exposed to leprosy in their homes. One reason for the success is that the whole, killed organism produces an immune reaction. However, the report lists several areas of basic research that needs to be done. One would be to investigate ways to engineer Escherichia coli and other organisms to produce the antigens of M. leprae. Work must also be done on diagnostic kits, and on further understanding of the immune system's reaction. Researchers also need an animal model to enable the study of how the disease damages its victims' nerves.

Filariasis is a group of diseases caused by filarial worms and transmitted by bloodsucking flies. The most notorious is onchocerciasis, or "river blindness", which affects about 40 million people. Despite the gravity of the problem, no safe drugs exist for treating large numbers of people. However, in the past two years, scientists supported by the special programme have screened thousands of compounds in animals. Two of them are almost ready for tests in humans. The most promising is ivermectin, an antibiotic derived from Streptomyces avermitilis. Meanwhile, researchers have detected filarial antigens in the body fluids of patients. This research opens the possibility of developing a technique to diagnose the disease in the serum, before its effects take hold.

African trypanosomiasis is another disease with devastating consequences, but with no adequate drugs for treatment. Research here is focusing on tests to detect infection early. The problem with diagnosis in the field is that, in infections of Trypanosoma brucei gambiense, the number of parasites in the blood varies greatly from day to day. Parasites may be difficult to spot, even in large samples of blood examined under the microscope. Scientists working for the special programme have developed a centrifuging technique that concentrates any parasites in a blood sample. This is still limited, however, by the "on-off" nature of the disease.

Some potentially useful drugs are coming out of research. One compound, an ornithine decarboxylase inhibitor administered in combination with an antibiotic, cured mice of infection by Trypanosoma brucei brucei. Pharmaceutical companies are now carrying out further trials. Meanwhile, two of the 100 compounds screened by the programme have proved active.

Chagas' disease is the result of infection by a South American trypanosome T. cruzi. Most of the research is concentrated on controlling the vector, the triatomine or "kissing bug". Screening tests in the laboratory have identified 21 compounds potentially suitable for ridding transfusion blood of the parasite. In another project, scientists are testing a diagnostic kit based on monoclonal antibodies. (Extracted from New Scientist, 2 January 1986)

Research on animal genes

Leaner livestock

Production of fat-free livestock is now possible, thanks to a novel technique developed by biochemists at Britain's Hannah Research Institute in Scotland. Led by David Flint, the research team has developed a serum containing antibodies which attack and destroy body fat.

The serum contains a mixture of antibodies, each of which is able to bind to specific sites - or antigens - on fat cells. Fat cells, like other cells, have a lipid bilayer membrane. The antibodies attach to antigens that are unique to fat cells. Once bound, the antibodies mark out the fat for destruction. However what happens to the dead fat cells has yet to be fully established, but Flint believes that they are degraded to free fatty acids which circulate in the bloodstream. Flint speculates that free fatty acids may provide energy, or building blocks from which body cells other than fat cells are formed.

In tests carried out on sheep the researchers found that apart from destroying the animals' fat, the antibodies also promoted the synthesis of protein.

So far, work at the institute has focused mainly on sheep. The researchers inject the animals with fat cells taken from rats. The sheep then produce antibodies to the rat cells that can be raised in vitro. Theoretically the technique can be applied to any species - pigs, poultry, sheep, or even humans, Flint explained.

The prospect of slimming down obese humans with a single injection is obviously attractive, but there are a number of complications.

For one, there are difficulties in raising human antibodies, though Flint expects that these will be overcome in the near future.

The other major fear is that fat, once it is destroyed, may get deposited in arteries, leading to high blood pressure and heart disease.

Nevertheless, the animal-based research is progressing well, and Flint expects that commercial trials will begin within about three years, with products reaching the market-place two years later. (Extracted from New Scientist, 5 December 1985)

Fertile mule makes history

A report in the Journal of the Royal Society of Medicine describes the first scientifically attested fertile mule and her foal. The animal gave birth in 1981. Four years later Ruizhang Rong Xiuqin Yang, Huedi Cai and Jun Wei, of the Institute of Genetics in Beijing, confirmed that the mother was indeed a true hybrid mule, and that the sire of her filly was probably a donkey who had been stabled with the mule for a long time.

The mother died in 1983, but analysis of her chromosomes showed that she was without doubt a hybrid. In particular, her two X-chromosomes were clearly one of horse and one of donkey. Her offspring, called Dragon Foal, had 62 chromosomes, the same number as a donkey, and both of her X-chromosomes were donkey. Her sire was assumed to be the donkey familiar with her mother, so she had a complete set of donkey chromosomes, but she also had several paired donkey chromosomes. The conclusion is that she received the paired chromosomes from her mother. The mother also contributed some horse chromosomes to her foal.

Interestingly, Dragon Foal looks more like a chimaera than a hybrid. That is, she shows a patchwork of horse, donkey and mule characteristics, rather than a blend.

Exactly how the dam's mixture of horse and donkey chromosomes segregated to form a fertile egg is not clear. Historically, stories of fertile mules recur and have a common pattern. An idea called affinity could account for this pattern. If the mule's paternal set of donkey chromosomes were to stick together through some kind of affinity they might all be extruded in the egg's polar body after meiosis. The maternal set of horse chromosomes would then be present in the egg, waiting to be fertilised by either a horse spermatozoon, to produce a horse, or by a donkey spermatozoon, to produce another mule. Unfortunately for the affinity theory, Dragon Foal, the first proven offspring of a mule, received horse and donkey chromosomes from her mother.

Dragon Foal is now four years old, and "is strong enough to plough a field by herself". She also shows strong cycles of oestrous behaviour, and may be fertile herself. (Source: New Scientist, 3 October 1985)

Jellyfish protein detects calcium

Genetic Information Experimental Laboratories of Kyushu University Medical School has cloned the gene for aequorin, a jellyfish protein involved in calcium-dependent bioluminescence. In collaboration with Chisso Corp., Tokyo, it is expressing the protein from Aequorin victoria in Escherichia coli as the first step in developing a photometric assay. (Source: McGraw-Hill's Biotechnology Newswatch, 18 November 1985)

Tunichrome characterized

Bright yellow tunichrome pigments selectively concentrate certain metals in the blood cells of tunicate marine organisms, according to researchers at Columbia University, who have now isolated and characterized a tunichrome for the first time. TB-1 is the major component of at least four major and four minor polyphenolic yellow pigments found in the blood of the tunicate Ascidia nigra, which selectively concentrates vanadium from seawater. Other tunicates concentrate other metals such as iron, niobium, tantalum and manganese. TB-1 was isolated under anaerobic conditions using centrifugal countercurrent chromatography. Its structure has been determined using chemical and spectroscopic methods. The research may help clarify the biochemical role of vanadium, which is a required trace element in humans. (Extracted from Chemical and Engineering News, 16 September 1985)

Research on plant genes

Second generation gene transfer in plants

In recent years scientists have focused considerable attention on the development of transformation systems for higher plants. In 1980 M. R. Davey and co-workers at the University of Nottingham showed that dicotyledenous plant protoplasts could be directly transformed by the introduction of Ti plasmid DNA isolated from Agrobacterium. Initially Davey tried poly-L-ornithine - which had been successfully used by Japanese workers to obtain reproducible virus infection of isolated protoplasts - to stimulate the uptake of plasmid DNA. However, the frequency of transformation in 1980 was only about 1 in 100,000. Since then, various additional chemical stimuli (including polyethylene glycol) and delivery systems (such as liposomes) have been tried with little significant increase in transformation frequency.

Recently Ingo Potrykus and colleagues at the Friedrich Miescher Institute (Basel, Switzerland) reported the development of a highly efficient method for the direct transfer of DNA to plant protoplasts. Approximately two per cent of all colonies they recover without selection are transformed. This dramatic improvement is due to a combination of equally important factors, including treatment of the protoplasts with a high voltage electric pulse (electroporation), optimization of the polyethylene glycol concentration, addition of polyethylene glycol after the DNA, and the application of a brief heat shock.

These results could seriously tempt many plant molecular biologists to give up using whole Agrobacteria as the delivery agent for the transformation of plant protoplasts. Such co-cultivation generally gives transformation frequencies on the order of one per cent, and it does not work at all for a number of species. More important than the slight improvement in frequency, electroporation appears to work on both dicotyledons and monocotyledons. Plant scientists should also find it easier to work with isolated chimeric DNAs, which can be produced in quantity, rather than depending on the insertion of desired genes into Ti plasmids.

High frequency gene transfer also provides the opportunity to obtain cells transformed for more than one trait (co-transformation) by incubation of the protoplasts with high concentrations of DNA representing the desired genes. This eliminates the need for elaborate plasmid constructions. (Extracted from Biotechnology, Vol. 3, December 1985)

Cotton grows in Texan test tubes

While growing suspensions of cotton cells in culture, Texas Technical University researchers noticed that the previously undifferentiated calli began to send out filaments. Prof. J. R. Goodin and co-workers at the biology department who made the observations are hoping to isolate the genes responsible for the filament growth, develop a model system for cellulose synthesis and eventually put modified genes back into the plant. (Extracted from McGraw-Hill's Biotechnology Newswatch, 4 November 1985)

United AgriSeeds regenerates soybeans from single somatic cells

United AgriSeeds, Inc., has succeeded in regenerating whole soybean plants from single cells. The technique should cut development time for new varieties by 20 to 40 per cent, says Roderick M. Stacey, the firm's president. The company plans to field test the first crop of regenerated plans during the 1986 growing season, with distribution of improved varieties following as soon as 1989. The AgriSeeds team that removed the regeneration roadblock was headed by Dr. Jerome P. Ranch. Their paper appeared in the November 1985 issue of In Vitro/Cellular & Developmental Biology. (Extracted from McGraw-Hill's Biotechnology Newswatch, 2 December 1985)

Genetic engineering: progress on herbicide-resistant crops

Development of commercial crop plants resistant to particular herbicides is an early goal of scientists involved in plant biotechnology. The latest step in that direction has been taken at Monsanto, which disclosed a genetic engineering technique to make plant cells and whole plants resistant to the herbicide glyphosate. Robert T. Fraley and Dilip Shah of the biological sciences group inserted a modified gene that codes for 5-enol pyruvyl shikimate-3-phosphate synthase (EPSP synthase) into petunia or tobacco plant cells to yield plants resistant to the herbicide glyphosate, the active ingredient in Monsanto's Roundup herbicide.

Developing crop plants resistant to particular herbicides could lead to increased sales of those herbicides. Farmers who plant seeds of such crops would be locked into using the herbicides. But these seeds also would be a boon to farmers, who could sow them and then treat the fields for weeds without affecting the crops. Farmers might be able to rely for total weed control on fewer applications of smaller amounts of fewer herbicides. Such seeds might be on the market by 1990.

Fraley and Shah told the International Congress on Plant Molecular Biology in Savannah, Ga., that they cultured cells of petunia plants in media containing glyphosate. Working with Monsanto colleagues Robert B. Horsch, Harry Klee, and Stephen G. Rogers, they isolated and grew mutant cells that would tolerate the herbicide. The Monsanto team also had inactivated the part of the plasmid gene that produces the plant tumors of crown gall disease. The researchers regenerated whole tobacco plants from disks of leaves they had infected with the bacteria. They showed that the plants were resistant to glyphosate.

In similar research, Calgene scientists Greg Thompson and William Hiatt isolated an aroA gene that codes for glyphosate-resistant EPSP synthase from Salmonella typhimurium after growing the bacteria in glyphosate-containing medium. They announced their results in February to the Weed Science Society in Seattle and to the Recombinant DNA Congress in San Francisco. Calgene scientists have since inserted the gene into tobacco, soybean, tomato, and oilseed rape plant cells.

Calgene scientists have also isolated a gene for resistance to bromoxynil, made by France's Rhône-Poulenc. The mechanism for the herbicidal action of bromoxynil is unclear, but it may involve inhibition of a quinone-binding protein in the electron transport chain of photosynthesis. Currently, in research for Rhône-Poulenc Agrochimie, Calgene is exploring several strategies for inserting the gene into sunflower plant cells. Rhône-Poulenc has signed a contract with SeedTec International, Woodland, Calif., to develop sunflowers with high oil content.

In other research, Calgene has joint plans with Phytogen, an agri-business company in Pasadena, Calif., to develop cotton plants resistant to glyphosate. Calgene also has signed agreements to develop herbicide-resistant soybeans for Nestec, the research arm of Nestle, and herbicide-resistant turnip rape plants for Kemira Oy of Finland.

Elsewhere, workers at Molecular Genetics, Minnetonka, Minn., have cultured corn plant cells in media containing American Cyanamid's imidazolinone herbicides, isolated resistant mutant cells, and grown resistant plants from them. The company resorted to this approach for corn, which is a monocotyledon, because A. tumefaciens infects only dicotyledons. (Extracted from Chemical and Engineering News, 11 November 1985)

Effective micro-injection to plants

Calgene has successfully applied micro-injection technology to plant genetic engineering. Micro-injection has been effective in transferring genes to mammal cells but has not been efficient in transferring DNA into plants. Calgene researchers microinjected foreign genes into tobacco cells and integrated foreign DNA in cell cultures grown from injected cells. Integration of the foreign DNA was achieved in up to 14 per cent of the samples that were microinjected. New microassay techniques were developed to detect DNA and RNA in single plant cells. Previous methods required several thousand cells for nucleic acid detection. Calgene believes micro-injection could be used to genetically modify cereal grains such as wheat, rice and corn. It may also be useful in transferring biochemically uncharacterized multi-genetic traits such as stress tolerance or disease resistance. (Extracted from Chemical Marketing Reporter, 16 September 1985)

Sugar-cane makes its own nitrogen fertiliser

Brazilian scientists have shown for the first time that a variety of sugar-cane fixes nitrogen directly from the air. Dr. Johanna Döbereiner is the leading light in the nitrogen fixation research programme conducted under the federal agricultural research organisation (EM-BRAPA). Two years ago, at a research station outside Rio de Janeiro, her team planted four different cultivars of sugar-cane in 50-litre pots. After a year it became clear that one of them, CB 47-89, was taking in more nitrogen than the other three. The most recent tests show that CB 47-89 contains the equivalent of 30 per cent of the soil nitrogen - an astonishingly high uptake for any plant - when the soil has lost only 15 per cent of its original nitrogen composition.

Conclusive proof came from an experiment with the heavy isotope of nitrogen, N-15. Fertiliser labelled with N-15 was added to the soil of both the

test crop and to a control plant which was known not to fix nitrogen. The isotope concentration in the test crop proved significantly lower than in the control, indicating that the test crop was getting nitrogen from some other source than the soil. Dr. DÖbereiner's team is unclear about how such non-nodule forming plants as sugar-cane fix nitrogen. It has found plant-bacteria associations in the root systems - mostly in wheat, sorghum and maize. Four new Azospirillum and one new Bacillus species have been discovered.

The Azospirillum bacteria infect the roots and inoculated strains have been established under field conditions on the root surfaces. Yet the scientists have been unable to prove that these bacterial associations are responsible for most of the plant's uptake of nitrogen from the air.

Among the hundreds of commercially available cultivars CB 47-89 is not very popular; it gives a good first yield but then tails off badly. It is possible that older cultivars might prove to be good fixers. If sugar-cane can be bred to yield fully without nitrogen, the savings would prove huge. (Extracted from The Economist, 2 November 1985)

Plant genetic research model

A weed in the mustard family may provide a valuable model for plant genetic research, according to research carried out at the California Institute of Technology. Most plant genomes have large amounts of repetitive DNA of unknown function scattered in thousands of copies throughout the chromosomes. Many plants have entire copies of their entire set of chromosomes. Arabidopsis thaliana, however, contains only 1 per cent as much DNA as wheat, and 0.5 per cent as much of the repetitive DNA sequences. The plant has a life cycle of 5 weeks, is only five inches tall and produces thousands of seeds per plant, making it very suitable for research. Individual genes are similar to those in other flowering plants, and genes of interest can be easily located in the small genome. Proteins are controlled by fewer genes than normal in Arabidopsis. For example, chlorophyll's light-harvesting protein is produced by three genes, compared to the 16 or more genes used in petunias. (Extracted from Science News, 21 September 1985)

Chemical to regulate plant genes

A new chemical that regulates plant genes to increase photosynthetic efficiency is being developed by USDA's ARS. DCTPA is a mixture of 2-diethylaminoethylchloride and 3,4-dichlorophenol, and apparently acts to increase carbon storage in plants. This carbon acts as a raw material for synthesis of proteins, fats, etc. The compound could allow increased food production worldwide. The compound's operative mechanism has not yet been determined. Soybean yields rose 35 per cent after treatment with the chemical, including a 68 per cent increase in protein content and a 20 per cent increase in fat content. Cotton increased boll set 80 per cent. Natural rubber content of guayule rose 100 per cent after treatment with DCPTA. (Extracted from Chemical Marketing Reporter, 18 November 1985)

Research on yeast and fungus genes

Fungal inoculant increases seedling growth

At the conference on Global Impacts of Applied Microbiology held in Helsinki in autumn 1985 it was reported that D. Kandasamy and his colleagues from the Centre of Advanced Studies in Agricultural Microbiology at Tamil Nadu Agricultural University (Coimbatore, India) have studied the response of chili plants (Capsicum annum) to inoculation with vesicular-arbuscular (VA) mycorrhizal fungi and/or "phospho-bacteria". They inoculated either in the nursery alone or first in the nursery and again after the plants had been transplanted to the field. Using Glomus fasciculatum and G. mosseae as the fungal mixture - with or without Bacillus species as the bacterial partners - they found in all cases that inoculation resulted in significantly enhanced seedling height, root length, leaf production, and dry weight. But with an average yield of 9866 kg/ha of green chilies (compared with 6750 kg/ha for controls lacking inoculant), they concluded that VA mycorrhizae added in the nursery alone was as effective as introducing the fungi in the field as well. Direct measurements of phosphorus and nitrogen showed that the uptake of these elements was heightened, too.

Parallel experiments indicated that VA mycorrhizae and Bacillus species also have a beneficial effect on shoot length and dry weight of okra (Abelmoschus esculentus). Although these tests were carried out in pots, the researchers expect to achieve similar results in forthcoming field trials. (Extracted from Bio/Technology, Vol. 3, October 1985)

Deep-sea enzyme

Explorers in the US have discovered a novel enzyme which could prove invaluable to genetic engineers. Isolated from bacteria found in the frozen wastes of the Antarctic, the enzyme is purported to be 50 times more potent than those currently used by genetic engineers.

The enzyme is an alkaline phosphatase and can be used to carve up and rearrange DNA, RNA and other biological macromolecules. It was found by explorers from the University of Southern California's marine biology department who are studying marine life in the Antarctic in a project funded by the US National Science Foundation. The enzyme was isolated from the first of 200 bacterial species.

An APase from Escherichia coli is traditionally used to remove phosphate groups, though its use has drawbacks. Not only is it slow, it also persists - unwanted - in the reaction mixture after performing its intended role. In contrast, the deep-sea enzyme is 50 times quicker, and can be destroyed in just one minute by heating the mixture to 40° C. (Extracted from New Scientist, 10 October 1985)

Advantages of fungi in experiments

Several companies have begun to put foreign genes into moulds. Possibly the most advanced is Allelix, a biotechnology firm based in Mississauga, Ontario, Canada.

Genetic engineering of yeast is well known. But yeast, though a fungus, lives like a bacterium in discrete cells rather than in continuous filaments. Yeast appealed to the pioneers of genetic engineering because it was familiar with laboratories: it has long been used for genetic experiments. Genetic engineers are now moving on to species that look more useful for industry. Drug makers have turned towards animal cells; industrialists towards fungi.

Some of the filamentous fungi are already important workhorses of biotechnology, notably the mould Aspergillus which is used to make antibiotics, industrial enzymes and food additives. So the fact

that they can be given new genes may herald a revival of optimism in industrial, as opposed to pharmaceutical, biotechnology.

Allelix has inserted the genes for interferon, just for the experiment. It has also inserted the genes for cellulase enzymes, which might one day find a market in destroying waste and surplus cereals. In such experiments it has proved not only that the genes get into the mould, but that they are expressed as well and can be switched on and off by certain chemicals.

The main advantage of such fungi over bacteria is that they secrete the products of their genes to the outside of the cell more readily. This greatly simplifies the business of purifying the product and so helps keep costs down. Yeast and E. coli might soon be redundant. (Extracted from The Economist, 4 January 1986)

Research on bacterial genes

Delivery system for B. thuringiensis

Mycogen has developed a non-living delivery system for a potent bacterial toxin (Bacillus thuringiensis) pesticide, anticipating U.S. Environmental Protection Agency's reluctance to approve field tests of live organisms. The toxin is used to fight most moth species and beetles. B. thuringiensis is ultra-violet sensitive and therefore has a short life-span outdoors. When the genes for B. thuringiensis are inserted into the DNA of pseudomas, a leaf colonizing bacteria, the transformed bacteria are fermented until they produce a lot of toxin, then the organisms are killed. Their cell walls are fixed to make them very rigid, microencapsulating the toxin before crop application. The package is well adapted for field use since it protects the toxin from ultra-violet light and other environmental assaults. The natural pesticide is 5-10 times more persistent than commercial B. thuringiensis and the toxin is slowly released after the pest eats it, creating a natural controlled release system. (Extracted from Industrial Chemical News, November 1985)

Meat-spoiling bacteria identified

Two scientists at the Swedish Meat Research Institute in Kävlinge claim to have identified the bacteria that cause meat to spoil. If their discovery is substantiated, it could lead to improved methods for the handling and processing of foodstuffs and to longer shelf life for packaged meat.

Over the last five years, Drs. Nolin and Ternström studied and described 250 strains of the bacterial family Psychrotrophic pseudomonae. They used 174 biochemical and physiological tests and found a cluster which they say could represent a new species of bacteria. They have named the species Pseudomonae lundensis, after the nearby university of Lund.

The newly described bacteria are, in fact, two strains, although the name of the second, Pseudomonas fragi, has been used for a long time without scientific justification. Both strains of bacteria thrive on meat and other organic substances, which they break down into carbon dioxide and other products. The bacteria apparently find the energy they require for this process in lactic acid, glucose, and amino acids in meat. They become active at 12° C, a temperature commonly found in household refrigerators.

Nolin and Ternström have published their findings in the Journal of General Microbiology (Vol. 129 [1983], 285-291). They acknowledge that other scientists abroad have carried out similar research, but the Swedes maintain that they have actually succeeded in identifying for the first time the bacteria responsible for the decay of meat. (Source: European Science News, 39-10 (1985))

Finland engineers B. subtilis that makes Alpha-amylase

Researchers at Alko, the Finnish State alcohol monopoly, are improving their industrial-scale production of alpha-amylase by using pKTH10, a recombinant plasmid carrying the gene from Bacillus amyloliquefaciens that codes for the enzyme. The recombinant host B. subtilis harbouring the plasmid (first described in Cell 19:81, 1982) generated up to five times as much alpha-amylase when grown on a laboratory scale in rich media than did the strain formerly used to produce the enzyme. The plasmid proved to be highly stable in a wild type host, but showed unacceptably poor stability in a strain possessing the papN9 mutation which increases the basal level of secretion. When the Alko team scaled up its cultivation of the wild type organism - using an industrially feasible medium containing low levels of free amino acids - synthesis of alpha-amylase was still about twice as high as that achieved by the traditional strain in the industrial-scale system.

B. amyloliquefaciens is known to be a better producer of extracellular enzymes than B. subtilis, but scientists have conducted very little research on its genetics. (Extracted from Bio/Technology, Vol. 3, October 1985)

Micro-organism involvement in corrosion of metals in the marine environment - some UK research

Reports given at a recent international conference on biological-induced corrosion at Gaithersburg, Maryland, USA seem to indicate that the mainline corrosion community is just coming to realise that biology could significantly influence the chemistry of corrosion. Research has now confirmed that sulfate-reducing bacteria and possibly other micro-organisms are involved in corrosion. A real key to managing the problem of bio-corrosion is first to recognize that bio-corrosion can be a threat, and then to design systems and carry out testing and maintenance.

Considerable research is now being conducted in fundamental aspects of microbiology that relate to metal corrosion.

The extent of microbiological problems in marine environments was amply illustrated by Mr. E. C. Hill of E. C. Hill & Associates, whose research facility in Cardiff is primarily concerned with microbiological testing and advisory services to ship, oil and chemical, aviation, and metalworking companies worldwide. Most work is concerned with microbial contamination, spoilage, and/or corrosion, and often involves petroleum products and process water.

Many problems are encountered with lubricating oils on ships, most caused by bacterial contamination of aerobic Pseudomonas-like organisms. Results of such oil infection include degradation of additives, increased acidity of the oil, plugging of filters, and eventual pitting corrosion. Occasionally, sulfate-reducing bacteria

become established if conditions become anaerobic, especially in ships that are out of operation for extended periods, leading to corrosion. Microbial contamination of engine oils in some cases has been severe enough to cause mechanical failure of engines. Most problems are found with low- and medium-speed diesel engines, which do not attain oil temperatures high enough to kill contaminating microbes. There appear to be fewer problems with steam turbine engines. Although Cladiosporium used to be a primary contaminant of fuels, most contamination is now bacteria and yeasts. This has proven to be an acute problem for diesel ships operating in the North Sea. Microbial contamination in fuels usually results in filtration problems, injector failure, and failure of coalescers. Attempts are being made to develop biocides that can sterilize the fuel system on a one-application basis on the short term (6 to 24 hours).

Hull corrosion of ships is occasionally a problem when cargos contain sulfur, e.g., sulfur-containing coal, where certain aerobic bacteria produce sulfuric acid leading to corrosion. An awareness is developing of the problem of sulfate-reducing bacteria in ships' bilges, where anaerobic conditions can develop. This condition can lead not only to corrosion but to dangerous levels of H_2S to personnel. A new biocide is currently being tested that appears effective against sulfate-reducing bacteria.

Hill's group has been very effective over the years in developing rapid detection techniques for microbial contamination in shipboard systems that can be used by personnel with little microbiological training.

The research by Dr. Robert Edyvean's group in the Department of Metallurgy at Sheffield University emphasizes the processes that are caused by microbial corrosion and that lead to failure of metal components in marine environments. His group is actively involved in research on the effects of marine fouling on the corrosion of offshore structures. Although Edyvean has published considerable work on corrosion as affected by marine microalgae, his current research emphasizes the effects of biologically active environments on the susceptibility of metals to corrosion fatigue, fatigue that results from the combination of a corrosive environment and applied cyclic stress to produce failure of a metal by the development and growth of cracks. Although seawater is a corrosive medium and a major source of fatigue loading on steel structures, marine fouling can also influence corrosion of metals in several ways: (1) by creating differential aeration cells at the surface; (2) by producing corrosion-promoting metabolites, especially acids and H_2S; and (3) by stimulating anodic reactions.

Since corrosion fatigue appears to be considerably enhanced by microbially produced H_2S, studies are being conducted to determine the effects of H_2S on the enhancement of fatigue crack growth rates in the laboratory, but under conditions that attempt to simulate the marine environment, under both static and cyclic load conditions.

Edyvean indicates that more information is certainly needed on the relationship between the corrosion caused by marine fouling and the formation and growth of fractures. In his estimation, intensive research is required in order to determine quantitatively the levels of H_2S, O_2, pH, and other microbial metabolites at the interface between the metal and biofilm.

Dr. E. Bellinger and his group at the Pollution Research Unit at the University of Manchester are addressing Edyvean's requirements by examining the micro-environment of metal surfaces when organisms are present. Specifically, they have developed micro-electrodes for measuring pH and O_2 in biofilms on metal surfaces.

In his estimation, information on pH and O_2 is critical in determining the effects of organisms on corrosion at a microscale level.

Dr. Mark White in the same unit has been studying microbial colonization and corrosion of metal surfaces under cathodic and noncathodic protection. Investigations using both scanning and transmission electron microscopy indicate that, when using visual characteristics, it is very difficult to distinguish between inorganic corrosion products and bacteria, especially on non-protected surfaces. The combination of vital staining (acridine orange) and electron microscopy is being used to distinguish the two. Microscopy work also indicates that organic matter appears to be the first layer of material deposited on metal surfaces, which is then followed by micro-organism colonization. Examination of initial colonization over the first few days shows that the organisms colonizing free-corroding (not cathodically protected) surfaces are different from those that are protected cathodically, with the latter surfaces supporting a more diverse microflora and microfauna.

The interest in initial colonization by micro-organisms on metal surfaces is shared by a number of research laboratories, with considerable emphasis on mechanisms of bacteria attachment. Dr. Madilyn Fletcher's research group in the Department of Environmental Sciences, University of Warwick, is primarily concerned with fundamental research in two areas of bacterial interaction with surfaces: (1) the mechanism of adhesion, and (2) the ways in which adhesion to surfaces alters the physiology of the organism. Although previous research has dealt with marine aerobic bacteria, current work involves aerobic bacteria in situ (freshwater) and laboratory work in defined media. Various environmental factors have been examined relative to the adhesion of bacteria in both single and mixed cultures. Effects of carbon source and nitrogen/carbon ratios as well as temperature and pH have been addressed.

Of particular interest is recent work with mutants of Pseudomonas fluorescens that have both better and poorer adhesion properties than the wild type. A "mucoid" mutant, with lesser attachment, produced an extracellular alginate lacking in the wild type. The mutant that demonstrated a greater ability to attach to surfaces lacked the alginate but had 40 to 55 per cent less polysaccharide in the outer membrane lipopolysaccharide fraction. Further work will examine the surface characteristics of similar mutants and phenotypes of specific bacteria.

Although Dr. Christine Gaylarde in the Department of Biological Sciences, City of London Polytechnic, is also concerned with attachment by bacteria, her group is primarily working with the anaerobic bacteria and their relationship to metal corrosion. Although her research includes some applied aspects, fundamental research is examining the structure of the outer membrane of Desulfovibrio bacteria to determine its importance in the adhesion mechanism of this group of organisms. Consideration is being given to the uptake of ferrous iron and its relationship to binding of the organism to surfaces. Desulfovibrio is an anaerobic,

dissimilatory sulfate-reducing bacterium which is able to induce the corrosion of ferrous metals in anoxic environments. Such characteristics have made this micro-organism prominent in such problems as anaerobic metal corrosion and souring of oil deposits by biogenic hydrogen sulfide. The prevention of such problems often requires treatment with biocides.

In other, more applied studies, Gaylarde and her research group are examining the effect of mixed cultures of sulfate-reducing bacteria and non-sulfate-reducing bacteria on corrosion of mild steel. Although the exact reasons are unclear, the rate corrosion by Desulfovibrio is often enhanced by the presence of a non-sulfate-reducing bacteria such as Vibrio. The most probable explanation that has been put forth for the increased corrosion is an increase in the adsorption of Desulfovibrio in the presence of Vibrio. Additionally, the application of biocides is often less effective in inhibiting sulfate-reducing bacteria when other bacteria are present. Perhaps the most important avenue of research to pursue is an understanding of initial adhesion of bacteria and the mechanisms involved in the buildup of biofilms on metal surfaces. This information is vital as a basis for an intelligent approach to devising preventive measures against microbial corrosion.

Several research groups at British Petroleum's (BP's) Research Centre at Sunbury-on-Thames are involved both with problems of corrosion arising from sulfate-reducing bacteria and with adhesion mechanisms. Dr. Paul Rutter's group is conducting research on the adhesion of microbes on surfaces, with a primary emphasis on the quantitative description of short-range forces influencing adhesion. Special emphasis is being given to specific binding molecules and extracellular polymers. Such research is important to understanding early stages in microfouling of surfaces in marine environments and the microfouling of surfaces involved in distribution systems such as pipelines.

Dr. Barbara Crouch is conducting research related to the formation of microbially produced biofilms or metal surfaces and their subsequent effects on corrosion. Particular attention is being given to biogenic sulfide films formed on steel surfaces by an interaction with marine sulfate-reducing bacteria (such as the species Desulfovibrio) under anaerobic conditions. Although the presence of sulfate-reducing bacteria on steel surfaces in anaerobic conditions results in only relatively low rates of corrosion, subsequent exposure of the surfaces to aeration results in very high rates of corrosion, with pitting a common characteristic. The formation of a biogenic sulfide film on the steel surface influenced by the sulfate-reducing bacteria appears to be a crucial component of the corrosion process under aerated conditions. The production of sulfide by sulfate-reducing bacteria often occurs whenever wet oil or an oil product is stored and transported. It is further suggested that these organisms may be involved in corrosion of storage vessels. The bacteria present in the water phase may originate from ballast water or seepage, and their activity is stimulated by the presence of crude oil.

Corrosion scientists at BP are also using the AC impedance technique to evaluate the effects of microbial growth on the corrosion of steel surfaces.

Techniques that seek to inhibit corrosion related to microbial colonisation obviously have effects on macrofouling processes as well. Dr. E. E. Williams' research group in the Department of Zoology at Sheffield University has been conducting research concerned with the effects of heavy metal pollution on the behavior and attachment of the common mussel, Mytilus edulis. Although much of their work is concerned with labile levels of metal ions that affect marine organism behavior and are biologically toxic, it does provide information valuable to understanding macrofouling of metal surfaces. Their development of a bioassay for copper-impaired seawater using the planktigrades of Mytilus edulis could be useful for assaying other protection mechanisms for preventing macrofouling. (Extracted from European Science News, 39-11 (1985))

Research on viral genes

Cold-fighting cells

The immune system has two ways of dealing with foreign invaders - with a generalized response, called cellular immunity, and a more specific response that involves antibodies. Researchers at the Food and Drug Administration in Bethesda, Md., and George Washington University in Washington, D.C., are studying the action of cytotoxic T-lymphocytes and have found a genetic factor in the ability of the cellular immune system to fight influenza viruses.

T-lymphocytes from 51 people were added to influenza-A infected cells. Cell types were defined by their HLA genes, a set of genes coding for proteins involved in cell recognition. There was a correlation between genetic subtype and disease-fighting ability - cells bearing HLA-DR4 genes were better able to kill infected cells, and HLA-DR7 cells were less able, than the rest of the subtypes tested. (Extracted from Science News, Vol. 128, 12 October 1985)

Research instrumentation

Team will market new DNA chemistry

An agreement has been reached for the worldwide marketing of cyanoethyl amidites - said to be the latest advance in DNA chemistry - by Biosearch (San Rafael, Calif.) and Biosyntech Biochemische Synthesetechnik (Hamburg, West Germany). Cyanoethyl amidites are used in DNA synthesizers, known as gene machines, to make synthetic DNA fragments. The gene fragments are used in genetic engineering research. Biosearch and Biosyntech will also co-operate in product development and other areas. (Source: Chemical Week, 25 September 1985)

Prenatal disorder diagnosis facilitated by extracellular matrix

Extracellular matrix (ECM)-coated tissue culture dishes play an important role in expediting the diagnosis of prenatal disorders. Produced by International BioTechnologies Ltd., the naturally produced ECM closely resembles the basal lamina of the body, allowing cells to grow under conditions similar to those existing in vivo. Cells plated on ECM maintain their differentiated properties; show attachment, flattening and rapid migration; proliferate faster and exhibit a longer life span. These properties of ECM yield the following advantages in the prenatal diagnosis of genetic disorders:

1. Reduced time interval between amniocentesis and diagnosis. Due to the limited time interval during which amniocentesis can be conducted, it is vital that the culture be successful. Because of its special properties, ECM provides the optimal substrate for the culture of human amniotic cells which are available only at

clonal densities. The resulting increased plating efficiency and proliferation rate serve to reduce by approximately half the time interval between amniocentesis and the first harvest of cells available for chromosomal analysis.

2. Increased success rate of cell growth. A major limitation of conventional plastic tissue culture dishes is that cells often fail to attach and remain floating in the medium. Because it so closely resembles the basement membrane-like matrix on which cells grow in vivo, ECM induces adherence and subsequent proliferation of cells, thus obviating the need for a repeat tap for amniotic cells. Furthermore, amniotic cells plated on ECM show reduced serum requirement while retaining a high growth rate. This serves to reduce the cost of prenatal diagnosis and minimizes the variability in cell growth and the chance of serum-induced toxicity. For further information, please contact Rosanna Milstein, Director of Marketing, IBT, Kiryat Hadassah, P.O. Box 12000, Jerusalem 91120, Israel. (Source: Company News Release, January 1986)

Machine to speed up genetic studies

A machine that can automatically separate chromosomes from human cell cultures in the laboratory, at a rate of one thousand a second, has been invented by one of the Medical Research Council's team of scientists.

The apparatus can identify and select any one of the 23 pairs of chromosomes, which are in the nucleus of all normal cells and contain the thousands of genes that form the blueprint of each individual.

The invention, by Dr. Daryll Green and Mrs. Judith Fantes, of the Clinical and Population Cytogenetics Unit at Edinburgh, uses a laser and computer analyser to identify the chromosomes. They are then extracted electrostatically to separate them from the other tissue. The two scientists developed the machine for work on the sex-linked X-chromosome and that early work led, indirectly, to advances in the understanding of a genetic disease: the identification of genes on chromosome number seven implicated in cystic fibrosis.

At the beginning the X-chromosome samples were contaminated with chromosome number seven, which then gave an almost indistinguishable signal to their mechanical sorter. Further purification of the Xs also provided number sevens deliberately, which were the basis of clone banks for the cystic fibrosis work at St. Mary's Medical School in London.

The developing science of flow cytometry also promises a rapid system for detecting damage from radiation exposure. Dr. Green and Mrs. Fantes have shown already that it is possible to pick out chromosome fragments, "background rubbish", resulting from radiation doses of 100 rads, more than a thousand times as fast as can be done by ordinary inspection and without the fatigue suffered by human workers. To extend the machine's sensitivity to see lower levels of radiation damage, they are seeking a way of staining the central parts of chromosomes, the centromeres, so the machine can count chromosome fragments resulting from radiation and measure the amount of exposure. (Extracted from The Times, 20 January 1986 p. 14)

Electronic system for automating gene transfer

BAEKON2000, an Advanced-Gene-Transfer-System, from BAEKON is a highly integrated complete electronic system for automating gene transfer into prokaryotic and eukaryotic systems. The System may also be used to induce cell fusion. It comprises a controller and a reactor. The controller is an electronic device that generates and precisely regulates the continuous output of electric field and energy to the gene-cell or cell-cell system through four precisely adjustable electronic parameters which are amplitude, number of pulse, burst time, and number of cycle. The actual gene transfer or cell fusion takes place in the reactor which houses the positive discharging electrode and the receptacle which is the holder for the gene-cell or cell-cell mixture. The distance between the discharging electrode and the gene-cell or cell-cell mixture can be adjusted by dialing the meter built in the reactor. By varying the distance (the 5th adjustable parameter), one can choose either the "non-contact" or the "contact" mode of delivering the electric field and energy to effect gene transfer or to induce cell fusion.

To ensure absolute sterility and to avoid cross contamination, the receptacle is individually packaged, sterilized by gamma-irradiation and is disposable. Each receptacle holds up to one ml of a gene-cell or cell-cell mixture. There is virtually no limit in the number of cells and the species and quantity of DNA that can be loaded into the receptacle for treatment. Additionally, the whole reactor can easily be placed in a tissue culture hood for operation.

By manipulating these five parameters, one controls the transmission of electric impulses from the controller through the reactor via an electrode to the gene-cell or cell-cell mixture so as to optimize, to the highest possible efficiency, electro gene transfer into bacterial, plant, and animal cells.

The operation of BAEKON2000 is simple and easy, it involves pipetting the gene-cell or cell-cell mixture into the receptable, setting the parameters, and triggering. It takes less than three minutes to complete a gene transfer or cell fusion experiment. The system is compact, weighs only 8 kgs and requires minimal space.

Further information may be obtained from Baekon Inc., 20333 Merida Drive, Saratoga, CA 95070, USA (Source: Company news release)

General

Genetic code

The link between genes and proteins is enshrined in the genetic code, which allows sets of three nucleotides (known as "codons") in our genes to incorporate specific amino acids into proteins. Many scientists regard the structure of the genetic code (that is, the rules governing which codons encode which amino acids) as a "frozen accident" - chanced upon in the early days of evolution and then virtually stuck for evermore. Challenging this view, two Soviet scientists have now suggested some good chemical reasons why each codon encodes the amino acid that it does. Jaanus Remme and Richard Villems of the Institute of Chemical Physics and Biophysics in Tartu, Estonia, have found an intriguing link between the stability of various codon-anticodon pairs (which should indicate how long, on average, they will hold their tRNAs on the ribosome), and the reactivity of their corresponding amino acids (which should indicate how quickly the amino acids will become linked up into a protein).

The 20 amino acids used to make proteins are encoded by 61 distinct codons. Thus the base sequences UUU and UUC both code for the amino acid phenylalanine; UGG codes for tryptophan and so on.

The most stable codon-anticodon pairs seem to hold the tRNAs that carry the least reactive amino

acids: and the least stable codon-anticodon pairs hold the tRNAs carrying the most reactive amino acids. (Extracted from New Scientist, 19/26 December 1985)

Amino acids from outer space

A meteorite found in Antarctica contains an unexpectedly large amount of amino acids. Deeper analysis has proved that these are not of terrestrial origin but came with the meteorite from space. However, the Japanese chemists who carried out the investigation proved that the amino acids were not produced from living things at all.

A few grams of this meteorite have now been subjected to close analysis by Akiro Shimoyama and Kaoru Harada, of the University of Tsukuba, and Keizo Yanai, of the National Institute of Polar Research in Japan.

Although organic substances, including amino acids, have been discovered in meteorites before, this is the first time they have turned up in such abundance. Twenty kinds of amino acids have been detected in Yamato 791198 and their amounts have been measured using an amino acid analyser with fluorescent and ninhydrin detection. To ensure that the chondrite was not affected by organic material of Earthy origin, the researchers took elaborate precautions to keep it uncontaminated while it was ground to a powder, and boiled with water and acid to extract the amino acids from it.

The amino acid in highest concentration was amino-isobutyric acid followed by the more familiar glycine and alanine. Some of the essential amino acids, such as threonine and leucine, were present in only tiny quantities. However it was the presence of all five butyric amino acids which showed that whatever the source of these extraterrestrial ones it was unlikely to be living matter.

The Yamato 791198 meteorite discovered by the Japanese Antarctic Research Expedition in 1979 is richer in amino acids than any discovered so far. Even so the amounts seem very small: 670 x 10^{-9} moles of amino acid per gram of meteorite. (Extracted from New Scientist, 19/26 December 1985)

D. APPLICATIONS

Pharmaceutical and medical applications

Human growth hormone sales approval

Genentech, Inc., has become the first biotechnology company to market its own recombinant DNA product, after the US Food and Drug Administration (FDA) approved the firm's human growth hormone (HGH), trade-marked Protropin last October, and just recently the company has been awarded a virtual US monopoly on sales of gene-spliced growth hormone by the federal government. The US Food and Drug Administration has granted the biotech company's Protropin human growth hormone orphan drug status for the treatment of both growth hormone deficiency and Turner's Syndrome.

Orphan drug status, under the federal food, drug and cosmetic act (1983), provides incentives for firms to develop drugs for exceptionally rare diseases or disorders for which the potential patient population is under 200,000. Under the act, Genentech has seven years' marketing exclusivity for Protropin for its approved indication.

The status now means that Genentech's Protropin is protected from competing substances even if it fails to win a US patent, for the next seven years. The FDA cannot consider requests from other companies who want approval to market other gene-spliced growth hormones for the treatment of dwarfism. Nevertheless, approvals can be sought for other indications. Companies can apply for investigational new drug (IND) applications with the FDA.

However, the second, third and fourth biotechnology companies with recombinant HGH products in the works are close behind, claiming a superior, non-methionated product. California Biotechnology, Inc. (CBI), Mountain View, Calif., Bio-Technology General (BTG), New York City, Elf Aquitaine, Paris and Eli Lilly & Co., Indianapolis, Ind. are some of the other companies involved in manufacturing HGG.

The chief investigator for Genentech's clinical trials, Dr. Selma Kaplan, is confident that the firm's HGH, which carries an extra moiety of methionine, is "physiologically equivalent" to the natural hormone, but she concedes that its persistent antigenicity is puzzling, though tolerable. At a West Berlin meeting last spring, scientists suggested that the immunogenicity might be caused by the extra methionine or improper folding when the hormone is produced in Escherichia coli host organisms. Celltech, the top UK biotechnology concern, has announced the completion of the development of its production process for recombinant human growth hormone (hGH). Serono Laboratories of the US, the sponsors of the programme, is now carrying out phase one clinical testing.

The company expects Serono will get the regulatory green light from the US authorities by the end of next year and hopes to launch the product itself in the UK within 18 months.

The key to Celltech's hGH success will be the fact that it is produced by mammalian cells in culture and consequently, is identical to natural growth hormone and requires no further modification. Other products that have recently been granted approval in the US and the UK are produced in bacterial cells and require extensive refolding. Gene-spliced human growth hormone (hGH) has finally been granted its first regulatory approvals. Genentech has got a green light from the US Food & Drug Administration while KabiVitrum of Sweden has received approval. KabiVitrum has won approval for sales of the drug in the UK and Belgium. The product, Somatonorm, is produced at the Swedish company's fermetation facility at Strängnäs and formulated in Stockholm. Kabi has applied for regulatory approval in all Western European countries.

Developed by Kabi after initial cloning work carried out under contract by Genentech, the compound is produced as a methionyl derivative by genetically manipulated E. coli bacteria. The company has plans to follow up with a second generation, "authentic" growth hormone product also produced in the bacteria, and is working on a number of other gene-spliced growth hormones.

Although Kabi says it will price the recombinant product around the same level as the natural hormone, sources in the UK have warned it may prove to be three times as expensive as the previous domestic product.

Now that growth hormone will be available more readily, some sports medicine specialists are concerned that the drug will be abused by athletes and others hoping to increase their height and strength. Genentech responds that the company will focus its marketing efforts on pediatric endocrinologists, the physicians who treat most

cases of growth hormone deficiency, and that the drug will be distributed only through hospital pharmacies. However, any physician has the authority to prescribe Protropin for any use. (Extracted from Chemical and Engineering News, 28 October 1985; European Chemical News, October 1985 and 6-13 January 1986; McGraw Hill's Biotechnology Newswatch, 4 November 1985)

Labelled MA's in cancer detection

Indium-111 labelled monoclonal antibodies can be used to detect some kinds of cancer in imaging applications, according to research carried out by the Royal Postgraduate Medical School, UK, and reported in The Lancet. Using a labelled antibody against placental alkaline phosphatase, researchers were able to locate testicular, ovarian and cervical cancer by means of radio-immunoscintigraphy. This method provided information unobtainable by other means including ultrasonography and computerised tomography. Repeated injections of the mouse monoclonal antibody could lead to an immune response from the patient. (Extracted from Clinica, 6 September 1985)

Targetted radiotherapy success in liver cancer

Doctors at Johns Hopkins University in Baltimore, US have developed a new treatment for advanced liver cancer which is giving better results than any conventional therapy. In the new treatment, the radioisotope iodine-131 is conjugated to a monoclonal antibody against ferritin, a protein secreted in high concentrations by hepatoma cells, and injected into the vessel serving the liver. Because the tumour is richly supplied with blood vessels and blood flow through it is slow, the antiferritin concentrates in the tumour.

Of 66 people with advanced liver cancer 41 per cent showed partial remission and 7 per cent complete remission. Partial remissions occurred in patients with tumours so large that no benefit had been expected. The longest duration of partial remission to date is five years and eight months and of complete remission three years and six months. Of the patients with remissions, 15 per cent survived more than two years. These results are undoubtedly better than any achieved with other forms of treatment. One patient has now survived six years with a condition for which previously the five-year survival rate was nil. It is the first effective treatment for liver cancer, but there is scope for improving it considerably. (Extracted from New Scientist, 21 November 1985)

Gamma interferon in Phase III clinical trials

Biogen believes that it is the first company in the world to have begun large-scale Phase III testing of gamma interferon, in this case its product Immuneron, in US and European cancer cetres. Dr. Seth Rudnick, the company's senior vice-president for pharmaceutical development, says that the product showed positive initial results against rheumatoid arthritis. The trials, which represent a major step towards regulatory approval and marketing, are in patients suffering from renal cell carcinoma, for which there is currently no effective therapy. Biogen's partner in developing Immuneron is Shionogi of Japan. (Source: Biotechnology Bulletin, Vol. 4, No. 9, October 1985)

Gamma interferon licensed

Ciba-Geigy licensed human gamma interferon - currently in clinical trials in Japan for treatment of solid tumors - from Kyowa Hakko Kogyo (Tokyo). Ciba-Geigy will have the right to sublicense the product in Europe and the US, and is planning clinical trials in both places. The interferon is said to differ in some amino acids from the recombinant gamma interferon of Genentech (South San Francisco) and Biogen (Geneva), so Ciba-Geigy says it does not expect patent challenges. (Source: Chemical Week, 18 December 1985)

Genentech begins human clinical trials with TNF

Discovered by Dr. Lloyd Old and colleagues at the Memorial Sloan Kettering Cancer Center, tumour necrosis factor (TNF) has since become a target for several companies - including Asahi, Biogen, Celltech, Cetus, Fujisawa and Sankyo. Now Genentech, whose scientists were the first to publish the structure and rDNA expression of TNFs in Nature in December 1984, has begun Phase I clinical trials with recombinant TNF in advanced cancer patients. Possible side-effects include bone marrow failure, nerve damage, and liver or kidney failure. Other possibilities are toxic shock and cachexia, in which the patient becomes emaciated. (Source: Biotechnology Bulletin, Vol. 4, No. 9, October 1985)

Interleukin-2 success

Scientists at the US National Cancer Institute have used interleukin-2 (IL-2) produced by Cetus to treat otherwise untreatable cancer patients. In a two-step approach, they first extract the patients' own white blood cells and then treat them with IL-2. This process transforms them into 'lymphokine-activated killer' cells - or LAK cells. These can destroy tumour cells, while leaving normal tissue unaffected. The LAK cells are then injected back into the patient to fight the cancer, with a further injection of IL-2 to help them multiply inside the body.

The initial results have been hopeful. In 11 of 25 cases treated with the new approach, known as 'adoptive immunotherapy', tumours shrank by more than half in patients suffering from melanoma (skin cancer), colon, kidney or lung cancers that had spread so far they were no longer amenable to chemotherapy or radiation techniques. Although 14 patients - particularly those with sarcoma (cancer of connective tissues) or cancer of the oesophagus - showed no improvement, these results are seen as tremendously heartening. Indeed, one patient's tumour regressed completely, although another patient is thought to have died from a combination of IL-2 side-effects and his advanced cancer.

Dr. Steven Rosenberg, chief of the National Cancer Institute's surgery branch, leads the research team which developed the new approach. The use of IL-2 however caused a number of side-effects which meant that the patients under treatment needed to be kept in intensive care. Interestingly though, British trials - which have been carried out on an even smaller scale - have not so far produced the side-effects reported by Dr. Rosenberg's team. The reason for this, noted Prof. Dudley Dumonde of St. Thomas Hospital, London, could be that the British research has involved the use of IL-2 made from natural human white blood cells, while the US work has used IL-2 produced by means of genetic engineering at Cetus. This may be evidence that the genetic engineers, once again, are not producing the IL-2 molecule quite to specification. (Extracted from Biotechnology Bulletin, Vol. 4, No. 11, December 1985)

Antibody-magnetic cancer imaging developed

By linking tumor-targeted monoclonal antibodies to paramagnetic metals, Johnson & Johnson (J&J) of New Brunswick, N.J., and Cytogen Corp. plan to develop an imaging technique for cancer diagnosis and monitoring.

In an agreement last November, J&J obta[illegible] unspecified equity position in the privately h[illegible] Princeton firm. In addition, J&J acquires worldwide market rights to the firm's monoclonal conjugates for use in magnetic resonance imaging (MRI). A J&J subsidiary, Technicare Corp., Cleveland, will use the monoclonal in its Teslacon MRI system.

Cytogen's proprietary, two-stage technology uses branched-chain linkers to attach metals such as gadolinium to a portion of the antibody, while leaving the active site on the constant region unimpaired. MRI, unlike its counterpart, nuclear magnetic resonance, uses no radioisotopes to detect hard and soft tissues, and to distinguish primary cancers from secondary metastases. Magnetically sensitive moities in the body resonate at different fequencies to magnetic fields imposed at right angles. The signals are then converted to a two-dimensional television image, and ultimately captured on film. By using monoclonals to carry enhancing agents to specific tissues earlier detection of anatomic change will be made possible. (Extracted from McGraw-Hill's Biotechnology Newswatch, 2 December 1985)

Monoclonal antibodies simplify leukaemia diagnosis

Monoclonal antibodies are providing doctors with a simple and neat way of diagnosing leukaemia and other abnormalities of plasma cells. Dr. Wendy Erber at the John Radcliffe Hospital in Oxford spent three years perfecting the technique and has tested it on more than 250 patients.

The conventional technique for diagnosing leukaemia is to raise antibodies to the abnormal cells. The antibodies are tagged with marker molecules which fluoresce when lit. If the antibodies are added to a sample containing suspected malignant or aberrant cells, the abnormal cells shine out.

Although this positively identifies leukaemia cells, the technique has drawbacks: the fluorescence microscopes used to observe the immuno-labelled cells are expensive; the blood cells must be concentrated by centrifuging before labelling; and the ability of the labelled cells to fluoresce begins to fade within days.

Erber's technique requires only the facilities available in any hospital's haematology laboratory and some monoclonal antibodies. The method uses an alkaline phosphatase (AP), an enzyme taken from mice which can be stained easily. AP is attached to a monoclonal antibody called anti-alkaline phosphatase (AAP). The APAAP complex is in turn linked to another monoclonal antibody from mice, which is specific for the cell to be labelled. The resulting chain of molecules has AP at one end and the cell specific antibody at the other end. Ordinary blood smears, preserved with fixative, are treated with the APAAP complexes and stained to disclose the AP, now associated with cells. Stained cells show clearly under a standard microscope, and the blood is preserved well enough for the condition of all cells to be assessed. Treated samples store well, without deterioration of the stain. (Extracted from New Scientist, 12 December 1985)

Hepatitis B vaccine

An experimental, yeast-engineered recombinant DNA vaccine against hepatitis B has recently proven successful in adults and infants and researchers are reporting good results with a recombinant vaccine manufactured by a mammalian cell line.

The currently marketed vaccine is produced from the blood of infected people. While the safety of the product has been proven, the source - hepatitis B carriers - could eventually disappear. John M. Zahradnik and his colleagues at Baylor College of Medicine in Houston and Georgetown University in Washington, D.C., vaccinated 20 healthy men with a mammalian recombinant vaccine and 20 men with the currently marketed vaccine. Within four weeks, 70 per cent of recombinant vaccinations "took", compared with only 25 per cent in the other group; eventually 95 per cent of the men in both groups were protected.

The US Department of Health and Human Services projects that the price of the recombinant vaccine will be less than that of the one now in use. (Extracted from Science News, Vol. 128, 12 October 1985)

Bioartificial pancreas made

Vivotech (Needham Heights, MA) - a joint venture between Damon Biotech (Needham Heights, MA) and Connaught Laboratories (Toronto, Canada) - has developed a means of encapsulating islets of Langerhans, the insulin-producing cell clusters scattered throughout the pancreas. The encapsulating film, alginate-polylysine-alginate, was developed by Anthony Hein-Fang Sun, a senior research scientist at Connaught and professor of physiology at the University of Toronto Medical School. The microcapsules, produced by Damon Biotech's patented Encapcel technology, are about a half millimeter in diameter, small enough to pass though an 18 or 19 gauge needle. The capsule membrane is permeable to small molecules such as glucose and insulin, but impermeable to large ones such as albumin or immunoglobulins. The surface of the capsules carries a negative charge which dissuades fibroblasts from attaching and growing.

Encapsulated islets of Langerhans have already proven successful as bioartificial pancreases in rats. When diabetic rats were injected intraperitoneally with about 5,000 encapsulated islets, they remained normoglycemic for about two years (a rat's life-span). The microencapsulated islets remained morphologically and functionally intact: islets removed from sacrificed rats continued to produce insulin in culture.

Scientists at Vivotech have now started experiments in large animal systems. They are using both bovine and porcine sources for the islets. Vivotech is now designing an instrument to handle large-scale harvesting islets. They separate islets from the pancreas by traditional collagenase digestion. The trick is to remove the islets from the collagenase before they, too, get digested. The new instrument is designed for "programmed" harvesting; digestion and harvesting occurs in two-minute intervals; whatever is not digested goes for another two minutes, and so on.

The large-animal studies are being done in dogs, the classical experimental model for diabetes. As in the rat study, the dogs will receive injections of 30 to 50 per cent of the normal complement of cells. The dogs will be injected with bovine islets; because these tend to very tremendously in size, the dosage will be measured in endocrine equivalents rather than number of islets. The capsules will probably have to be reinjected during the course of the study; unlike the rat system, which used rat islets, the bovine islets are in a foreign host and cannot receive all the proper nutrients that allow them to live for extended periods of time. The dog studies will take another two to three years to complete. Only then will human clinical trials begin.

Microencapsulated cells offer advantages over the transplantation techniques because they are

protected from attack by the body's immune system. This means two very important things: a patient will not have to take immunosuppressive drugs, and islets from a number of different species can be incorporated into the capsules. This is a great advantage, for scientists have found it difficult to get enough pancreases (and therefore islets) from human sources to consider surgery for any but a handful of diabetics.

Encapsulated cells have another advantage: if diabetes is an autoimmune disease, then transplanted islets might also be attacked by the immune system. Encapsulated cells would be protected from attack in the event of a recurrence of the initial disease. (Extracted from Biotechnology, Vol. 3, October 1985)

Prenatal probe developed

Prenatal detection of genetic disorders may soon be accomplished automatically. Cetus, the US biotechnology firm, has developed a method to screen for sickle cell anaemia, a rare blood disorder, using a new DNA probe technology capable of boosting the sensitivity several hundred thousand-fold.

Widespread use of gene probes has been restricted by poor sensitivity and lack of a suitable non-isotopic detection system. Cetus claims to have overcome both of these problems. The company's scientists are able to boost the signal using a method called polymerase chain reaction.

The system has the advantage of being performed in a liquid format which is significantly faster than conventional solid-state technology and since it involves the serial addition of reagents to a single tube, it lends itself to automation.

Currently, serological HLA methods are used in paternity determinations, tissue typing for organ transplantation and increasingly for the diagnosis of disease susceptibility to juvenile insulin-dependent diabetes mellitus and other auto-immune diseases. Using DNA genetic typing, subtle differences not distinguishable by HLA typing can be identified, the Cetus executive explains.

A further addition to Cetus' research tool portfolio is the introduction of five ras oncogene product antibodies to be used in cancer research. (Extracted from European Chemical News, 4 November 1985)

$23.1 million to fund cardiac tests for clots and dead tissue

Centocor, Inc., is trying to secure US and European regulatory approval for myosin and fibrin imaging tests. Linked to radioactive tracers, antifibrin monoclonals detect blood clots; the antimyosin molecules distinguish dead heart muscle from that which is merely damaged and capable of recovering, thus providing a basis for therapeutic choice.

Sales have already started in Italy, fast approvals in Europe are expected. The investors were largely private individuals such as physicians, followed by institutional investors and venture capitalists. (Extracted from McGraw-Hill's Biotechnology Newswatch, 7 October 1985)

Entire erythromycin gene complex cloned

Some 27 steps are required for Streptomyces erythreus to synthesise the antibiotic erythromycin. Lilly Research Laboratory however, has cloned the apparent complete set of genes coding for this erythromycin synthesis, and expressed them in a strain of Streptomyces that never made such an antibiotic before in its natural life.

Meanwhile, at the Society of Industrial Microbiology in Boston, and the International Union of Pure and Applied Chemistry in Manchester, UK, Lilly R&D team were reporting isolation and expression in Escherichia coli of the genes for the first antibiotic-forming step in the pathway that catalyzes penicillin and cephalosporin synthesis from their precursor molecules.

Antibiotics need frequent model changes. New microbe-killers are in constant demand to counter the resistance that pathogens develop to existing ones. And many infectious diseases are still without specific antibiotic therapy.

In cloning the erythromycin genes, the team's "main interest" is to hybridize them with those that synthesize tylosin - another macrolide antibiotic, produced by S. fradiae - and thus come up with novel clinical entities.

The Lilly gene-splicers reasoned that bacteria that produce antibiotics must be resistant to their own products, and that these resistance genes are closely linked to the structural gene sequences that code for the antibiotic-forming enzymes. For the 27-step erythromycin gene pathway, they constructed a roomy shuttle vector, the bi-functional cosmid pKC462, which replicates in E. coli as well as Streptomyces species. Into this cloning vehicle they inserted 35 kilobases worth of genomic sequences from S. erythreus, coding for both erythromycin synthesis and resistance. When this package was cloned into S. lividans, which normally produces no macrolide antibiotic at all, the transformed naive strain promptly synthesized it. (Extracted from McGraw-Hill's Biotechnology Newswatch, 7 October 1985)

IBT offers fibroblast growth factor

Fibroblast growth factor (FGF) is a potent growth promoting factor isolated from bovine brain. Used in the in vitro cultivation of cells, the presence of FGF can lower the serum requirment and increase the rate of cell proliferation. (Source: Biotechnology Bulletin, Vol. 4, No. 9, October 1985)

Biodegradable chemicals to promote nerve regrowth

Biodegradable chemicals can be used to promote regrowth of damaged nerves, according to research carried out at the Massachusetts Institute of Technology. Severed nerves in rats have been regrown to close a 0.67 inch gap. The same polymeric material can also promote skin growth. Nerves are regrown in a plastic silicone tube containing cowhide-derived collagen bonded to glycosaminoglycan (GAG) from shark cartilage. The polymer acts as a scaffold to support the nerve ending's new growths. Nerve fibres had completely bridged a 15 mm gap by the time the collagen-GAG degraded in six weeks. The silicone conduit alone allows regrowth over 12 mm gaps, but not over 15 mm gaps. Earlier work at St. Elizabeth's Hospital (Washington, DC) has investigated restoration of nerve function after severed nerves are rejoined. (Extracted from Science News, 21 September 1985)

Possible vaccines against VD

Vaccines against venereal diseases could be injected in the form of genetically engineered bacteria, according to researchers at Stanford University. The best immunity against gonorrhea and

cystitis seems to be achieved when antigens are applied directly to the surface of the vagina. Continual production of the antigens by live genetically engineered bacteria could produce long-term immunity. The pathogenic bacteria change their surfaces constantly, so that by the time the body's immune system produces antibodies, the antigens on the pathogens have changed. Researchers concentrated on the pili that the pathogens require to hook onto mucosal cells, and developed an antibody that prevents the cells from attaching. In parts of Africa, 25 per cent of all women are infertile by age 25 because of gonorrhea. About 15 per cent of all women experience at least one cystitis infection, and the disease sometimes affects the kidneys. There are no animal models for gonorrhea, so testing will have to move directly from cell culture to human subjects. (Extracted from New Scientist, 19 September 1985)

Diagnostic kit for systemic lupus erythematosus

RIA (UK) will introduce a DNA-based diagnostic kit for systemic lupus erythematosus. The Gamma-B anti-ds DNA kit has only three pipetting stages and an assay time of 1.5 hours. The kit gives highly reproducible results with high specificity, so allowing it to differentiate between systemic lupus erythematosus and other closely related autoimmune diseases. (Extracted from Clinica, 25 October 1985)

Detection test for AIDS carriers

Institut Pasteur (France) is currently developing a refined antibody detection test for AIDS carriers. The new test will distinguish between those carriers of the HTLV-III/LAV virus who are immunocompromised and those who are not. The test, which involves counting T4 lymphocyte subpopulations, is currently undergoing trials. (Source: Clinica, 25 October 1985)

AIDS drug test in US

Clinical trials with a potential Aids treatment, developed by Rhône-Poulenc and its US-based subsidiary Rhone-Poulenc Pharmaceuticals, have now started in the United States. Approval for the tests was granted by the US Food & Drug Administration earlier this year. Based on tungsten and antimony, the drug HPA-23 is believed to be capable of preventing the AIDS virus from proliferating. (Source: European Chemical News, 16 December 1985)

Two further AIDS tests approved

Two more diagnostic tests for detecting antibody to HTLV-III virus, identified as the cause of acquired immune deficiency syndrome (AIDS), have been approved by the Food and Drug Administration (FDA). The first test is manufactured jointly by Du Pont and Biotech Research Laboratories (Rockville, Md) and will be marketed primarily to blood banks worldwide on an exclusive basis by Du Pont. The other test is produced by Travenol-Genentech Diagnostic (Cambridge, Mass.), a joint venture of Baxter-Travenol Laboratories and Genentech, and will be used primarily to screen donated blood. (Source: Chemical Week, 30 October 1985)

Collaboration on new vitamin C production

Genentech, Lubrizol Corp. and Pfizer Inc. are to collaborate on the development of a new simplified process for the manufacture of vitamin C. The key to the new process is a unique micro-organism, developed by genetic engineers at Genentech. Using this micro-organism, a single fermentation step can replace the five steps of the current vitamin C production process, potentially cutting manufacturing costs.

The research team led by Robert Lazarus has worked out an alternative to the seven-step Reichstein-Grussner vitamin C production process. At its heart are genetically engineered Erwinia herbicola bacteria, which convert glucose to 2-keto-L-guloic acid. The team transferred a gene from Corynebacterium that enables one micro-organism to perform two separate fermentation processes.

Genentech and Lubrizol Enterprises have set up a joint venture, GLC Associates, to develop the new technology to the commerical stage. If this work is successful, the initial commercial production of vitamin C will take place at Pfizer, although GLC - in which the two companies have equal ownership - may build its own production facilities using the streamlined process. Hoffmann la Roche, the Swiss drugs major, is also investigating the potential of recombinant DNA technologies for vitamin C production. Despite the American announcement the Basle based firm is confident that it will maintain a tight grip on world markets. Hoffmann La Roche is believed to hold about half the global market worth $400 million.

Genetic engineers at Hoffmann la Roche are also working on similar technologies. (Extracted from Biotechnology Bulletin, Vol. 4, No. 9; Vol. 4, No. 11 and European Chemical News, 25 November 1985)

Livestock applications

Progesterone test for dairy cows

Boots-Celltech Diagnostics has signed an agreement with Bayer to develop a cow fertility test. The product has potential world market of an estimated $32 million. The UK diagnostics firm will develop the monoclonal antibody-based test and produce reagents for fabrication into the final test kit by Bayer. The West German company will have worldwide marketing rights outside Japan and China. Boots-Celltech will have exclusive rights in Japan and distribute the test through Sumitomo and Sankyo.

Developed jointly with University College, Cardiff, the Boots-Celltech test measures progesterone levels in milk. Field trials will start at the end of 1985 and are set for completion by March 1986. Commercialisation is scheduled for mid-1986.

Other companies offering immunoassay tests are: Cambridge Life Sciences, IO (Bio) and Nochtech, the latter based in Ireland. The IQ (Bio) product differs in that it is based on the company's proprietary enzyme amplification system. (Extracted from Biotechnology Bulletin, Vol. 4, No. 9, October 1985 and European Chemical News, 25 November 1985)

Making more out of straw

Biologists at the Department of Animal Sciences at the University of Illinois, and at the Northern Regional Center of the US Department of Agriculture, Illinois, have now found a way to make straw more readily digestible by ruminant animals.

M.S. Kerley and colleagues fed sheep and bullocks on a diet of corncobs, cornstalks and wheat straw treated with alkaline hydrogen peroxide. They suspended the material in distilled water containing 1 per cent hydrogen peroxide, added sodium hydroxide to make the mixture alkaline and stirred the suspension at room temperature for 16 hours. The feed was made from the insoluble residue collected at the end, washed until it was neutral and oven

dried. Experiments on bullocks showed that the rate of digestion almost doubled for the treated material, as did the extent of digestion over 48 hours.

Growing lambs that were fed untreated straw lost weight; lambs fed treated straw gained weight - almost as much as those fed on corn grain - which indicates that they were getting as much energy from the waste material as they could from prime feeds. Mature sheep, too, thrived on a diet of treated material.

In the gut, cellulose is digested through the action of cellulolytic bacteria. In normal circumstances the bacteria are unable to colonise the straw to any great extent and so digestion is poor. Kerley and his team collected straw particles from the fluid in the rumen of the sheep and looked at them under a scanning electron microscope. They found that particles of untreated straw were poorly colonised, and then only on cut and broken edges of the plant tissue. Particles taken from sheep fed treated straw were very different. A dense population of bacteria covered the particles uniformly, allowing more rapid breakdown of the cell walls.

Although the team have not yet identified the factors that regulate bacterial attachment to the straw, it is clear that their treatment removes some barrier that normally prevents colonisation, which opens up the possibility of using many crop residues as animal feeds. (Source: New Scientist, 2 December 1985)

Agricultural applications

Immunogold tracks down intracellular targets

When studying such processes as nitrogen fixation in leguminous plants, it helps to know what is going on where. A powerful cytological staining technique being developed by the Monoclonal Antibody Centre at the Institute of Animal Physiology and the John Innes Institute involves hooking up colloidal gold to monoclonal antibodies. A recent development in colloidal gold technology means that gold particles can be generated in discrete size categories (e.g. 5 nm, 10 nm or 15 nm). These particles can then be coupled to antibodies capable of binding to specific molecular antigens present in thin sections of plant or animal tissue prepared for electron microscopy. (Source: Biotechnology Bulletin, Vol. 4, No. 11, December 1985)

Plant growth substance

A microbial plant growth substance has been patented by Bio-Organics of Orlando, Florida. The preparation contains bacteria and algae according to the patent. According to the firm, the promoter dramatically raises the rate of photosynthesis, the process that is central to plant growth. Field tests with oranges, tomatoes and ferns have shown the process to be effective, the spokesman claims. Studies on wheat and corn are now planned and marketing to growers is scheduled for 1986. (Source: European Chemical News, 2 December 1985)

Genes for plant resistance

Monsanto has announced that a new method to make plants resistant to the herbicide glyphosate, the active ingredient in Roundup (T), has been developed.

Researchers in the company's biological sciences group have altered the impact of the herbicide using modified plant genes. Glyphosate is effective in knocking out a key plant enzyme called EPSP synthase, which catalyses the production of three amino acids. A method to insert a modified EPSP synthase gene that triggers overproduction of the enzyme can override the effect of the herbicide providing the plant with resistance to glyphosate.

The modified gene is inserted into a plasmid gene from Agrobacterium tumefaciens, a bacterium which, in nature, can insert its DNA into the DNA of plant cells. So far the scientists have only tried the system with petunia and tobacco.

Calgene, Inc., of Davis, Calif., has expressed a glyphosate-resistance gene from bacteria in tobacco. However, the foreign enzyme remains in the cytoplasm, whereas the Monsanto protein is transported to the chloroplast. At concentrations of herbicide above 40 per cent normal strength, Calgene's plants are no longer resistant. Even if higher concentrations of Roundup (T) don't kill the plant, it is important to determine if the treatment still permits full seed and fruit set. (Extracted from European Chemical News, 11 November 1985 and McGraw-Hill's Biotechnology Newswatch, 18 November 1985)

Seed gene deal

American Cyanamid, the US agro-chemical manufacturer, is hoping to breed herbicide-resistant maize. The company has entered into an agreement with Pioneer Hi-Bred International, a leading US seed house, to test the efficacy of genes resistant to imidazolinone weed killers.

Initially, the imidazolinones could only be used with soya because the herbicides showed little crop selectivity. However, researchers at Molecular Genetics in Minneapolis, funded by Cyanamid, have produced a maize hybrid that has an in-bred tolerance to the imidazolinones.

Pioneer Hi-Bred International is now testing the resistance gene in a hybrid of Cyanamid and PHI maize. The company plans to convert several other strains. Although field trials have started, the value of the work is not expected to be obvious for a number of years. William Marshall, president of PHI's microbial genetics division told ECN. (Source: European Chemical News, October 1985)

Food production and processing

Cheese improvement

Imperial Biotechnology Ltd. has signed a £100,000 agreement with the UK Dairy Industry Research Policy Committee, targeted on the development of faster cheese ripening technology. Hard cheeses, such as cheadars, need to be stored for long periods to develop their typical flavours, tying up capital. IBT aims to cut the ripening time in half with improved enzymes. (Source: Biotechnology Bulletin, Vol. 4, No. 9, October 1985)

Switch to fungal host for commercial production of r-DNA rennin

At the International Union of Biochemistry held last autumn in the Netherlands, Genencor scientist Gregory L. Gray reported that his firm was using the fungus Aspergillus nidulans as a host to make rennin, the primary enzyme in cheese production. The traditional source of the milk-clotting enzyme has been the fourth stomach of calves. The eukaryotic Aspergillus process is more cost-effective than synthesis in bacterial hosts.

because in prokaryotes "there is no refolding of the protein molecule to achieve the active conformation of its tertiary structure". Cheesemaking trials for the recombinant protein are scheduled later this year at the University of Kentucky. (Extracted from McGraw-Hill's Biotechnology Newswatch, 7 October 1985)

Chemical applications

Contract for advanced bioreactor for low-value chemicals production

Battelle's Columbus Division has been awarded a contract by the US Department of Energy to develop an advanced bioreactor for the mass production of low-value chemicals. Working with Battelle are the Bechtel Group, a major chemical company, and consultants from the University of California at Davis and Ohio State University.

In the bioreactor, an immobilised cell or enzyme is mixed in the reactor with an insoluble solvent or liquid. As the cells, solvent and liquid interact, the solvent continuously absorbs the chemical that is being produced by the biochemical reaction. This chemical is then recovered from the solvent, which is recycled so the process can repeat itself. According to Dr. B.R. Allen of Battelle, the multi-phase fluidised bed (MPFB) concept improves technologically and economically on conventional submerged culture bioreactor and separations technologies for producing target chemicals.

When in full-scale use, such a bioreactor might be used to produce low-value chemicals such as ethanol, acetone and butyric acid, which are currently produced by refining petroleum. A bench-scale MPFB process will be designed, built and operated to demonstrate the feasibility of the continuous fermentation, solvent regeneration and product recovery aspects of the technology. (Extracted from Biotechnology Bulletin, Vol. 4, No. 11, December 1985)

Chemicals from biotechnology forecast

Biotechnology could prove competitive for the production of several chemicals in the next few years.

In a new study analyzing the potential of a new number of biological routes - using enzymes and/or microbes - to compete with existing conventional routes, US consultants Chem Systems Inc. conclude that hydroxylated aromatics, like hydroquinone, and acrylamide are possible targets. Biological systems have a unique capability to hydroxylate aromatics, Chem Systems says.

The cinnamic acid-based phenylalanine process developed by Genex has capital cost advantages but raw material cost disadvantages compared with traditional fermentation processes. In addition, bioreactor technology involving cell recycle, if successfully scaled up, could further reduce costs and increase the attractiveness of producing lactic acid biologically rather than by the current acetaldehyde-based technology.

The enzymatic route, developed by Cetus Corp, and microbial route, by Exxon and Warwick, to propylene oxide are not yet competitive with traditional chlorhydrin and hydroperoxide technologies, the consultants say. As far as specialities are concerned, however, microbial polysaccharides may provide opportunities for production of unique performance chemicals.

Further details are available from Chem Systems Inc., 303 S. Broadway, Tarrytown, New York 10591, USA. (Source: European Chemical News, 4 November 1985)

Energy and environmental applications

Ciba-Geigy sponsors work on microbial detoxification

Ciba-Geigy AG is supporting work at the Swiss Federal Institute of Technology designed to break down some of the more problematic wastes produced by the company. According to Bioprocessing Technology (November 1985, p.3), mixed cultures of Klebsiella, Pseudomonas and Rhodococcus are being used to break down such wastes as atrazine, produced during the synthesis of Ciba-Geigy's striazine herbicides. A great deal of work remains to be done to get the process up to an acceptable industrial scale, however. Details from: Alisdair M. Cook, Microbiology Department, Swiss Federal Institute of Technology, CH-8092 Zurich, Switzerland. (Source: Biotechnology Bulletin, Vol. 4, No. 11, December 1985)

Industrial microbiology

Fungi could be used in textile industry

Scientists are trying to make fungi produce chemicals for the textile industry.

Researchers at Britain's Shirley Institute near Manchester, first set up in 1919 to serve the research needs of Britain's cotton industry, have been interested in mildew for a long time because it produces enzymes that break down cellulosic materials, like cotton or viscose, the textile made from wood pulp. It was this interest that led them into biotechnology.

Their first idea was that it might be worth trying to turn the sugary and filamentous "mycelium" produced by certain fungi into cloth. The filaments form a fabric quite different from conventional fibres: they are about one-fifth the diameter of cotton fibres, and grow out in branches, not single strands. But what interested the scientists the most was the filament's cell wall, which contains chitin.

Textiles made from chitin might have two specialist applications. Tests on animals and humans have shown that chitin (in this case extracted by a more expensive process from shellfish) accelerates the healing of open wounds. Nobody is quite clear why, but the chitin seems to act as a synthetic skin. Second, chitin has the ability to bind particular heavy metal atoms like copper, which means that the materials could also be used in mineral extraction.

The chitin cloth is easily made by mass-production of the fungi, using traditional fermentation processes. The fibres are then poured into typical "wet-laying" machinery of the paper-industry, where the water is squeezed out until they take the form of the non-woven material. So far the fungi have been grown in small five-litre vats, which produce up to 100 grams of dry fibre each over two days. Commerical production might cost £1,000 a tonne.

The dried chitin filaments have proved too brittle on their own, so they are mixed with conventional fibres, such as viscose or cotton. The project is supposed to be completed in 18 months when the fungus-produced material is to be tested for

wound healing in hospitals. (Extracted from The Economist, 7 December 1985)

Industrial equipment

Alfa-Laval backs MIT separations unit

Bio-equipment supplier Alfa-Laval is underwriting a multi-million dollar bioprocess separations research centre at the Massachusetts Institute of Technology (MIT). Projects will be directed by Charles L. Cooney, professor of chemical and biochemical engineering at MIT. Alfa-Laval's subsidiary Chemap will supply a 1,500-litre fermentation pilot plant and a 75-litre feed fermenter. Details from: Prof. Charles Cooney, Building 66, Massachusetts Institute of Technology, Cambridge, MA 02139, USA or on (617) 253 3108. (Source: Biotechnology Bulletin, Vol. 4, No. 9, October 1985)

Harwell club aims to develop second generation biosensors

A new multi-company biosensor R & D 'club' is being launched by AERE Harwell. The proposed programme will develop materials and technology needed for the second generation of biosensors, used in biochemical detection. These devices are expected to have unprecedented sensitivity - down to the single molecule level - and should find applications throughout the health care, food, chemical and process industries. The medical market alone is forecast to exceed $1 billion annually by the end of the century.

Biosensors combine biological sensing components (enzymes, antibodies) with physico-chemical technology (transducers, microprocessors) to achieve signal recognition, amplification and display. They are opening up many new possibilities for medical diagnosis, hospital patient monitoring, and process control, but their full impact will be achieved when their sensitivity has been extended to measure concentrations of viruses, bacteria, antibodies, food toxins and hormones.

In the medical field, biosensors which detect binding reactions such as the immune (antibody-antigen) response are a key requirement. These will mimic the natural cell-membrane detector systems, in which membrane receptors recognise specific molecules and bind to them, changing the permeability of the membrane. The Harwell programme will concentrate on the development of immunosensors, which use readily available monoclonal antibodies as the detector component. The first year of research will cover the development of robust synthetic membranes, detector coating techniques, response mechanisms, and signal amplification and processing.

Membership of the Club is restricted to UK companies or organisations with a substantial manufacturing presence in the UK. The subscription fee is £10,000 for a full year's membership. The Club will be operated at Harwell by the Chemical Technology Centre, and will be affiliated to the Chemical Sensors Club of the Department of Trade and Industry. Details from: Dr. Andrew Chadwick, Manager, Chemical Technology Centre, Harwell Laboratory, Didcot, Oxon OX11 ORA or on (0235) 24141, ext. 5208. (Source: Biotechnology Bulletin, Vol. 4, No. 9, October 1985)

SERC considers future support for membrane research

The current commercial interest in synthetic membranes centres on their use in separation processes. In the food industry, for example, membrane separation can be much more energy efficient than alternative processes such as distillation. Membrane technology holds considerable promise, too, when it comes to the business of commercialising biotechnology. Current worldwide sales of membranes and associated plant are running at £2 billion a year, with growth over the next ten years forecast to top 10 per cent a year.

The UK is not currently heavily involved in membrane science and technology, but five Science and Engineering Research Council (SERC) committees commissioned Prof. Patrick Meares of Exeter University to look into ways in which the situation might be improved. His report sets out to identify those areas where research in academic laboratories could provide a basis for the UK to compete in the development and application of new membrane technologies.

The five SERC committees involved - Biological Sciences, Biotechnology, Chemistry, Materials and Process Engineering - have given their general support to Prof. Meares' recommendations, and he has been appointed co-ordinator for the period to August 1986 to implement the recommendations for encouraging research and training. Details from: Prof. P. Meares, Department of Chemical Engineering, University of Exeter, Exeter EX4 4QF or on (0392) 263263. Copies of the report can be obtained from Ms. J. Orme, SERC Biotechnology Directorate, on (0793) 26222 ext. 2310. (Source: Biotechnology Bulletin, Vol. 4, No. 11, December 1985)

Tunable laser used to recover substances

Ishikawajima-Harima Heavy Industries and Nippon Zeon have used a tunable laser in biotechnology to obtain cytochromes, nucleic acids including DNA, insulin and S-adenosylmethionine. The firms recovered 80 per cent of a useful substance in an experiment in which a yeast was diluted with distilled water and radiation conditions - including wavelength, power output (200-300kW) and time - were delicately changed. The substances were produced by puncturing the cell walls of yeasts and bacteria. (Extracted from Chemical Week, 2 October 1985)

Biohazards

Safety in biotechnology

An Ad Hoc Group of experts from OECD Member countries on Safety and Regulations in Biotechnology met on 2-5 December 1985. The group asked its Chairman, Dr. Roger Nourish, of the UK Health and Safety Executive, to issue a statement of its work:

"The debate on safety and regulatory issues in this field since the Asilomar (USA) international conference on genetic engineering a decade ago has now taken a new turn. The current resurgence of interest, and indeed some public concern, has accompanied the commercialisation of the products of rDNA technology and in particular agricultural and environmental applications of such organisms.

The transfer of rDNA organisms from the laboratory bench to the factory and to the environment raises a set of new questions:

- What are the risks involved?
- Do these risks differ from the risks in laboratory-based research, or indeed from the risks in the "conventional" biotechnology industry which has developed over several centuries with a remarkably good safety record?

- What new approaches need to be taken in risk assessment and control so as to adequately take into account the different parameters involved in the use of rDNA organisms in industry and in the environment, as distinct from the construction of rDNA organisms in the laboratory?

- How can the various national approaches best be harmonized while protecting intellectual property yet ensuring widespread exchange of information?

The work which focused on industrial, agricultural and environmental rDNA applications, was to provide some answers to these difficult questions.

A common understanding of these safety issues should provide a basis for taking initial steps toward international accord on health and protection of the environment, while contributing to the promotion of international commerce, and the reduction of barriers to trade in the field of biotechnology.

Participation by some 60 high level government representatives including scientists and policy makers demonstrated the considerable political and social importance which countries attach to the issue of safety and regulations.

The central task of the mandate was to identify what criteria have been or may be adopted for the monitoring or authorisation for production and use of recombinant DNA organisms in industry, agriculture and the environment.

The experts limited their considerations to the application of rDNA techniques. Work started in December 1983. After several international meetings, the Group has successfully completed its deliberations and formulated its recommendations on the safe introduction of rDNA technology. Initial differences of opinion were resolved over the two-year period.

The concluding meeting was noteworthy in the uniform determination of participants to produce a balanced, scientifically accurate document. This was accomplished in an atmosphere of harmony and mutual trust". (Source: OECD Press Release, 9 December 1985)

E. PATENTS AND INTELLECTUAL PROPERTY ISSUES

Plant gene patent marks a breakthrough

The US Board of Patent Appeals and Interference's decision to grant Molecular Genetics a patent on a new seed-corn genetic structure can be seen as a key moment in the development of commercial plant biotechnology. Analysts expect the decision to shake up the $3 billion US seeds industry, allowing some of the smaller companies to patent new plant genes at the test-tube stage - and to raise finance to take them through to marketing. Under Federal law, a patentee has exclusive protection for his product for 17 years. Molecular Genetics is active in a number of fields, but recently signed an agreement with American Cyanamid covering work on plant genes conferring herbicide tolerance. (Extracted from Biotechnology Bulletin, Vol. 4, No. 9, October 1985)

Debate over plant patents grows in Europe

The International Coalition for Development Action (ICDA), based in Amsterdam, has found uncharacteristically common cause with the International Union for the Protection of New Varieties of Plants (UPOV). They both oppose a demand from European companies that plants created by recombinant DNA techniques - as well as the techniques themselves - should be patentable.

The conflict arises for two reasons. First, plant breeders in Europe have virtually never been allowed to patent their products. Instead, their rights are enshrined in the convention which established the UPOV in 1961. Supported by 17 European countries, the convention is now administered through the World Intellectual Property Organisation in Geneva. It gives breeders ownership of new varieties they create, regardless of who owns the parent stock. A 1973 European Patent Convention codified the position further, stating that patents would not be permitted for plants, animal varieties, or "essentially biological processes for the production of animals or plants".

Second, and despite the existence of these measures, the Federal Republic of Germany's Patent Office is now considering an application covering the process developed by Josef Schell and his colleagues at the Max Planck Institute for Plant Breeding Research (Cologne) for the transfer of genes using the Ti plasmid of Agrobacterium tumefaciens. Bayer AG (Dormagen, FRG), the chemical company which already holds provisional rights to Schell's process and which contributes over $300,000 each year to his Institute, has a substantial interest in the outcome. The company argues that without patent protection, such investment would be pointless.

Already opposed to plant breeders' rights enshrined in the UPOV convention, the ICDA argues that patents would make matters much worse for the developing countries by giving multinational seed companies monopoly control over crop plants. This, indeed, was one of the reasons why Europe did not follow the U.S. earlier this century in authorizing the patenting of plant varieties. (Source: Bio/Technology, Vol. 3, October 1985)

OECD reports on bio-patenting

There is no other field of patenting, according to a new report published by the Organisation for Economic Co-operation and Development (OECD), where patent laws vary so widely and on so many points as in biotechnology. Overall, a group of experts concluded, patent laws in the United States and Japan appear to give biotechnology better protection than laws in other OECD countries. The report warns that the impact of the new biotechnologies may affect the economies of OECD countries sooner than they expect - and their effects could be far-reaching. Biotechnology and Patent Protection: An International Review is by F. K. Beier, R. S. Crespi and J. Straus and is available from OECD sales agents. (Source: Biotechnology Bulletin, Vol. 4, No. 9, October 1985)

Swedish committee looks into patentability of micro-organisms

In 1982, the Swedish Government appointed a committee to make an inquiry into ethical, humanitarian and social issues, arising from the use of genetic engineering (recombinant DNA techniques). On the initiative of the committee, the inquiry involved a discussion of the patentability of micro-organisms genetically altered by recombinant rDNA techniques.

The committee commissioned Dr. Tore Oredsson (who recently retired as Chairman of the Court of Patent Appeals) to write an article on "Biological Inventions and Swedish Patent Legislation". The

article has now been published in English in the Swedish publication Nordiskt Immateriellt Rättsskydd NIR (1985), p.229-259.

In Article 2 of the Convention on the Unification of Certain Points of Substantive Law on Patents for Invention, adopted by the Council of Europe on 27 November 1963, the option was given to Member States of not granting patents for plant varieties or animal breeds or essentially biological processes for the production of plants or animals, although patents could be granted for microbiological processes and the products resulting from such processes. Provisions of that kind can be found in the European Patent Convention, Article 53, in the Swedish Patents Act and in the Patents Act of many other countries participating in EPC. The article is therefore of a more common interest than the title may indicate.

The report of the President's Commission on Industrial Competitiveness stated according to Washington Post dated 17 February 1985, that the existing legal system was not designed to deal with genetically engineered organisms, many developments in this field are obsolete by the time the law is ready to handle them, and the continuing stream of new scientific advances calls for rethinking the very concepts derived from earlier centuries on which the intellectual property rules are based.

New concepts of what intellectual property is and how it should be protected - beyond patents, trade-marks, trade secrets and copyrights - may well be needed, as may sweeping changes in intellectual property laws and the ways they are administered and enforced.

In the light of the explosive development of molecular biology and the technical and industrial utilization of it ("biotechnology"), the problem to find an internationally acceptable system for protecting biological inventions is urgent. It is very important to act fast and if possible find solutions, which without any waste of time can be realized and give immediate protection, the scope of which can be examined judicially without delay. It is also important that the solutions are truly international and useful and of the same value to all countries in the world.

The conclusion of the article outlines a new system, which may solve at least some of the deficiencies of the present system.

Mugwort wins first Japanese patent for modified plant

The first-ever product patents for a plant were registered in Tokyo last September, more than eight years after application. Nippon Shinyaku Co. Ltd., Kyoto, received two certificates for "A New Plant Species Belonging to the Mugwort [Artemisia] Genus".

The patents protect a perennial herb, the pests mugwort, and an insecticide that Shinyaku developed from it after selective breeding. Both patents (Nos. 1281544-5), were filed in 1977 and officially announced in January 1983, but their issuance was long-deferred by objections from the Japan Seed Trade Association, Tokyo. The Japanese Patent Office (JPO) held that the chromosome analysis described in the patent application certified the originality and reproductibility of the species, and was therefore patentable.

This issuance by the JPO is similar to 1983 US patent No. 4,378,655, which was assigned to Red River Commodities, Inc Fargo, N. Dak., for a hybrid sunflower plant and its seed. It should open the door for patenting genetically engineered plants in Japan.

A typical biotechnology patent, after application and request for examination, now takes at least four to five years to issue - time that must be subtracted from the patent's 20-year life span. Only a thousand Japanese examiners handle over a quarter-million applications per year, more than double the number in the USA. The problem is particularly compounded by biotechnology patents from foreign inventors, which are translated by some 2,500 local patent attorneys, often incomprehensibly. These applications are initially rejected out-of-hand by the JPO for lack of clarity and add months to the approval process.

In the race for patent priority on cloned, human tumor necrosis factor (TNF), Dainippon Pharmaceutical Co. Ltd. of Osaka is the first of five competing firms worldwide to have its patent application published. Dainippon, which had not previously disclosed its TNF gene sequence, claims priority filings dated March 6, 1984.

Other companies vying for TNF patents include:

- Asahi Chemical Industries Co. Ltd., Shizuoka, Japan, in conjunction with the Beckman Research Institute of the City of Hope, Duarte, Calif.
- Biogen, NV, Geneva, with BASF, Ludwigshafen.
- Cetus Corp., Emeryville, Calif.
- Genentech, Inc., South San Francisco, Calif.

(Extracted from McGraw-Hill's Biotechnology Newswatch, 4 November 1985)

French will sue US over AIDS-test patent

Sanofi, the French pharmaceutical giant, and its partner, Pasteur Diagnostics, intend to bring suit in the US courts to force the US Patent Office to act promptly on its ELAVIA test kit for detecting AIDS. The litigation is being undertaken without animus, but rather as an "amicable" way of "expediting" its apparently sidetracked patent application. It aims at breaking the impasse between the test's French inventors and the US government, which gave fast-track approval to the competing HTLV III detection system developed by Dr. Robert Gallo at the US National Cancer Institute.

Besides US patent rights, the French are awaiting approval of the Food and Drug Administration for its US licensee, Genetic Systems, Inc., Seattle, to market its AIDS kit. Sanofi is also setting up a unit to manufacture recombinant human growth hormone and "other peptide chemicals" at Notre Dame de Boudeville, near Rouen, Normandy, and should be onstream by mid-1986. (Extracted from McGraw-Hill's Biotechnology Newswatch, 4 November 1985)

F. BIO-INFORMATICS

Directory of US courses in biotechnology for developing country scientists (published by the National Academy Press, Washington, DC)

The purpose of this directory is to provide information on US graduate degree programmes, special courses, and internships in biotechnology for developing country scientists.

The information was obtained from colleges, universities, research institutes, professional associations, and industries during the spring of 1984. Although not all of the institutions contacted chose to submit information, it represents

a fairly complete picture of the types of opportunities for study that are available in the various biotechnology disciplines.

The directory includes separate lists for institutions, degree programmes, and special (non-degree) courses. The listing of institutions includes addresses and telephone numbers for key contacts as well as information on consortium memberships and previous experience with admitting developing country students. Consortium memberships can be significant because they provide expanded opportunities and resources for students.

The listings for the degree programmes and special courses include a title and brief description of the subject matter and admission requirements, information on advisors or instructors, and degrees or certificates awarded. Unless otherwise indicated, the starting time for degree programmes is in the fall and the language of instruction is English; masters' programmes require 1-2 years and Ph.D. programmes 3-5 years to complete. Information on costs is included for special courses. Cost information is not included for degree programmes because of continuing changes in tuition, fees, and living expenses.

The index is divided into sectoral listings, with courses shown under Agriculture, Engineering, Environment, Health, Interdisciplinary Programs and Basic Studies, and Veterinary Sciences.

This directory is intended for use as a first step in determining where specific types of training can be obtained and to facilitate communication with the institutions identified. Full details on the specifics of courses, costs, timing, and prerequisites are readily available from the institutions of interest.

This report was prepared by the Board on Science and Technology for International Development, Office of International Affairs, National Research Council, for the Agency for International Development, Office of the Science Advisor. (Copies may be obtained from: Board on Science and Technology for International Development, National Research Council, 2101 Constitution Avenue, N.W. Washington, D.C. 20418 USA)

Comprehensive biotechnology (published by the Pergamon Press, price $750.00 for all four volumes)

Recent advances in biotechnology indicate a need for a comprehensive treatment of the basic principals, methods and applications of biotechnology as an integrated multidisciplinary subject. Comprehensive Biotechnology fulfils this need and is intended to be the standard reference work in the field.

Comprehensive Biotechnology is aimed at a wide range of users. Since beginners as well as veterans in the field are addressed, each chapter or group of chapters begins with the basics before proceeding to in-depth specialist material. The work starts with the scientific and engineering fundamentals of the field (Volumes 1 and 2), and then proceeds to descriptions of their applications and implications in various processes and products (Volumes 3 and 4), including pharmaceuticals, foods and beverages, fuels, chemicals, waste treatment, agriculture, mining and medicine.

Comprehensive Biotechnology is comprehensive but concise to enable completion within a set of four volumes published simultaneously. Individual volume and cumulative indexes and a glossary of terms are designed to facilitate the use of this work by a broad readership. The publishers plan to update regularly the contents of this work in Biotechnology Advances, an annual review journal, and with supplementary volumes as appropriate.

Researchers, teachers, students, administrators and others in industry, government and academia should find Comprehensive Biotechnology essential as a source of information, data and ideas in this rapidly expanding area of science.

Outline of volume contents

VOLUME 1: The Principles of Biotechnology:

Scientific Fundamentals

Section 1. Genetic and Biological Fundamentals
Section 2. Chemical and Biochemical Fundamentals

This volume delineates and integrates the unifying, multidisciplinary principles of biotechnology in terms of relevant scientific fundamentals.

VOLUME 2: The Principles of Biotechnology:

Engineering Considerations

Section 1. Bioreactor Design, Operation and Control
Section 2. Upstream and Downstream Processing

This volume delineates and integrates the unifying, multidisciplinary principles of biotechnology in terms of relevant engineering fundamentals.

VOLUME 3: The Practice of Biotechnology:

Bulk Commodity Products

Section 1. Healthcare Products
Section 2. Food and Beverage Products
Section 3. Industrial Chemicals, Biochemicals and Fuels

This volume describes the various large-scale biotechnological processes and products which are involved in industrial practice.

VOLUME 4: The Practice of Biotechnology:

Speciality Products and Service Activities

Section 1. Specialized Activities
Section 2. Governmental Regulations and Concerns
Section 3. Waste Management and Pollution Control

This volume describes the various specialized biotechnology activities which are involved in industry and government.

The new biotechnology: European governments in search of a strategy by Margaret Sharp (published by the University of Sussex, price, £10.00)

The "new biotechnology" is about the harnessing of the new techniques of genetic engineering with other developments in microbiology and chemical engineering to create a powerful new technology. Potentially it could have an immense impact upon medicine, the chemical and energy industries and, above all, agriculture and food production. This new biotechnology is still in its infancy. Many of the techniques being used are barely ten years old even as scientific techniques, let alone as industrial activities. A study of biotechnology in its present phase of development therefore captures many of the issues which arise in the translation of activity from science laboratory to firm - from the uncertainties of scaling up laboratory processes to issues of finance, patents and property rights.

This study looks at the way in which this new technology is evolving in the countries of Western

Europe. It contrasts industrial and government strategies, emphasising the importance of the linkage between academic science and industry. It finds both strengths and weaknesses in Europe's position, but disputes the gloomy prognosis of those who write off Europe's contribution.

This study will be of interest to those concerned about the position of Europe - and its leading countries - in new technologies, as well as to practitioners and policy makers in biotechnology. It contains a wealth of information about developments in Europe, Japan and the United States.

ATCC offers cell lines, hybridomas and viruses

The 5th edition of the ATCC Catalogue of Cell Lines and Hybridomas (price $6.50) describes 2,650 human, animal and plant cell lines; a listing of cell lines involved in patenting; recommended media and growth conditions for many cell lines; and formulae for standard cell culture media and reagents. Thirty-six new animal viruses, Rickettsiae and antisera are also available and are described in ATCC's Virus Catalogue. Additions to the animal virus collection include Ehrlichia risticii (Potomac horse fever), two rabies viruses, several human rotaviruses and antisera, and a human cytomegalovirus. Details from: Sales Department, American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD 20852, USA or on (301) 881 2600. (Source: Biotechnology Bulletin, Vol.4, No.11, December 1985)

Biotechnology and the law by Iver P. Cooper (published by Clark Boardman Co., Ltd. USA, price $86.50)

This is the long-promised update of a treatise whose 1982 edition has become popular among biotechnology patent lawyers. Other books cover biotechnology patent law specifically, but Cooper fills in the general non-biotechnology background as well. Although written for the attorney, it is comprehensible to the determined non-lawyer. Released in August 1985, it includes the 1982 Ex parte Jackson case, which, the author believes, went too far in excluding generic claims for micro-organisms. It also discusses Ex parte Lundak, 1984, which held that an informal academic group maintaining a hybridoma cell line did not meet the qualifications for a depository - contrary to Cooper's expectation in the first edition. This updated re-issue also covers the Patent Term Restoration and Patent Law Amendment Acts of 1984, litigation over property rights in biological materials, copyright protection of DNA molecules, Section 101 protection of plant varieties and animal breeds, patenting of monoclonal antibodies and hybridoma lines. (Source: McGraw-Hill's Biotechnology Newswatch, 18 November 1985)

The biotechnology business: A strategic analysis by Peter Daly, Biotechnology Unit, National Board for Science and Technology, Ireland (published by Frances Pinter, London, price £16.50)

This book analyses the main forces which are shaping the industry structure and the competitive strategies and choices facing the biotechnology companies. Descriptions of the technologies, the application areas and company activity (with emphasis on the US scene), are presented. The characteristics of an emerging industry such as early entry barriers and technological uncertainty are examined along with the unique relationship between science and technology. The role of national governments is considered in relation to the enhancement of national competitiveness.

Case studies are presented for a number of leading companies including Genentech, Genex, Cetus, Centocor, Celltech, Eli Lilly and Monsanto each illustrating a particular strategic response. The strategies adopted by the new companies are classified and the benefits and risks of each strategy type are discussed. The strategies of the established companies are considered in relation to technological strategy and timing of entry.

Computer-aided techniques in food technology (published by Marcel Dekker, Inc. USA., price approx. US$90.00)

For many years, an acute need exists for a computer book that is suitable for food practitioners. To meet this need, this book is primarily designed to be a reference book for professional food engineers, food technologists, food scientists, and industrial personnel who wish to update their knowledge on computer-aided methods and techniques. Some detailed case studies are included concerning operational research, design problems, data processing, and other related topics. The author, Dr. Israel Saguy is a Senior Research Scientist at the Agricultural Research Organization, The Volcani Center, Institute for Technology and Storage of Agricultural Products, Bet Dagan, as well as Senior Lecturer at The Hebrew University of Jerusalem, Israel. He and 15 other well-known experts contributed to this very interesting book.

Microbiology of fermented foods (published by Elsevier Applied Science Publishers Ltd., Price approx. £100.00)

Food fermentations are among the oldest applications of biotechnology. The two volumes of this set - edited by Dr. Brian J.B. Wood, Department of Bioscience and Biotechnology, University of Strathclyde, Glasgow, Scotland, Great Britain - give a comprehensive overview. All of the major groups of foodstuffs whose preparation involves a fermentation are discussed. Several chapters deal with aspects particularly relevant to developing countries. Two chapters on animal feed production by ensiling and related processes illustrate similarities in biochemistry and microbiology between the very different areas of human food fermentations and animal feed production. Genetic engineering may well make its contribution to the future development. This subject is explored in a chapter on strain maintenance and improvement.

Volume 1 covers:

Vinegar; The Microbiology of Vegetable Fermentations; Cheese Fermentations; Fermented Milks; Fermented Protein Foods in the Orient, with Emphasis on Shoyu and Miso in Japan; Microbiology of Bread Making; Yeast-Lactic Acid Bacteria Interactions and Contribution to Fermented Foodstuffs; Biology and Technology of Mushroom Culture; Bio-enrichment; Production of Vitamins in Fermented Foods; Production of Industrial Enzymes and Applications in Fermented Foods.

Volume 2 covers:

Fermented Fish and Fish Products; Fermented Sausages; Silage Fermentation; Fermentative Upgrading of Wastes for Animal Feeding; Tea, Coffee and Cocoa; African Fermented Foods; Food Fermentation in the Tropics; Miscellaneous Food-Related Fermentations; Strain Selection and Improvement.

The Biotechnological Challenge (published by the Cambridge University Press, price approx. £20.00).

S. Jacobsson and A. Jamieson, Research Policy Unit, University of Lund, Sweden; H. Rothman, Centre for Research in Industry, Business and Administration, University of Warwick

Socio-economic implications of various biotechnologies for developing countries are analysed in this unique volume. An introductory chapter sets the framework for the book by discussing broad issues related to biotechnologies as socio-economic innovations. The first main section reviews the technologies themselves (genetic engineering, enzymes and fermentation) and discusses the main technical and economic issues that surround their successful development. The second main part describes in detail three case studies that are particularly relevant to Third World development (the impact of iso-glucose on the world sugar market, the role of biotechnologies in raising the output of proteins and the industrial base and strategy behind the Brazilian ethanol programme). (Source: Cambridge University Press, January-July 1986)

C. MEETINGS

2-4 April 1986: Cell and tissue transplantation into the adult brain, New York, USA. (Contact: Conference Department, the New York Academy of Sciences, 2 East 63rd Street, New York, NY 10021, USA).

7 April 1986: Scale-up in biotechnology, Bretton, near Peterborough, UK. (Contact: Christine Tusting, Association for the Advancement of British Biotechnology, AFRC Food Research Institute, Colney Lane, Norwich NR4 7UA.

7-11 April 1986: MIT short course: controlled release technology: polymeric delivery systems for drugs, pesticides and foods, Paris, France. (Contact: Industrial Liaison Program, Room E38-400, Massachusetts Institute of Technology, Cambridge, MA 02139, USA or on 617-253 2691).

7-10 April 1986: Energy from biomass and wastes: this three-and-a-half day conference includes an exhibition and a trade show. It will be held at the Hotel Washington Hilton, Washington, DC. Organized by the Institute of Gas Technology, it includes a technical programme and addresses research topics as well as business and non-technical issues that affect the contributions of biomass and wastes to primary energy demand. Further details from the Institute of Gas Technology, 3424 South State Street, Chicago, IL 60616, US.

8 April 1986: Biotechnology and the agri-industries/ plant biotechnology, Edinburgh, UK. (Contact: Dr. Keith Jones, Department of Surgery, University of Edinburgh Medical School, Teviot Place, Edinburgh EH8 9AG or on 031-667 1011 ext. 2278).

8-10 April 1986: BIOTECH RIA '86, Florence, Italy. (Contact: Organising Secretariat, Fondazione Giovanni Lorenzini, Via Monte Napoleone 23, 20121 Milan, Italy or on 02-70 22 67).

21-22 April 1986: International Conference on Biotechnology. Alexandria, Va. Write CEEM, Box 536, Fairfax, Va. 22030.

5-7 May 1986: Chemical aspects of biotechnology. Sponsored by the American Chemical Society and the National Bureau of Standards, Gaithersburg, Maryland, USA. The conference will cover the crucial role that chemical sciences and technology play in the development of biotechnology. For additional information contact Ms. Susan Moses, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D.C. 2003, USA.

13-15 May 1986: BIOTECH 86. Wembley Conference Centre, London, U.K. For further information contact Online International Ltd., Pinner Green House, Pinner, Middx., HA5 1AE, U.K.

20-22 May 1986: EMBO-EMBL Workshop on Control of Gene Expression in Stemm Cell Differentiation and Mouse Development. For further information contact Erwin F. Wagner, European Molecular Biology Laboratory (EMBL), Mayerhofstrasse 1, D-6900 Heidelberg, FRG.

11-14 June 1986: Conference on Molecular Biology and Pathology of Matrix sponsored by the Jefferson Institute of Molecular Medicine, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pa., USA. For further information contact D. J. Prockop, Jefferson Institute of Molecular Medicine, Thomas Jefferson University, 11th and Locust Streets, Philadelphia, Pa. 19107, USA.

16-18 June 1986: Conference on Cellular and Molecular Biology of Hormone and Neurotransmitter containing secretory vesicles, New York Hilton Hotel, New York. For further information contact the Conference Department, The New York Academy of Sciences, 2 East 63rd Street, New York, NYT 10021, USA.

17-22 July 1986: Third World Congress on Genetics Applied to Livestock Production, University of Nebraska, Lincoln, Nebraska, USA. The conference will cover breeding objectives, breed utilisation, optimum design of breeding programmes and the application of gene transfer technology. For further information contact Gordon E. Dickerson, Chairman of the Co-ordinating Committee, 229 Marvel Baker Hall, University of Nebraska, Lincoln, NE 68583-0908, USA.

1-5 September 1986: Biotechnology Seminar. Recent trends in biotechnology production methods will be analysed at this seminar under the auspices of the EEC. It will be hosted by the government of Bulgaria at Varna. The programme will include food additives and new specific chemicals. Details from: The Industry and Technology Division, United Nations Economic Commission for Europe, Palais des Nations, CH-1211 Geneva 10, Switzerland. Telephone 022 34 60 11. Telex: 28 96 96.

22-25 September 1986: Biotechnology Information '86. University of Sussex, Brighton, UK. For further information contact European Biotechnology Information Project, the Science Reference Library, 9 Kean Street, London, WC2B 4AY, UK.

23-25 September 1986: BIOTECHNICA '86, Hannover, FRG. For further information contact Deutsche Messe- und Ausstellungs- AG, Hannover, Fed. Rep. of Germany.

20-22 October 1986: Sixth International Symposium on HPLC of Proteins, Peptides and Polynucleotides, Baden-Baden, FRG. For further information contact the Secretariat, Sixth ISPPP, P.O. Box 3980, D-6500 Mainz, Fed. Rep. of Germany.

PROJECT OBJECTIVE:	YEAR PLANNED	RISK SEEN	AGRICULTURAL EXPERIMENT STATION
Aluminum toxicity, phosphorus deficiency; cell-fusion resistance mutants	1987-1990	none	U. Calif., Davis
Angiosperms, elucidate mechanisms of growth and differentiation	>1990	none	U. Minnesota
Apple, establish genomic library, reintroduce commercially important traits	>1990	none	U. Illinois
Bacterial pathogens attenuated as biological control agents for diseases	1987-1990	none	U. Calif., Riverside
Bacterial plant pathogens, identification, diagnostic tests	1987-1990	slight	U. Calif., Berkeley
Baculovirus insecticide improvement, commercial production	1987-1990	slight	U. Idaho
Bean, *Phaseolus vulgaris*, legume-bacteria interactions, disease, pests	1987-1990	none	U. Calif., Berkeley
Carrot, mechanisms of membrane fusion	>1990	none	N. Carolina State U.
Chlorosis, pathogen and toxic induced; resistance genes to phytotoxins	1987-1990	none	Rutgers U.
Corn, expression of DNA sequences in endosperm	>1990	slight	U. Florida
Corn and loblolly pine, transposable elements, ribosomal RNA genes	>1990	none	N. Carolina State U.
Corn and tobacco, develop mitochondrial transformation systems	>1990	none	N. Carolina State U.
Corn, controlling elements, embryo lethality, development, disease	1986	none	U. Missouri
Corn, cytoplasmic male sterility, amino acid ratio, develop gene transfer	1987-1990	none	U. Minnesota
Corn, enhance yield, pest resistance	>1990	slight	U. Florida
Corn, improved tissue culture methods	1987-1990	none	U. Minnesota
Corn, pollen transformation, embryo manipulation	1987-1990	none	U. Illinois
Corn, vector development from plasmid-like mitochondrial DNAs	>1990	none	N. Carolina State U.
Corynebacterium corn, wheat, pathogen; develop transfer, expression systems	>1990	none	U. Nebraska
Dairy starter culture, meat, vegetable fermentation, plasmid transferability	1987-1990	none	U. Minnesota
Dairy starters, *Streptococcus cremoris*, characterization of plasmid DNA	>1990	none	Utah State U.
Deciduous forest trees, resistance to *Nectria gallinginia* via cell fusion	>1990	none	U. Delaware
Embryo and gene transfer in laboratory and domestic mammals	>1990	none	Texas A&M U.
Entomopathogenic fungal improvement via cell fusion	1987-1990	none	U. Florida
Extrachromosomal gene amplification in plants, hybrid enzymes, chimeric genes	1987-1990	none	Texas A&M U.
Flavin hydroxylase action, structure and function	1987-1990	none	Texas A&M U.
Florists crops, chemical control of growth, water use, transpiration	1987-1990	none	U. Tenn.
Forest trees, faster growing strains	1987-1990	none	Michigan State U.
Fruits and vegetables, control of post-harvest decay	>1990	none	U. Mass.
Grape, resistance to pests, disease, stress via cell fusion	1987-1990	none	U. Calif., Davis
Herbicides: resistance-gene transfer in cyanobacteria, plants	1987-1990	none	Rutgers U.
Ice-minus bacteria on leaf surfaces to avoid frost injury (*Newswatch*, Nov. 18, p. 3)	1986	none	U. Calif., Berkeley
Insect pathogenic viruses, expansion of host range	>1990	none	U. Florida
Insecticide, genetic manipulation of *B. bassiana* fungus	>1990	none	U. Idaho
Insecticidal virus, cloning of neurohormone gene into insect baculovirus	>1990	none	Texas A&M U.
Insecticide, biodegradable juvenile hormone esterase regulation	>1990	none	N. Carolina State U.
Insecticides, develop insect baculovirus expression vectors	1987-1990	none	Texas A&M U.
Insecticides, develop parasitoids via symbiotic parasitoid viruses	>1990	none	Texas A&M U.

PROJECT OBJECTIVE:	YEAR PLANNED	RISK SEEN	AGRICULTURAL EXPERIMENT STATION
Isozymes, construction of chromosomal linkage maps	1986	none	New Mexico State U.
Lactic acid bacteria, gene transfer system for lactobacilli, pediococci	1987-1990	none	N. Carolina State U.
Legumes for forage nitrogen fixation, resistance to cold, nematodes	1987-1990	none	U. Florida
Lettuce, disease resistance, broaden genetic base	1987-1990	none	U. Calif., Davis
Mitochondrial gene flow and diversity in plant populations	1987-1990	none	U. Arizona
Nematocide controls grape pathogens, nematode virus disease complex	1986	none	U. Calif., Davis
Nitrogen fixation improvement, *Rhizobium japonicum* gene mapping	1987-1990	none	Iowa State U.
Nitrogen fixation in *Azotobacter vinelandii*, transposon, plasmid gene transfer	>1990	none	N. Carolina State U.
Nitrogen fixation, *Rhizobium*-soybean symbiosis, extrachromosomal elements	1987-1990	slight	Clemson U.
Nitrogen fixation, *Rhizobium* host-strain specificity	1987-1990	slight	Wash. State U.
Nitrogen fixation, altered *Rhizobium leguminosarium*, *R. japonicum*	1987-1990	none	U. Calif., Riverside
Nitrogen-fixation, hydrogen-transfer genes in *Rhizobium*	1987-1990	none	Oregon State U.
Nitrogen fixation, legume infection, nodule development, stress tolerance	1987-1990	unknown	Mississippi State U.
Nitrogen fixation, nodulation, of Chinese *Rhizobium*, response to soy cultivars	1987-1990	none	Iowa State U.
Oat and wheat salt tolerance, drought resistance via cell fusion	1986	none	Colorado State U.
Organelle DNA, characterize variability, devise taxonomic hierarchy	>1990	none	N. Carolina State U.
Ornamental plants, cloning propagation	1987-1990	none	U. Tenn.
Peas, selection of cultivars for resistance to physiological stress	1987-1990	none	Washington State U.
Perennial plant propagation via cell culture and fusion	1987-1990	none	U. Illinois
Pesticide degradation by microorganisms, glyphosate resistance genes	1987-1990	slight	Louisiana State U.
Pesticides, viral and biochemical agents, cellular interactions	>1990	slight	Oregon State U.
Pine-tree regeneration; cotton, soybean organogenesis	>1990	none	N. Carolina State U.
Plant modification, selection, regeneration	1986	none	New Mexico State U.
Plant vectors, herbicide resistance in photosynthetic bacteria, aflatoxins	1987-1990	none	Auburn U., Ala.
Potato virus, characterize RX gene, elucidate resistance	1987-1990	none	U. Maine
Potato, transfection and transformation for crop improvement	1987-1990	none	Texas A&M U.
Potatoes, recombinant-improved varieties	1987-1990	none	U. Maine
Poultry germ-plasm, identification and transfer for useful genes	>1990	none	U. Minnesota
Protoplast membrane regeneration, fusion, callus formation	>1990	none	N. Carolina State U.
Regeneration of crop plants with pathogen, pesticide, stress tolerance	>1990	none	U. Florida
Regeneration, embryo culture, microinjection, cell fusion	1987-1990	none	Colorado State U
Regulation, expression of foreign genes in plants and associated bacteria	>1990	none	N. Carolina State U.
Rhizobium and *Agrobacterium*, symbiotic, tumorigenic association, DNA transfer	>1990	none	U. Missouri
Rice, germplasm improvement via cell fusion	1987-1990	none	U. Calif., Davis
Salmon, triploids of exceptionally large size	1986	slight	Michigan State U.
Tissue-culture improvement of New Mexican crops	1986	none	New Mexico State U.
Tobacco, decrease undesirable chemical components in cured leaf	1987-1990	none	U. Kentucky
Turf and forage grasses, genetic improvement	1987-1990	none	U. Massachusetts
Turkeys, live *pasteurellas multocide* vaccine for fowl cholera	1987-1990	none	Clemson U.
Vaccine, cloning of bovine brucellosis antigen	1987-1990	slight	Texas A&M U.
Vectors for chimeric genes, chloroplast expression in crop plants	1987-1990	none	U. Arizona
Viral vector for gene transfer into higher plants	1987-1990	none	U. Kentucky
Viruses, attenuation of sindbis, western equine encephalitis, bovine diarrhea	>1990	none	N. Carolina State U.
Viruses, differences in transcriptional expression of tobacco viruses	1986	none	N. Carolina State U
Wheat, foreign gene transfer	1986	none	Kansas State U.
Wheat, map, transfer genes for resistance to insects, disease	1986	none	Kansas State U.
Wheat-agropyron hybrids, gene transfer, cytogenetic analysis	1987-1990	none	Kansas State U.
Zein genes, modification of amino acid deficiency	1987-1990	none	Louisiana State U
Zein, cloning and sequencing control regions, flanking regions	1987-1990	none	U. Minnesota

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