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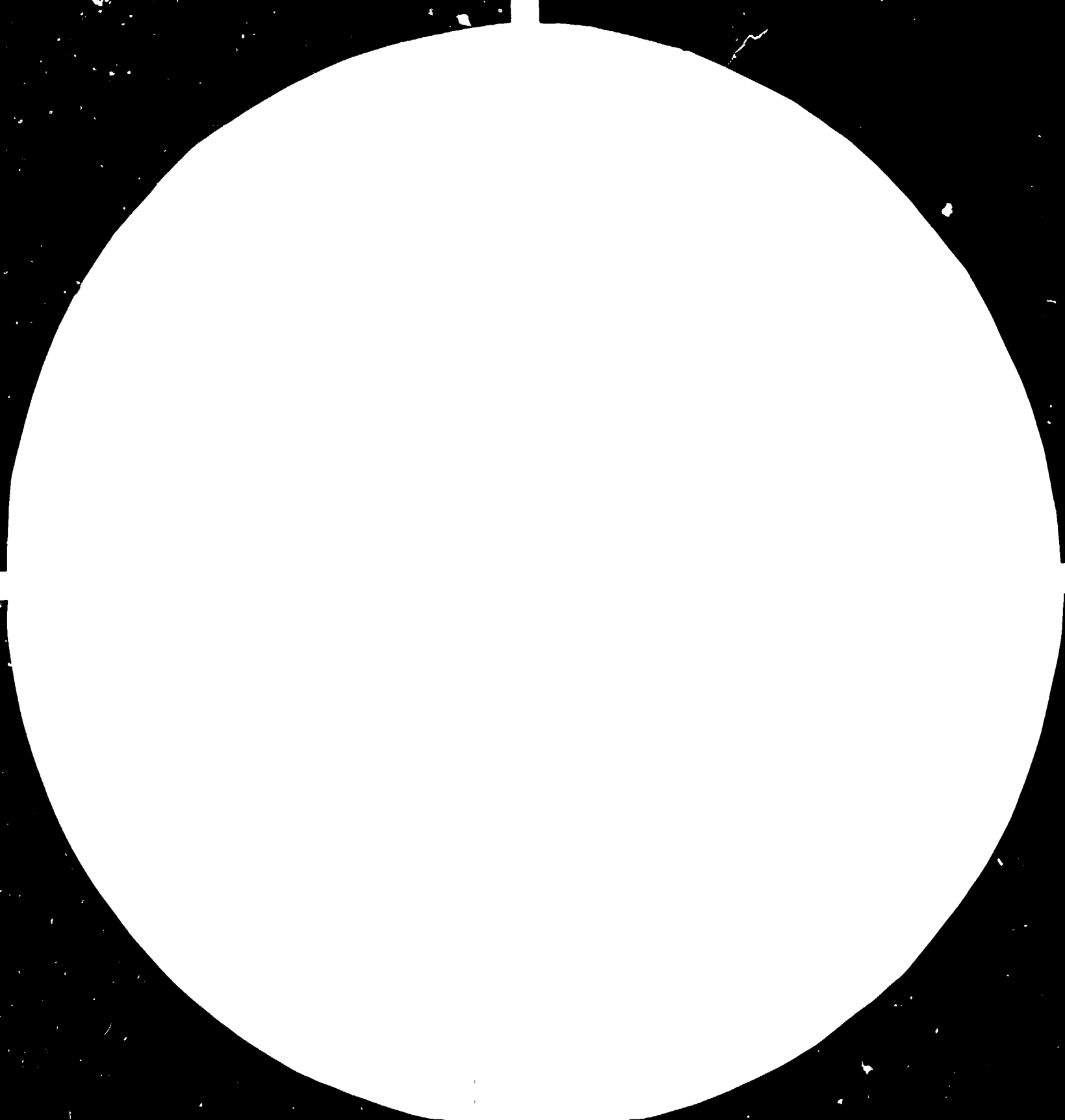

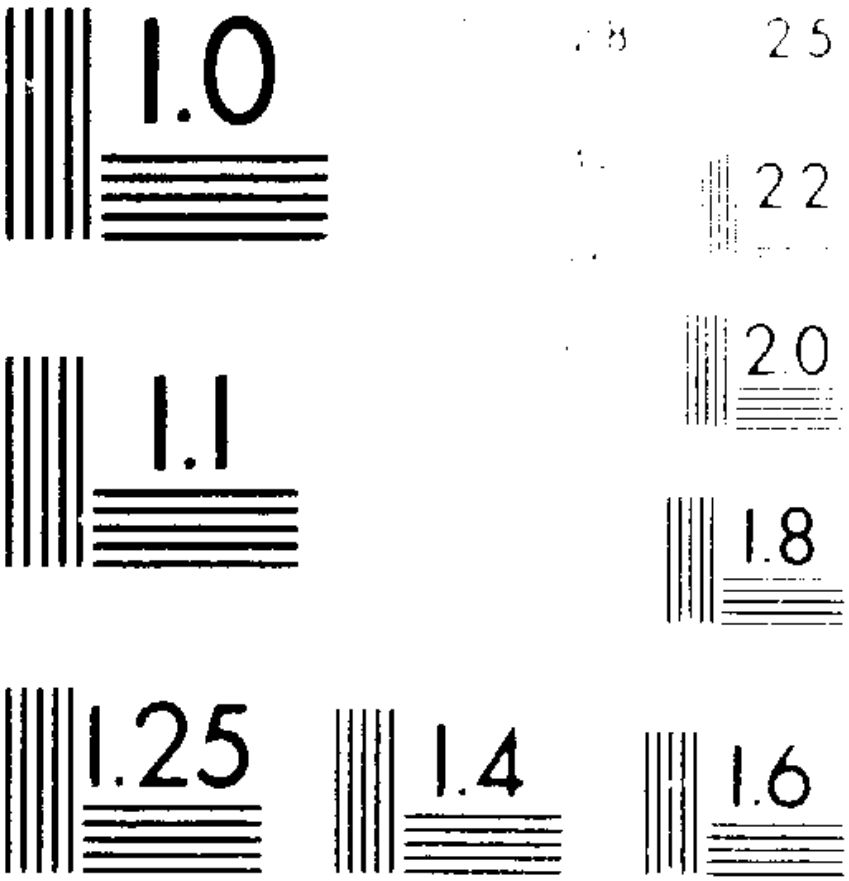
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UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

Genetic Engineering and Biotechnology Monitor

Issue Number 10 November/December 1984

Dear Reader,

Since the last issue of the Monitor considerable progress has been made in the preparations for setting up the International Centre for Genetic Engineering and Biotechnology. The Preparatory Committee held two meetings - one in September 1984 in Vienna and another in December 1984 in Trieste. Its next meeting will be held in New Delhi in April 1985. It is probably important to mention that the Committee decided to invite high level scientists to join a panel of scientific advisers constituted by it and it was most encouraging that of the 16 scientists addressed, 14 have accepted the invitation to join the panel, including three Nobel laureates. The Preparatory Committee and the UNIDO Secretariat are indeed fortunate to have this overwhelming support from the international scientific community at its highest levels. A list of the names is to be found in this issue. The first meeting of the panel will be held in Vienna in February 1985.

Another important step has been the selection of Dr. Burke K. Zimmerman as Project Leader to attend to activities relating to the setting up of the ICGEB until the appointment of its Director. Dr. Zimmerman is expected to assume his duties very soon.

Other UNIDO activities related to genetic engineering and biotechnology are proceeding at the same time. Information on the International Symposium on Lactic Acid Fermentation, jointly organized by UNIDO and the Universidad Autonomica Metropolitana de Mexico, may be found in this issue. Another important event was the discussion on biotechnology by African scientists at an expert group meeting on the implementation of new technologies held in Swaziland last October.

The Monitor wishes all its readers all the very best of the Season's greetings.

G. S. Gouri
Director
Division for Industrial Studies

V.84-93895

Compiled by the Technology Programme of UNIDO P.O. Box 300, A-1400 Vienna, Austria

A. POLICY, NEWS AND OTHER EVENTS

UNIDO News

Work programme proposed for International Centre for Genetic Engineering and Biotechnology

A draft work programme for the world's first International Centre for Genetic Engineering and Biotechnology (ICGEB) devoted to the needs of developing countries was discussed at Trieste, 3-5 December 1984. During its fifth session the Preparatory Committee on the establishment of the Centre also discussed matters related to management structure, headquarters agreements and affiliated centres, as well as its own progress in preparation for opening of provisional facilities. Information received from India and Italy points to March 1985 as the target for opening of provisional facilities.

The Preparatory Committee endorsed the draft work programme presented by the Secretariat and proposals made to the meeting by India and Italy as a preliminary basis for further review and elaboration and decided to transmit them, along with its foregoing remarks, for review and advice by the Panel of Scientific Advisers. The Panel was requested to examine this matter together with the Project Leader and the two host countries. Based on the remarks of the Panel, the Preparatory Committee would consider further the elaboration of the work programme for eventual transmission to the Board of Governors.

As presented in the Secretariat's draft, the work programme - estimated to cost $40.7 million - covers the first five years of operation of the Centre's two "components" at New Delhi and Trieste.

The proposed programme is based on the assumption that three years will be required to bring the Centre to full operating capacity. By the fourth year, it is envisaged that 31 scientists, as well as 20 post-doctoral fellows and 30 technicians, will be working at each component. A total of some 88 trainees are expected to complete their 24-month courses by the end of this first five year period.

The Trieste facility will focus on industrial microbiology, with four interrelated programmes. One of the proposed elements, bioconversion of biomass, for example, could lead to breakthroughs in converting cellulose waste from plants into fodder, sugars, alcohol fuels and synthetic polymers on an economical basis.

Other areas to be covered at Trieste include the study of micro-organisms that could help refine crude oil cheaply, break up oil slicks and release trapped oil from otherwise exhausted oil wells. Industrial-scale fermentation and protein engineering would also be part of the work programme.

The New Delhi component will conduct R+D and training in agriculture, animal health and human health. Included in agricultural research is biological nitrogen fixation and oil microbiology, stress tolerance in plants and improvement of plants for nutritional content. The animal health subprogramme covers growth, development and reproduction, as well as vaccines and immunology. Tropical diseases would be a major focus of human health research.

Common to both sites would be scaling-up facilities in the form of fermentors. Because it is essential to industrial microbiology, the full-size pilot plant is to be located at Trieste. A fermentor of at least 100 litre capacity, however, would be needed at New Delhi for producing sufficient quantities of new vaccines and organisms for testing. A gene bank, containing genetic stocks and information, is planned for at least one of the sites.

Safety relating to human health and the environment will be a major consideration at New Delhi and Trieste. While long- and short-term safety of genetic engineering has lacked an international focus until now, UNIDO, in conjunction with the World Health Organization (WHO), has begun a study of the safety of industrial biotechnology.

Stemming from a recommendation of the Preparatory Committee in September, a panel of top scientists - including Nobel laureates Jonas Salk, Arthur Kornberg, Luis Leloir and Joshua Lederberg - will be guiding the Centre into operational status. The panel of scientific advisors is tentatively scheduled to have its first meeting at Vienna from 11 to 13 February.

The Preparatory Committee also endorsed the appointment of Burke Zimmerman of Berkeley, California for the post of project leader. His main responsibility, after assuming his post in January 1985, will be "... to handle problems at the sites of the Centre till the appointment of the Director to facilitate the early establishment of the ICGEB".

Organized by UNIDO and hosted by the Italian Government, the meeting also examined offers by member countries to host affiliated centres, which would participate in the main Centre's activities. Although details have yet to be worked out, proposals have been submitted by Argentina, Bulgaria, China, Egypt, Greece, Venezuela and Yugoslavia.

The Preparatory Committee is composed of the 33 States that have signed the Centre's statutes. To date these are Afghanistan, Algeria, Argentina, Bhutan, Bolivia, Bulgaria, Chile, China, Congo, Cuba, Ecuador, Egypt, Greece, India, Indonesia, Iraq, Italy, Kuwait, Mauritania, Mexico, Nigeria, Pakistan, Peru, Senegal, Spain, Sudan, Thailand, Trinidad and Tobago, Tunisia, Venezuela, Viet Nam, Yugoslavia and Zaire. Its sixth session is to take place at New Delhi from 3 to 5 April.

The Preparatory Committee adopted the following list of distinguished scientists for consideration as members of the Panel of Scientific Advisers:

(1) Prof. Paul Berg (Nobel Laureate)
Professor of Biochemistry
Stanford University Medical Center
Stanford, Calif. 94305, USA

(2) Prof. Pierre Chambon
Professor of Biochemistry
Université Louis Pasteur
Université de Strasbourg I
11 rue Humann
67085 Strasbourg Cedex, France

(3) Prof. Luigi L. Cavalli-Sforza
Professor of Genetics
Stanford University Medical Center
Stanford, Calif. 94305, USA

(4) Prof. Ananda M. Chakrabarty
Department of Microbiology and Immunology
College of Medicine at Chicago
University of Illinois
P.O. Box 6998
Chicago, Illinois 60680, USA

(5) Prof. Robert Haselkorn
Chairman of the Department of Biophysics
and Theoretical Biology
University of Chicago
920 E. 58th St.
Chicago, Illinois 60637, USA

(6) Prof. Arthur Kornberg (Nobel Laureate)
Professor of Biochemistry
Stanford University Medical Center
Palo Alto, Calif. 94305, USA

(7) Prof. Joshua Lederberg (Nobel Laureate)
President
Rockefeller University
1230 York Avenue
New York, N.Y. 10021, USA

(8) Prof. Luis F. Leloir (Nobel Laureate)
Professor of Biochemistry
Director
Institute of Biochemical Research, Campomar
Obligado 2490
1428 Buenos Aires, Argentina

(9) Dr. Saran Narang
National Research Council
Montreal Road
Ottawa, K1A 0R6, Canada

(10) Prof. Yu. Ovchinnikov
Director
Shemiakin Institute of Bioorganic Chemistry
Moscow, USSR

(11) Dr. William J. Rutter
Professor of Biochemistry
Department of Biochemistry and Biophysics
University of California
San Francisco, Calif. 94143, USA

(12) Dr. Jonas Salk (Nobel Laureate)
Director
The Salk Institute
P.O. Box 85800
San Diego, Calif. 92138, USA

(13) Dr. M. S. Swaminathan
Director General
International Rice Research Institute
P.O. Box 933, Manila, Philippines

(14) Prof. Ray Wu
Department of Biochemistry
Cornell University
Wing Hall, Ithaca, N.Y. 14853, USA

(15) Prof. Francisco G. Bolivar Zapata
Director
Research Centre for Genetic Engineering
Universidad Nacional Autonoma de Mexico (UNAM)
Mexico, D.F.

(16) Prof. C. C. Tan
Adviser to the President and
Director of Genetics Institute
Fudan University
Shanghai
China

Symposium on the importance of lactic acid fermentation in the food industry

Scientists and technologists from four continents (Africa, America, Asia and Europe) gathered in Mexico City during the last week of November 1984 to assess the state of the art of lactic acid fermentation. The symposium, organized by UNIDO and the Universidad Autonomica Metropolitana de Mexico, was part of the events held in this young university commemorating its tenth anniversary. The aims of the symposium were also to identify the needs of developing countries for further research and development in the manufacture of traditional fermented food as well as feed for cattle.

Papers presented at the symposium covered the general principles of biochemistry and taxonomy, traditional fermented food, non-food application of lactic bacteria and the genetic engineering of lactic bacteria. Discussions followed the technical presentations and it was concluded that:

(i) Lactic bacteria alone or in mixed culture is being utilized in many fermentation processes;

(ii) Lactic fermentation is being extended to non-traditional raw materials thereby widening the field of industrial opportunities for this type of fermentation;

(iii) Lactic bacteria with unique characteristics (i.e. amylase activity) are being isolated;

(iv) New developments in the field of genetics and recombinant DNA technology are opening new opportunities to the improvements of processes;

(v) The stability of industrial micro-organisms has been adversely affected by phage infection. This is an area where some efforts are being devoted, particularly in the dairy industry of industrialized countries and similar efforts should be undertaken in developing countries.

Several preliminary proposals were presented for both South-South and North-South collaboration in this promising field.

Papers and a report on the symposium are being prepared for printing and may be had on request by writing to the UNIDO Technology Programme, Division for Industrial Studies, United Nations Industrial Development Organization, P.O. Box 300, Vienna International Centre, Vienna, A-1140, Austria.

UN and other organizations' news

ILO reports on blending of new and traditional technologies

The UN International Labour Office has published its case studies on the blending of emerging and traditional technologies, which include a number of biotechnologies. The biotechnology case studies focus on metal extraction in the Andes; the impact of cloning technology on the palm oil industries of Costa Rica and Malaysia; and the use of biotechnology to upgrade some traditional African fermented foods. Details are available from Mr. A. S. Bhalla, chief, Technology and Employment Branch, Employment and Development Branch, International Labour Office, CH-1211 Geneva 22, Switzerland. The first and third studies mentioned above are based on more detailed studies commissioned by UNIDO.

Nitrogen fixation programme at FAO

Dr. R. N. Roy (Fertilizer and Plant Nutrition and Training Officer from FAO (Food and Agriculture Organization) says that the FAO mandate is to transfer economically viable technology to the developing countries, especially to the small and marginal farmers ... who would be taught how to innoculate seeds, how to conserve innoculant, the benefits and economics of biological nitrogen fixation, etc. At the present moment the Department of Microbiology at Helsinki University is under contract to the FAO to test the suitability of various African peats for use as carrier material in the preparation of Rhizobium inoculum. For further information write to Dr. R. Roy, AGL Division, Room B703 FAO of the UN, Via Delle Terme Di Caracalla, 00100 Rome, Italy. (Source: MIRCENET Newsletter)

MIRCEN centres network
(Source: MIRCENET Newsletter (14))

There are currently 11 MIRCEN centres. The directors and addresses are:

1. Prof. J. R. Jardim Freire
   IPAGRO
   Caixa Postal 776
   90000 Porto Alegre
   Rio Grande do Sul
   Brazil
   (This is a "Rhizobium" MIRCEN)

2. Prof. S. O. Keya
   Departments of Soil Science and Botany
   University of Nairobi
   P.O. Box 30197
   Nairobi
   Kenya
   (also a Rhizobium MIRCEN)

3. Prof. P. Atthasampunna
   Thailand Institute of Scientific and Technological Research
   196 Phahonyothin Road
   Bangkhen
   Bangkok 9
   Thailand
   (This is a Biotechnology MIRCEN)

4. Prof. A. El-Nawawy
   Ains Shams University
   Faculty of Agriculture
   Shobra-Khaima
   Cairo
   Arab Republic of Egypt
   (This is a biotechnology MIRCEN)

5. Prof. V. B. D. Skerman
   Department of Microbiology
   University of Queensland
   St. Lucia Brisbane
   Queensland 4067
   Australia
   (This is a World Data Centre MIRCEN)

6. Prof. Carl-Göran Heden
Department of Bacteriology
Karolinska Institute
S 104 01 Stockholm
Sweden (a biotechnology MIRCEN)

7. Professor Carlos A. Rolz
Applied Research Division
Central American Research Institute for Industry (ICAITI)
Ave. La Reforma 4-47, Zona 10
Apartado Postal 1552
Guatemala, C. A. (a biotechnology MIRCEN)

8. Prof. J. Halliday
NifTAL Project
University of Hawaii
P.O. Box "0"
Paia, Hawaii 96779
U.S.A. (a Rhizobium MIRCEN)

9. Prof. D. F. Weber
Cell Culture and Nitrogen Fixation Laboratory, Room 116
Building 011-A, BARC-West
Beltsville, Maryland 20705
U.S.A. (a Rhizobium MIRCEN)

10. Professor M. Gueye
Centre National de Recherches Agronomiques
d'Institut Senegalais de Recherches Agricoles
B.P 51
Bambey
Senegal (a Rhizobium MIRCEN)

11. Prof. H. O. W. Eggins
Biodeterioration Centre
St. Peter's College
University of Aston on Birmingham
College Road, Saltley
Birmingham B8 3TE
United Kingdom

Further information on research activities is published in "MIRCEN NEWS" which can be obtained free of charge from: Dr. Edgar J. DaSilva, Division of Scientific Research & Higher Education, UNESCO, 7, place de Fontenoy, F-75700 Paris, France.

Social issues

Lawsuit filed to block USDA's animal breeding programmes

Jeremy Rifkin, the social activist and persistent critic of genetic engineering and Michael Fox, a veterinarian representing the Humane Society of America have filed another lawsuit against biotechnology research. The current target is the U.S. Department of Agriculture's mammalian gene-transfer programme at its Beltsville, Maryland, facility.

The lawsuit, which was filed in the U.S. District Court of the District of Colombia on 1 October has clearly frustrated some USDA officials. It is seeking to block some of the department's most ambitious forays into genetic engineering research, and comes just when congressional resistance to enlarging the department's overall biotechnology programmes was beginning to give way. The immediate aim of the lawsuit is to stop experiments involving the transfer of growth hormone genes from other, "foreign" mammalian species into sheep and pigs. The principal source for the foreign hormone gene now being used in the USDA experiments is man. Because of its relatively convenient availability, the human version of a growth hormone gene has been studied most frequently by scientists conducting these kinds of gene-transfer studies. In the experiments, genes are inserted by microinjection into fertilized eggs that have been removed from the sheep and pigs. The eggs are then reimplanted into the uterus of surrogate mothers to continue through a more or less normal gestation.

According to USDA officials, such experiments eventually could lead to genetically engineered farm animals that grow more quickly and efficiently to a standard size, thus bringing meat to market more cheaply. The experiments are also prototypes for introducing other desirable genes, such as those conferring disease resistance, into valuable species that lack them. The experiments would not be possible were it not for the fact that there is great biological similarity between human growth hormone and the hormone in other species.

On economic grounds, Rifkin argues that such breeding programmes, particularly when they involve "monoculture", can lead to animals with dependence on special diets and drugs that result in increased costs for consumers. And on ethical grounds, he and Fox claim that the USDA's breeding practices have led to inhumane treatment of farm animals by making them obese, subject to skeletal abnormalities, and unable to mate properly. They also argue that gene-transfer experiments violate the rights of animals by "robbing them of their unique genetic make-up". (Extracted from Science, Vol. 226, 19 October 1984)

Regulatory issues

Japanese guidelines for recombinant DNA usage

On 2 February 1984 the Science Council of the Japanese Ministry of Education (MOE) established guidelines for innoculation of transformed microorganisms or cells using recombinant DNA directly into animal or plant cells. These guidelines consist of two points of view, "guidelines concerning experiments involving innoculation of recombinants into animals" and "guidelines concerning recombinant DNA experiments using plants as hosts and experiments involving innoculation of recombinants into plants". This type of experiment required special approval in the past, but with the establishment of these guidelines, the experiments may now be conducted freely within the rules. The substance of the guidelines is as follows:

A guideline concerning experiments involving innoculation of recombinants into animals: In order to examine the safety of experiments involving innoculation of recombinants into animals, excluding humans or prenatal primates, the following matters should be thoroughly considered. (1) regarding the physical containment of experiments, the existing standards on physical containment are applicable; (2) offspring should not be produced from animals innoculated with recombinants; (3) the innoculated animals will be labelled and cared for in breeding cages or a breeding room from which they cannot escape; (4) excrements, wastes and carcasses of innoculated animals will be disposed of by disinfecting or incineration, etc.; (5) animal use will be in accordance with the laws concerning protection and management of animals and treaties concerning international dealings with wild animal species in jeopardy of extinction; (6) when supplying innoculated animals to other researchers, approval is required from the Minister of Education; (7) the control and experimental status of innoculated animals will be reported to the Director of the Science and International Affairs Division of the Ministry of Education semiannually.

Guidelines concerning recombinant DNA experiments using plants as hosts and experiments involving innoculation of recombinants into plants: Experiments using plants as hosts and innoculation experiments with plants excluding field cultivation experiments shall be conducted based on the following guidelines: (1) the plants, their spores, pollen, seeds, etc. shall not be taken out of the laboratory containing the plant cultivation facility for experiments; (2) in producing spores, pollen, or seeds, care must be taken so as not to scatter them outside of the laboratory; (3) propagation of spores, pollen, and seeds by insects, etc. should be prevented; (4) the proper containment of recombinant microorganisms will be practiced.

In order to practice these basic guidelines, specific considerations include in the case of using closed culture containers such as test tubes, flasks, etc.: (1) experiments will be conducted under the recombinant DNA experiment conditions for plant culture cells; (2) the plants, spores, pollen, seeds, test tubes, flasks used will be disinfected or incinerated; and (3) in case of storing used plants, spores, etc., they shall be controlled according to handling regulations of the existing guidelines for recombinant DNA experiments.

Furthermore, in the case of cultivation using open cultivating containers such as planting pots, (1) people other than the personnel involved in the experiment should not be allowed to enter the laboratory or the area of plant cultivation; (2) plants, spores, pots, and soil used in experiments shall be disinfected or incinerated, taking special measures such as storing the waste water when recombinants that propagate via water are used; and (3) in the case of experiments to produce spores, etc., containment measures to avoid scattering of spores shall be taken prior to their maturity. (Extracted from Nikkan Kogyo Shimbun, 3 February 1984)

MAFF to revise joint research regulations

In order to promote research and development connected with improvement of plants and breeding of agricultural and forest products, such as rice plants in the private sector, the Japanese Ministry of Agriculture, Forestry and Fisheries announced on 2 August that it will partially revise its joint research regulations. There has been an increased desire for research and development in the areas of improvement and breeding of plants in private enterprises in co-operation with the Ministry of Agriculture, Forestry and Fisheries, which is in possession of the genetic resources, breeding techniques for crops and dissemination policies. Thus, MAFF set up a new breeding technology research council with private enterprises last year, and having learned the opinions of the private sector, investigated ways of responding with joint research. The main points of the revisions are: (1) even though plants are central, all areas of MAFF are targeted; (2) joint research subjects will be divided into subcategories; (3) research and development will be divided into five year periods, but extension within five years is possible. Especially important points are: (4) the offer of genetic resources, such as seeds, held by MAFF; (5) execution of special licensing examinations of developed products according to what has been developed in Japan; (6) joint application of developed products in accordance with the seeds and seedlings law. With this, there has been substantial improvement in the limitations on research and development by the private sector concerning such important plants as rice.

One reason why private enterprises possessing the most up-to-date biotechnology were unable to move full-scale into plant improvement and breeding of principal crops is that MAFF held the seeds and intermediate parenting materials necessary for research and did not share them with the private sector. Likewise, another major reason is that the procedures necessary for practical application of the plants, such as special licensing examinations, take time. Given the implementation of this joint research, these restrictions will be dissolved, thereby greatly stimulating private enterprise research in plant improvement and breeding. (Extracted from Kagaku Kogyo Nippo, 3 August 1984)

Controversy over field testing genetically modified microorganisms

Applications of genetic engineering technology are once again stirring public controversy as researchers prepare to begin field testing of genetically modified microorganisms. Major issues raised by genetic engineering include release of genetically engineered microorganisms in plants into the environment, and use of the technology in human gene therapy and development of new or more potent biological weapons for the military. In May 1984, US District Court Judge Sirica enjoined certain scientific tests involving genetically altered bacteria from being carried out. The experiments have been reviewed and approved by the US National Institute of Health's Recombinant DNA Advisory Committee in 1983. One of the experiments temporarily halted by the injunction involved tests of a bacterium, Pseudomonas syringae from which a gene had been deleted with the same rDNA techniques to yield a microorganism capable of protecting crops from frost damage. Tests were halted voluntarily by the University of California (Berkeley) researchers when a group of plaintiffs headed by social activist and author J. Rifkin filed suit in September last year to block NIH approval. The suit charged that NIH had violated the National Environmental Policy Act by failing to prepare an environmental impact statement (EIS) analysing changes made in the rDNA guidelines in 1978 and for failing to require an individual EIS for each of the experiments. A temporary injunction granted to the plaintiffs is being appealed by NIH. The decision does not affect private firms whose deliberate-release experiments have been reviewed by RAC. Other experiments halted by the decision involved a field test of genetically modified corn plants to be conducted by Stanford University and a field test of genetically modified tomato and tobacco plants by Cornell University. (Extracted with permission from Chemical and Engineering News, Vol. 62, No. 33, 13 August 1984 from an article written by Rudy M. Baum, copyright 1984, American Chemical Society)

General (miscellaneous information)

Culture collection at Kew

The Culture Collection at the Commonwealth Mycological Institute (CMI) has recently received support from the UK Department of Industry to extend its services to industry, particularly biotechnology. As a result, two new posts have been created. Dr. D. Allsopp, previously Information and Service Manager of the Biodeterioration Centre, University of Aston, has been appointed to the post of Industrial Mycologist, many of the activities of the former Aston Biodeterioration Centre are to be continued at CMI. Ms. S. Avery has been appointed the post of Industrial Information Officer. The Culture Collection incorporates the UK National Collection of Fungus Cultures with Dr. A. H. S. Onions as Curator and Mr. D. Smith as Preservation Officer. In April the Collection was recognized as an International Depositary Authority under the Budapest Treaty. A new acquisitions policy is

now being implemented and more isolates of industrial interest are being added to the Collection, supported by an improved world specialist identification service. Advice, consultancy work and contract research will be available to industry with Dr. H. O. W. Eggins acting as senior consultant for biodeterioration. NATLAS accreditation has been applied for, which will enable the laboratory to carry out microbial testing of materials to both British and foreign standards. An improved range of information services are offered in mycology, biotechnology and biodeterioration including on-line computer searches, specialist bibliographies and contract studies.

The Collection now comprises more than 10,000 isolates of interest in plant pathology, biocontrol, biotechnology, industry, biodeterioration studies, taxonomic and biochemical research and education, including many used for the biosynthesis of organic compounds, physiological assay, and soil analysis.

The greatest emphasis is on the maintenance of phycomycetes, ascomycetes and conidial fungi. Yeasts, Basidiomycetes (other than plant pathogens or those of education interest), fungi pathogenic to man and animals, actinomycetes, bacteria and algae are not kept.

The majority of cultures (over 8,000) which will survive the process have been freeze dried (lyophilized). Many special cultures (over 3,000 isolates) such as those derived from types, biochemical strains, patent strains, particularly delicate fungi or those that will not lyophilize, are also maintained at ultra low temperatures in liquid nitrogen. Sensitive strains are preserved by more than one means and may have special treatment, e.g. aquatic Phycomycetes are kept in water, genetic strains of Neurospora and Aspergillus are process in silica gel and Fusarium species are grown in soil. Various media, temperatures and degrees of illumination are employed when growing cultures for preservation.

Cultures are available on request and charges made according to a scale depending on the source of the request.

Donors of acceptable cultures are given free exchange (an equal number of cultures) and are entitled to have their gifts returned if they require them again. New isolates are always welcome and at present deposit of economically interesting biotechnological isolates is particularly sought.

The collection is an International Depositary Authority for Patent isolates under the Budapest Treaty so is open for deposit of "Patent Cultures". A service for safe confidential deposit of research and industrial organisms is also available.

The records are computerized and a catalogue will be produced biennially. Strain information is available by letter or telephone from the Information Officer.

The CMI has always had an identification service but special confidential services and industrial consultancy are now being undertaken.

The Culture Collection and Industrial Services also issues a newsletter, free of charge covering news, lists of recent acquisitions, short courses, meetings, publications and current prices of cultures and service charges.

For further information please contact the Curator, Dr. A. Onions, Culture Collection and Industrial Services, Ferry Lane, Kew, Surrey, TW9 3AF, UK.

Independent research groups

Three independent gene technological research groups will be established in the following areas at the Max Planck Institutes in Martinsried, Munich, FRG:

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

2. Molecular embryology with preference on early mammalian development.

3. Transcription (gene expression) in eucaryotes: mechanisms and controls, preferentially regarding differentiation.

The Max Planck Institutes for Biochemistry and Psychiatry together with the gene centre at the University of Munich, supported by the industry, provide an environment for co-operation. Each group will have about 150 m^2 lab space, positions for scientific and technical assistants and appropriate financial support for equipment and running costs. Contracts with the heads of the teams will be guaranteed for five years. (Source: Outlook on Science Policy).

Nordic Gene Bank

The Nordic Gene Bank at Lund (Sweden) has a unique feature in that it has a duplicate set of germ plasm stored in an island north of Norway. This duplicate set of germ plasm is stored in an old coal mine whose ambient temperature is -3.7 C throughout the year and thus does not require any refrigeration or maintenance of refrigeration equipment. This unique facility could also be used for other purposes like microbial cultures.

The Nordic Register of Microbiological Culture Collections

The Nordic Council of Ministers is sponsoring a project called "Nordic Steering Group for Microbiological Cooperation". The aims of this group is to enhance the co-operation between microbiologists in the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) and to guide the establishment of a computer register on culture collections and their contents in these countries.

The register project is carried out at the Department of Microbiology at the University of Helsinki. COM will be used as one means of communication within this project. (Source: MIRCENET No. 4)

EEC common market in biotechnology

Science and research ministers from the ten member countries of the European Economic Community (EEC) were asked in June to endorse a 5-year, $134-million programme of joint research, training, and other activities designed to create what the EEC's Commission in Brussels describes as the basis of a "Common Market in Biotechnology". The explicit aim of the new programme, would last from January 1985 to December 1989 and be jointly funded by the EEC and national governments and support a variety of actions to help European biotechnology industry become competitive with those of Japan and the United States. These actions will range from research in key areas of "technical and scientific bottlenecks" which need to be resolved before large-scale applications of biotechnology can be reached, to support for common databases, perhaps jointly financed with the private sector.

In addition, however, the programme has a number of political attractions. The first of these is that its heavy emphasis on research into the possible agricultural applications of biotechnology - for example, the improvement of high-value crop yields, or the processing of agricultural products - offers problems caused by the EEC's current agricultural policies, and in particular its chronic overproduction of certain low-value products. This aspect is said to have particularly appealed to the French Government, which currently holds the presidency of the EEC and is keen to find a solution to the community's broader political problem, as well as to some of its domestic problems caused by the current agricultural policy. The second attraction is that it is a possible device for harmonizing the regulations of different countries on both biotechnology research and the diffusion of new products. This would be a step toward the creation of a unified European market which many leading biotechnology companies argue is essential for the growth of European industry.

The Commission itself would like to see the new biotechnology programme supported as a counterpart to the recent $1.3-billion, 5-year research programme into microelectronics (ESPRIT) approved by member states in February. So far, however, the member countries have been reluctant to commit funds of the same order of magnitude, and even approval for the relatively modest programme now being proposed could be held up by their current differences on broader political issues. (Extracted from Science, June 1984)

CAMR's new animal cell culture bank

The PHLS Centre for Applied Microbiology and Research is moving ahead with the construction of its animal cell bank, due to be Europe's largest. The Department of Trade and Industry, which is also supporting CAMR's fermentation work as part of its £16 million biotechnology programme, is contributing £500,000 to the cell bank budget. Once in operation, it will provide space for some 20,000 samples.

CAMR has already applied to the World Intellectual Property Organisation for registration as a recognized repository of patented cells. The cell bank will serve two main purposes: it will build up a national collection and it will also provide a more expensive "safe deposit" service, which will be completely confidential. (Extracted from Biotechnology Bulletin No. 5, June 1984)

New research unit

A molecular genetics research unit will be established at the University of Michigan Medical Center by the Howard Hughes Medical Institute, which will set up a core research group including three leading scientists, junior faculty members and supporting staff. Howard Hughes Medical Institute conducts research at laboratories affiliated to 15 other university medical centres, and its research is concentrated in the fields of immunology, genetics, neuroscience and metabolic regulation. (Extracted with permission from Chemical & Engineering News, Vol. 62, No. 30, page 21, 23 July 1984, copyright 1984, American Chemical Society)

Oncogene, proto-oncogene collection set up

A collection of molecularly cloned oncogenes and proto-oncogenes that can be distributed to investigators is being set up by the American Type Culture Collection with support from the American Cancer Society. The collection will include transforming sequences from retroviruses, DNA tumour-viruses, and human and animal tumours as well as normal proto-oncogenes homologous to retrovirally transduced oncogenes. The genes are supplied as lyophilized preparations of the host bacteria harbouring the plasmids into which the genes have been inserted. Some 20 genes are currently available; more are expected to be added. The American Type Culture Collection, Rockville, Md., is a nonprofit organization with the largest collection of reference cultures of microorganisms, animal cells, and viruses in the world. (Source: reprinted with permission from Chemical and Engineering News, Vol. 62, No. 35, page 16, 27 August 1984, copyright 1984, American Chemical Society)

Biotechnology insurance

Representatives of biotechnology companies may soon be considering insuring themselves against the risk of having their research interrupted by events such as fire, theft, or vandalism. Coverage against interruptions caused by government regulation is, however, unlikely - insurance companies apparently regard such a risk as uninsurable.

The idea, which is said to be novel, is one of several being proposed by the Association of Biotechnology Companies (ABC) in Washington, D.C. The association is surveying several hundred biotechnology and allied companies to see whether an industry-wide insurance programme can be put together.

Johnson and Higgins, the New York insurance brokerage firm that designed the survey, is mainly interested in selling conventional insurance to biotechnology companies, with perhaps coverage against the risk of having research interrupted. Other unusual coverage being considered for biotechnology companies includes protection against patent infringement liability and against inadvertent omissions from papers filed with the Securities and Exchange Commission. (Source: Science, Vol. 225, 7 September 1984)

"Brokers" in monoclonal antibodies

The first independent service to assess the potential of monoclonal antibodies has been set up by the year-old biotechnology company Bioscot (Edinburgh). The same company has also sold to Fermentech (Southampton, Scotland) the manufacturing rights for a continuous fermentation process for the production of Protein A, which has potential as a monoclonal-antibody purifying agent.

Set up as a joint venture between Edinburgh University and Heriot-Watt University (Edinburgh), Bioscot has a dual charter. It acts as a biotechnology brokerage service by arranging contract research agreements between outside firms and the two universities. Bioscot also develops monoclonal antibodies for diagnostic tests that detect various blood proteins, such as those involved in clotting and in blood typing.

Bioscot began its monoclonal antibody evaluation service, says Haddock, because many small- and medium-sized antibody producing and purchasing companies "don't have the all-encompassing facilities and expertise that we have because of our association with the universities". The service will assess an antibody produced by a university or company and will be offered to chemical, pharmaceutical or other type of antibody-purchasing company. Bioscot will also assess antibodies for financial institutions considering investing in a monoclonal-antibody-producing company or for universities that are researching antibodies.

Bioscot's sale to Fermentech of the manufacturing rights for a continuous fermentation process for the production of Protein A by a bacterium of the genus Staphylococcus, should reduce the price of the protein from $30,000/gramme to $3,000/gramme. Presently, Protein A is produced by an expensive, batch method that results in a retail price that makes the

protein prohibitive for all but research use. Protein A's value is that it binds to a monoclonal and can be used in the purification of low-molecular-weight antigens. (Extracted from Chemical Week, 10 October 1984)

Museum begins collecting biotechnology artifacts

The medical sciences division of the National Museum of American History of the Smithsonian Institution in Washington has begun to collect three-dimensional artifacts of genetic engineering. The first donation accepted specifically for the collection was the prototype of the Vega model 280 DNA synthesizer, the first commercial "gene machine"

One of the biggest problems in starting such a collection is space. Many items in the field are very large, and there has been a delay in the expansion of storage facilities that are planned for the Smithsonian. Another problem is the decision as to what is important. Historical importance is a prime concern. The museum would prefer to have an item that was used by a recognized leader in the field, rather than just the piece of equipment. It is hoped scientists will donate some of their personal equipment that have historical significance. One long term plan is to mount a biotechnology exhibit at the Smithsonian, which could later travel within the country and to Europe and Japan. The purpose of this exhibit would be to educate the public. Scientists in this speciality have shown a great deal of social responsibility. An example is the two-year moratorium researchers imposed on themselves on certain experiments with recombinant DNA while guidelines and containment procedures were drawn up. This is the only time when the worldwide community of scientists has agreed to take such an action. What was unique about the incident was that this action was initiated by the scientists, not the government. (Extracted from Genetic Engineering News, October 1984)

BNF Resource Centre in South East Asia - a reality

In May 1983 Jake Halliday, NifTAL director and Yookti Sarikaphuti signed a memorandum of understanding establishing a BNF resource centre for the Southeast Asia region ... The Centre's first project was to host a BNF (Biological Nitrogen Fixation) Resource Centre Planning Workshop in Bangkok, Thailand, where a workplan for the Centre's activities for the next three years was worked out. The Southeast Asia Resource Center is the first of three such centres proposed for Asia, Africa, and Latin America. The scope of the work will not be limited to Rhizobium symbiosis, but will include the various forms of nitrogen fixation utilizable in farming systems in the tropics ... Persons interested in the Southeast Asia Center should contact Dr. Douglas Beck, Rhizobium Building, Soil Microbiology Dept, Div of Soil Science, Dept of Agriculture, Phaholyothin Rd., Bangkhen, Bangkok 10900 Thailand. (Source: MIRCENET Newsletter)

Cairo-MIRCEN Culture Collection Services

In general, all strains of technological, scientific and educational importance in the region can be deposited at the Cairo MIRCEN. Scientists wishing to deposit a strain should give as much information as possible regarding the culture on accession forms available from the Cairo MIRCEN. Two cultures should be sent for each strain deposit. A CAIM number is assigned after receipt of both cultures and the accompanying completed accession form. Cultures accepted for deposit are checked for viability, purity and authenticity. They are normally maintained lyophilized or in gelatine discs. Cultures of newly deposited strains are usually not distributed until the identity of the preserved CAIM subculture is confirmed by the depositor.

The Cairo MIRCEN also accepts deposit cultures which are the subject of patent applications. Detailed information may be obtained from Cairo MIRCEN.

Cultures are supplied by the Cairo MIRCEN to research and industrial laboratories and to educational establishments in the region. Requests from private individuals are not encouraged.

The MIRCEN, when possible, performs the identification of bacterial strains. Only pure cultures are accepted and any information about the strains is welcome.

Cairo MIRCEN also undertakes the freeze-drying of small numbers of cultures for laboratories which do not have such facilities.

When data are published on Cairo MIRCEN strains, it would be appreciated if the CAIM number is cited and Cairo MIRCEN is acknowledged as the source. (Source: MIRCEN News No. 5, May 1983)

Nairobi-MIRCEN research activities

The Nairobi based MIRCEN acts as a regional focus for the better exploitation of microorganisms for food production, biotechnology and environmental management. Special emphasis is given to symbiotic nitrogen fixation by Rhizobium. In East Africa the main form of protein available to the general population is plant protein. As nitrogen is the most common limiting plant nutrient in this region, biological nitrogen fixation plays an important role - particularly where subsistence farmers do not use chemical fertilizers.

The objectives of the Nairobi Rhizobium MIRCEN are:

1. to determine the needs for innoculating legumes;
2. to collect, identify, maintain and distribute cultures of Rhizobium to users within the region;
3. to find suitable innoculant carriers and to produce innoculant in bulk for distribution within the region;
4. to assess the fate of Rhizobia introduced into the natural soils;
5. to evaluate new legumes for nodulation and nitrogen fixation;
6. to train manpower required to sustain the work in the region;
7. to disseminate research findings and information on innoculant technology to extension workers and researchers.

Research activities: Some of the projects initiated by the Nairobi MIRCEN are: (1) photosynthetic capacities constraining nitrogen fixation in monocultures of local legumes intercropped with maize; (2) Evaluation of locally available carbon sources for mass culturing of Rhizobium; (3) Evaluation of different methods for storage of cultures; (4) Survey of non-symbiotic nitrogen-fixing organisms in some Kenyan soils; (5) Evaluation of different local materials as carriers for Rhizobium innoculants; (6) Agronomic evaluation of different lines of beans (Phaseolus vulgaris); (7) Testing of Rhizobium strains for use in different soils; (8) Evaluation of the effects of various soil amendments, innoculation and pelleting on the growth, nodulation and nitrogen content of beans; (9) Agronomic evaluation of cowpea varieties in various ecological zones of Kenya; (10) Study of the black wattle (a tree legume) with the aim of exploiting its nitrogen-fixing potential. (Source: MIRCENET Newsletter)

Biotechnology education report

Mary Ann Liebert Publishers' Inc. recently received a letter from a reader who requested information about possible sources of research, fellowsnips, training and other sponsored programme support for students and faculty. There are probably a fair number of readers who would like to have access to the same information. On the other hand, those who are aware of such sources are understandably reluctant to relinquish such information. One would hope that there are some people who might like to open some doors for the education and training of aspiring students of biotechnology. If you are aware of any existing programmes, or desire to announce new ventures in support of biotechnology education, please inform Mary Ann Liebert Publishers, about them. Address: 157 East 86th Street, New York, N.Y. 10028. They will be happy to include announcements of these sources in their newsletter.

The Worcester Polytechnic Institute of Massachusetts, USA announced that the Department of Biology and Biotechnology had undergone some revision. The undergraduate degree programme in biotechnology emphasizes the fundamentals of modern biology supplemented with additional work in an area relevant to some aspect of the biotechnology industry. An example described students receiving training in computer applications, chemical engineering, or industrial management. A student can take a course in recombinant DNA methodology at the end of his or her junior year. The degrees in biology and biotechnology require an independent research project by the student. The M.S. programmes also emphasize research training, with all students completing an original research project. The M.S. biotechnology degree includes a substantial component of work outside the department. WPI also participates in a Ph.D. programme in Biomedical Sciences with Clark University, the University of Massachusetts Medical School, and the Worcester Foundation for Experimental Biology.

There are currently eight faculty members in the Department of Biology and Biotechnology, which also houses four teaching laboratories and five research laboratories. These include space set aside for molecular biology, cell and molecular biology,

microbiology, aquatic microbiology and a preparatory area. Work has commenced on renovation of space to provide research laboratories and support facilities for three new faculty members.

For more information on the programmes at WPI, contact Dr. Bagshaw in Worcester, MA 01609; telephone (617) 796-5000;

The University of Pittsburgh's Department of Biological Sciences offers graduate programmes in Genetic, Cellular, Developmental, and Neurobiology, leading to the Ph.D. and M.S. degrees.

Areas of research listed are: DNA cloning and sequencing, control of mRNA synthesis and translation, molecular biology of gene regulation, cytodifferentiation and morphogenesis, bacteriophage assembly, and genetic dissection of oncogenesis.

The Department of Biology of New York University has developed a course of study to train biologists in recombinant DNA technology. The department is now accepting applications for a Master of Science degree in biology with thorough training in the theory and application of DNA technology. The programme is built around a laboratory course providing students with hands-on experience in all aspects of recombinant DNA technology. This includes experience in cDNA and gene cloning as well as the characterization and manipulation of cloned sequences. Students also pursue projects of specific interest to them which may include construction of special purpose genes or vectors, use of DNA mediated gene transfer, the production of monoclonal antibodies, or virtually any other application of modern recombinant DNA techniques. Courses included in the programme are Biochemistry, Genetics, Molecular Biology, Developmental Biology, Virology and Cell Biology. The programme is designed to meet the needs of students entering with diverse backgrounds, including those with little or no recombinant DNA experience.

The Department of Biology at the University of South Carolina (Colombia Campus) offers graduate programmes in Genetics, Developmental and Molecular Biology. Research emphasis is placed on fundamental problems of biological regulation and development at the cellular and molecular levels. Members of the department interact with other faculties in the Department of Microbiology and Immunology (School of Medicine), and in the Department of Chemistry.

The Center for Genetics at the University of Illinois, Chicago, in conjunction with the Department of Microbiology and Immunology and the Department of Biological Chemistry, offers programmes of study leading to the Ph.D. degree. Current programmes are in areas of mammalian somatic cell genetics and cytogenetics, gene transfer and expression, recombinant DNA, DNA sequencing, mechanisms of mutagenesis, tumor biology and cancer genes, nucleotide me abolism and gene structure, function and regulation. Advanced courses are taken in the second year following the successful completion of written preliminary exams. The students are involved primarily in research in the third year. The dissertation is usually completed at the end of the fourth or fifth year.

The University of Maryland Baltimore County offers a M.S. Degree Programme in Applied Molecular Biology with emphasis in Recombinant DNA Technology. This curriculum is offered jointly by the Departments of Chemistry and Biological Sciences, and complements the existing M.S. and Ph.D. programmes currently administered by the respective departments. The course of study has been developed in close collaboration with several biotechnology companies in the Baltimore-Washington-Frederick area.

Two routes to the M.S. degree in Applied Molecular Biology are available: a 2-year graduate programme in which baccalaureate graduates of other institutions may enroll, and a 5-year combined B.A.-M.S. programme. For the latter programme, formal acceptance of upper-level undergraduates (at UMBC or elsewhere) into the AMB Programme will be at the fourth year level. Applicants must have completed the following courses, or their equivalents, prior to enrolment in the programme: general chemistry (2 semesters); organic chemistry (2 semesters); genetics (1 semester); cell biology (1 semester); physics (2 semesters); calculus (1 semester). (Extracted from Biotechnology Education Report, Vol.2, No. 3)

B. COUNTRY NEWS

Bulgaria

Bulgaria's growing interest in biotechnology

The importance of enzyme preparations has increased sharply after mastering the technology of immobilized (linked, fixed) enzymes and the methods of genetic engineering. The achievements in these two areas have predetermined, to a great extent, the rapid

development of engineering enzymology and the successes of fine microbiological syntheses of amino acids, vitamins, nucleo-amino acids, and others. The Medical Chemistry Combine in Botevgrad plans to implement basic enzyme preparations which are being produced around the world. The following enzymes are produced: simple and thermostable alphaamilase, glucoamilase, and glucoisomerase. The needs for the alkali proteose enzyme have increased in the chemical industry for home use. With the present production of four enzymes, by 1986 it is anticipated their number will increase to 11, and by 1998, to 21. In this respect, the amount of enzyme production will increase 4.5 times by 1990, 6 times by 1995, and 10 times by the year 2000, on the basis of a significant expansion in existing production capacities. Real possibilities for exporting part of the production will be created by 1985, and by 1990 the export (expressed in value) will increase 1,015 times, by 1995 12.6 times, and by 2000 16.3 times, compared to 1984. Bulgaria could specialize in the production of the alkali proteose enzyme, pectinase, glucoamilase and glucooxydase in order to satisfy the needs of the member countries of the Council for Mutual Economic Assistance. In connection with the complete satisfaction of the country's needs for enzyme preparations, an expansion of the existing fermenting capacities at the Medical Chemistry Combine in Botevgrad is being planned.

The tremendous development of biotechnologies during the last 10 years, and more specifically the development of bioengineering, has made it possible to realize the dream of a qualitatively new stage in industrializing food production. Due to a shortage of traditional raw materials during the last few years, synthetic raw materials for the biosynthesis of proteins have been used more and more successfully. Among the synthetic raw materials, methanol is the most important, being the least expensive, water soluble, and the best mass production raw material.

The average annual shortage of raw protein (100 per cent) during the Seventh 5-Year Plan amounted to 190,000 tons of livestock per year in our country alone; and it is expected to reach 240,000 tons per year during the Eighth 5-Year Plan. All this requires accelerated work on the biosynthesis of proteins in Bulgaria. In compliance with the National Co-ordinating Programme for Proteins, the Central Institute for Chemical Industry and its co-executive units within the system of the National Agro-industrial Union, the Ministry of Public Health and the Bulgarian Academy of Sciences have conducted the basic technological and biomedical studies on the biosynthesis of proteins. Under the conditions of the experimental installation at the Medical Chemistry Combine in Botevgrad, over 50 tons of produce, destined for detailed tests, have been produced.

The technology for the biosynthesis of proteins based on methanol, developed by the collective at the Central Institute for Chemical Industry, is competitive with all the indices of the leading firms such as ICI and Hoechst, thanks to the successful combination of methanol-oxidizing and methanol-nonoxidizing micro-organisms. Bilateral co-operation with the Soviet Union has been established, so that one can foresee the development of design apparatus processes designed by the USSR and biotechnological supply by the Bulgarian People's Republic. During 1984, an experimental installation for biosynthesis of proteins based on methanol, with a 32-cubic metre fermenter, will be built at the Medical Chemistry Combine in Stara Zagora. Other prototypes of Soviet and Bulgarian fermenters will also be tested here.

On the basis of the accumulated experience, the creation of industrial installations for the biosynthesis of proteins based on methanol will also begin. In order to satisfy more completely the needs for industrial single-cell protein (SCP), about 100,000 tons per year will be required. Building such a capacity could be carried out gradually by consecutive construction of production lines, the first of which could be for 25,000 tons per year, and the next for 40-50 tons per year. (Extracted from Khimiya i Industriya, No. 5, 1984)

Canada

Fuel for sugar waste

A Canadian process for making fuel from the waste products of sugar production will be used in a $4-million demonstration plant in Brazil. The process was developed by Professor Laszlo Paszner of the University of British Columbia's forestry department. Bagasse, the woody waste remaining after sugar juice is extraced from cane, is cooked in a solvent at a high pressure in the process. In less than five minutes, the wood is dissolved. After the solvent is extracted for reuse, the sugars are precipitated out and processed into ethanol. In production, a plant using the process could convert 300 tonnes of bagasse a day and make 50 million litres of ethanol a year. (Source: Canada Weekly, 17 October 1984)

China

Bioengineers need to advance skills

China has made some headway in bioengineering, which now yields about one per cent of the GNP. The varieties of biological products now amount to more than 100, including 70 kinds of antibiotics. Output of amino acid has reached 50,000 tons annually. Production of enzymes, biological catalysts, has also expanded. More than 40 factories have been built since 1970 to turn out 30 varieties of enzymes for the textile, sugar refining, tanning, medical and detergent industries.

Since 1976, China has given priority in scientific research to genetics. Beijing and Shanghai have succeeded in the cultivation of new vaccines of interferon and insulin. China's techniques in antheral cultivation and monoploid seed breeding are up to world standards. In application, China has evolved high-yielding and disease-resistant strains of tobacco, rice, wheat, corn, sugar cane, flowers and trees. A newly developed vaccine has raised the productivity of penicillin by 60 per cent. In addition, microbes have been applied in the control of crop diseases, treatment of sewage and production of energy and metals.

Compared to industrialized countries, China's biological production consumes more energy and grain with less output. For example, one ton of yeast processed in China requires 5-6 tons of molasses and 2,000 kwh of electricity, more than the four tons of molasses and 1,000 kwh required in other countries. Productivity of some MSG factories here is just a few per cent of what Japanese enterprises turn out. While computer control of fermentation is quite common abroad, it is rarely practised in China.

The new interferon, insulin, animal somatotropin (growth hormone) vaccines are already being produced in some developed countries, but most of them are still in experimental stages in China. Only one kind of amino acid is being produced in China, but 18 kinds are produced abroad.

To catch up with developed countries in bioengineering, China should give priority to the following: personnel training; creating research centres; stressing the development of applied technology; stressing its application in agriculture. (Extracted from China Daily, 16 June 1984)

Joint venture agreement

Interferon Sciences (New Brunswick, NJ) and Fudan University (Shanghai, China) have signed a joint genetic engineering R&D agreement aimed at developing high-yield, high-nutritional strains of rice, other cereal crops, and beans. The project calls for scientists from ISI and from Fudan University's Genetics Institute to co-operate in the development of artificial cloning systems through recombinant DNA techniques. Interferon Sciences will have exclusive commercial rights, subject to certain royalty obligations, in North and South America, Europe, Japan, Australia, New Zealand, Israel, and S. Africa to products and technologies developed under the joint programme. Visiting scientists from Fudan University will work at the ISI laboratories in New Brunswick, while ISI will contribute funds, equipment, and supplies to support the programme in China. (Source: News release by Interferon Sciences Inc., 24 July 1978)

France

Status of biotechnology

Government circles seize every opportunity to re-assert the priority status given to biotechnologies and new initiatives are in fact under way. Rhône-Poulenc, the number one French firm in bio-industry with 10,000 cubic metres of fermentation capacity and Fr 3 billion of turnover in products of biological origin, is entering the seed industry in association with the American firm Seedtec International of the Kay Corp. petroleum group, which had a $600 million turnover in 1982. The two partners will establish a research firm specializing in sunflower improvement. Also in the seed field, the National Institute for Agronomic Research (INRA) announces the creation of its first affiliate, Agriobtentions. Its mission is to commercialize the plant genetic material perfected by the institute. The Lafarge-Coppee group, for its part, is preparing to invest Fr 250 million to strengthen the positions of its affiliates Orsan (first European producer of sodium glutamate) and Eurolysine (number one European lysine producer) in the amino acids sector.

In the energy field the Association for Development of Fuels by Fermentation (Ascaf), consisting of the French Energy Control Agency (AFME) and the French Petroleum Institute (IFP), has just now finally decided to launch its pilot project to produce an acetone-butanol

mixture (ABE) by means of biotechnology. The method used is enzymatic hydrolysis of lignocellulose substrates such as straw and corncobs. ABE is a "tertiary solvent" indispensable for adding methanol or ethanol to automobile gasoline. An experimental unit, representing an investment of Fr 150 million financed with public-sector assistance, will be set up at Soustons in the Landes. It will be built by Technip, and is planned to enter service in late 1986.

These initiatives - coming after such others as the creation of Transgene, Biosys and Germe, and the entry of the petroleum firm Elf-Aquitaine into the seed sector and of Moet-Hennessy into horticulture - are proof that since the publication in late 1979 of the report "Life Sciences and Society" by MM Gros, Royer and Jacob, France is in the biotechnological race.

Formerly limited essentially to such food products as wine, beer, and cheese, biotechnologies will henceforth intervene in multiple sectors including pharmaceuticals, chemistry, energy, plastics, and environmental management - in varying degrees, to be sure, and at times to a very small extent. But diffusion of biotechnologies through the industrial fabric is only just beginning.

By way of comparison with electronics, who could have imagined in 1971, when Intel launched its first microprocessor, that the electronics market would experience such an explosion? For bio-industries the forecasts indicate a strong growth of the world market. It should at least double in 1980-90 to reach $30 to $40 billion. Some forecasting institutes even advance the figure of $100 billion by 2000. So the stakes are considerable. (Extracted from l'usine Nouvelle, 23 February 1984)

France concludes biotechnology agreements with Taiwan and China

The Institut Pasteur Production (Pasteur Institute) is to supply the Taiwanese Ministry of Health with serum genetically engineered against the hepatitis B virus (Hevac B Pasteur). This agreement is of enormous importance to Taiwan where approximately 90 per cent of the 18 million Taiwanese are afflicted with hepatitis. A plant which has yet to be built is supposed to begin producing the serum in Taiwan in 1986. In addition, both countries had agreed on close co-operation in the field of genetic engineering. A delegation from the Chinese national Committee for Science and Technology also recently visited the Pasteur Institute and a research agreement with China has been concluded. (Extracted from Europa Chemie, 16 April 1984)

France 'too timid' on biotechnology

The major conclusions of a new study by the Paris-based publishing and consultants group, Biofutur, state that French industry has been "too timid" in its approach to biotechnology. As a result (in spite of the mobilization programme launched by the research and industry minister, Jean-Pierre Chevènement, two years ago with the aim of securing France a 10 per cent slice of the world biotech pie within the same number of years), the country is now well behind the US, UK, Israel and Australia in this area. The study further states that Rhône-Poulenc Santé, Sanofi and Roussel-Uclaf, the only French drug concerns with any significant biotech activities, are faced with 30 competitors worldwide while French agricultural and food companies are faced with a greater threat.

France's lack of new specialist biotechnology companies is blamed on the lack of the right environment. French venture capital pools have been investing mainly in the US owing to the lack of interest in domestic projects.

The study, Biotechnologies en France, is available from Biofutur, 56, Rue de l'Université, 75007 Paris. (Extracted from European Chemical News, 29 October 1984)

Hungary

Central development programme on biotechnology

Research in biotechnology has become one of the central development programmes of the Hungarian National Medium-Term Research and Development Plan. Implementation is being co-ordinated by the OMFB (National Technical Development Committee) chiefly through the Office of Protein and Biotechnology. The programme is intended to expedite application of research findings so that they can be put to use within 4-5 years. The areas included in the programme are primarily ones on which specialists have been working for a number of years but for whose application the necessary support background must be established. Once the projects in the programme are successfully completed, the end products are expected to realize $60-80 million for Hungary either in exports or savings on imports, depending on how

much money is available for the necessary investments. The OMFB is supporting the programme with 140 million forints. The enterprises and ministries will spend double this amount on biotechnology R&D in 1984-1985. However, this will only suffice for the development of products ready for manufacture. The enterprises must use their development funds or bank credits to finance investments which will establish production prerequisites.

To economize on the need for hard currency, the programme supports not only product-oriented research but domestic development of facilities and equipment needed for production. Hungary will make no attempt to invest in the costly, high-speed centrifuges needed for cell separation. On the other hand, Hungarian industry can easily make the special apparatus, containers and fermenting equipment required in production of pharmaceuticals. At present, there are hardly any specialists who have the theoretical background in genetics, microbiology, biochemistry and the techniques used in genetic engineering. Representatives of the various disciplines find it hard to communicate and co-operate because of their diverse training. As a temporary solution, biologists are being taught certain engineering techniques while education in biological genetic engineering is being promoted at the technical university. (Extracted from OTLET, 22 March 1984)

Ireland

Development of biotechnology industry

Development of the biotechnology industry in Ireland is to be encouraged by the new National Biotechnology Co-ordinating Committee, set up by the Industrial Development Authority and the National Board for Science and Technology to develop its biotechnology industry. The NBCC is to identify resources and opportunities, promote awareness of biotechnology's potential and stimulate research, particularly in Ireland's universities. Ireland is established in brewing, distilling and dairying - traditional biotechnology - and the IDA has already promoted the pharmaceutical sector, making Ireland the tenth largest exporter of these products in the world. (Source: Chemistry and Industry, 6 August 1984)

Israel

Enzyme isolated that synthesizes cellulose molecule

Researchers at the Hebrew University have isolated an enzyme that efficiently synthesizes the cellulose molecule. Biochemists up until now have had little success in finding a plant enzyme that will join glucose units together to make cellulose, probably because the enzyme complex is so large that during its extraction from plant tissue, it is easily damaged. The Hebrew University's team first homogenized the plant tissue in polyethylene glycol, then centrifuged its membranes at a very low g value. The membranes were only completely active if calcium, magnesium and cellobiose were added, together with the substrate uridine diphosphate glucose. The membranes' cellulose synthetase was fifty times more active under these conditions than in any other system. (Source: New Scientist, 3 May 1984)

Growing biotechnology industry

Israel's growing biotechnology industry provides an outlet for one of the largest scientific communities in the world without a large industrial infrastructure, according to a report by the US Office of Technology Assessment. Currently, over 1,000 companies employ over 1,000 people, backed by over 3,000 researchers working in the field of life sciences at universities and research institutions. The top firms, InterPharm Labs, Bio-Yeda and Bio-Technology General, are located 12 miles south of Tel Aviv, the home of the Weizmann Institute of Sciences and Hebrew University's faculty of agriculture. InterPharm is genetically engineering beta-interferon from mammalian cells, versus bacterial cells used by most other firms, and is scaling up for industrial production and clinical testing. Bio-Yeda produces antibodies, immuno-chemicals and reagents for biochemical and clinical laboratories, and will develop complete diagnostic and analytical kits in the future. Bio-Technology General supplies growth hormones, and is forming an agricultural subsidiary to work on Trichoderma, a fungus that attacks other fungi; Azospirillum brasileans, a bacterial biofertilizer that fixes nitrogen, and microinsecticides. Biotechnology General started out working with agricultural and veterinary compounds, and has not emphasized popular genetically engineered products such as human interferon. It concentrates on genetically engineered bacteria that stimulate plant growth, increase milk production in cows, or attack destructive fungi, bacteria and insects. It reached a $750,000 leasing agreement with American Cynamid for field testing of its Bovine Growth Hormone earlier in 1984, and hopes to commercialize the product by 1986. The company is also working on a human growth hormone, and an enzyme for treating heart disease. It has produced a bacteria that secretes hyaluronic acid, which is used in eye surgery and for facial creams and moisturizers, at one

eighth of the cost of a similar product from Pharmacia (Sweden). Pharmaceutical-grade hyaluronic acid sells for $8 million per kilo. The substance is found in minute quantities in the rooster's comb. (Source: Chemical Week, 6 June 1984 and New York Times, 12 August 1984)

Japan

Electrolysis system for efficient reduction of co-enzyme developed

The Fermentation Research of MITI's Agency of Industrial Science and Technology developed an electrolysis technique for efficient reduction of NAD (nicotine [nicotinamide] adenine dinucleotide), a co-enzyme present in large quantities in the liver, etc. which aids enzymatic functions. The technique uses a glass-like carbon material for electrodes in electrolkysis. The above institute anticipates it to be useful in recovering or the reutilization of co-enzymes used for new bioreactors, etc. that manufacture new foods by the catalytic reaction of enzymes.

The method developed by the Fermentation Research Institute involves electrolysis designed to regenerate NADH from NAD by using the reaction of oxalacetic acid conversion to L-malic acid. In this method, oxalacetic acid and NAD as well as an enzyme, diaphorase, and a reaction medium, methyl viologen, were placed as a solution in an electrolytic cell using a carbon material as the anode. As a result of this electrolysis, they say they were able to confirm that malic acid is produced at over 76 per cent electrolytic efficiency. The enzyme, diaphorase, used in this electrolytic reaction is extracted from pigs' hearts and is characterized by low cost and stable action. In addition, NADH regeneration from NAD is fairly strong in this reaction, and the outlook is that in the near future, its reaction will be raised to about the same level as that resulting from use of formic acid. (Extracted from Nikkei Sangyo Shimbun, 15 December 1983)

Institute of Physical and Chemical Research starts microbe bank

The Institute of Physical and Chemical Research (located in Hirosawa, Wako, Saitama Prefecture; director, Ryuko Miyajima) has opened a "microbe bank" which will preserve in genealogical order various micro-organisms required in genetic-splicing experiments, in the manufacture of new antibiotics and in the fermentation industry, and will supply these organisms according to the needs of researchers. In the past many useful bacteria stocks were destroyed due to the lack of adequate storage facilities. Important bacteria stocks will henceforth be preserved permanently at the bank. In 1980, a two-storey facility occupying about 1,500 square metres was built within the Institute of Physical and Chemical Research. Collection of micro-organisms began two years ago; so far it has about 3,000 stocks preserved in liquid nitrogen at 196°C below zero. Beginning in April, about 610 categorized stocks will be supplied to researchers. The ice containing the desired bacteria is vacuum-dried and placed in a capsule 5 mm in diameter and 5 cm long for distribution at 6,000 yen a stock. The recipient breaks the capsule and adds water and nutrients to the powdered stock to revive the "hibernating" bacteria. (Extracted from Asahi Shimbun, 4 January 1984)

Electrophoresis equipment

The electrophoresis system produced by the company of Takara Shuzo, the model "TAKARA-VE1", is for experimental use to separate the base components of DNA using high potential differences and determine the DNA structure by the base sequential arrangement. Compared with previous mainly imported electrophoresis equipment, its features include a price of approximately half of its counterparts; as high voltage is used, electrophoresis is completed in a short time; it is simple to operate and allows easier viewing of the display of base arrangement bands showing experimental results, etc. Currently, the domestic market is said to be around 1,000 units per year, which is expected to expand rapidly as research in genetic engineering progresses in the future. (Extracted from Nikkei Sangyo Shimbun, 6 January 1984)

Automatic DNA Synthesizer

As a result of a three-year effort, two companies, Shimadzu Seisakusho Ltd. and Wakunaga Seiyaku, announced they jointly developed the first fully automatic DNA synthesizer system developed in Japan which they plan to market.

Four kinds of bases, A (adenine), G (guanine), C (cytosine), and T (thymine) are arranged in various sequences in DNA. This system synthesizes a prescribed DNA having

10-40 bases by automatically repeating the synthesis process when an operator inputs the required DNA sequence using a microcomputer, then sets the resin and nucleic acid reagents for the reaction vessel and the turntable respectively, and turns on the switch for starting.

Main special features are that (1) the pretreatment of nucleic acid reagents is unnecessary, (2) being the world's first equipment in which even dimers of two different reagents combined can be automatically condensed, the synthesis time is shortened, (3) reaction monitoring is possible by automatic measurement and calculation of reaction yields by a built-in spectrophotometer, etc. In its development, Shimadzu Seisakusho was responsible for the hardware, and Wakunaga Seiyaku, the software for chemical synthesis, respectively. (Extracted from Nikkei Sangyo Shimbun, 13 January 1984)

Some recent joint ventures

Denmark's international enzyme manufacturer, Novo Industrie (Copenhagen), and Hayashibara have begun a co-operative business venture. The subject of the co-operation was the assignment to Novo of Hayashibara's patented method of manufacture of starch chain cutting enzymes. It is expected that Novo will make a full-scale move into the Japanese market in this field.

Branch cutting enzymes cut the branched parts (1, 6 bonds) of starch, which largely consists of glucose molecules bonded together, to produce the straight-chain form. In starch enzymes, which decompose starch and produce isomerized sugars, etc., this is a decisive factor for their relative merits. Recently they have been used to raise the purity of isomerized sugars contained in soft drinks.

The Canadian biotechnology enterprise, Institut Armand Frappier, of Montreal, and Mitsui Drug Manufacturing have joined in an agreement for co-operative development and commercialization of applied-technology pharmaceuticals. Frappier is an enterprise possessing a unique structure uniting a research institute and a production and marketing company; it produces and sells pharmaceuticals for microbiological diagnostic testing, vaccines, etc.

Special co-operative research projects have been set up by both companies, and apart from exchange of information, research is furthered by an interchange of researchers.

Roche and Takeda Pharmaceutical Industries began co-operative clinical trials in 1983 of gamma-interferon (virus growth-inhibiting factor), mass-produced by E. Coli genetic recombination. Large-scale clinical trials and co-operative research were carried out on each kind of cancer and on virus diseases such as hepatitis B. The Green Cross Corporation, Kyowa Fermentation, Suntory and others are continuously making rapid arrangements with the Roche-Takeda group for clinical trials, and competition in gamma-interferon development is being increasingly encountered.

For the clinical trials, a gamma-interferon research unit led by Professor Tetsuo Taguchi of the Osaka University Institute of Microbiological Disease Research is to be set up. Effectiveness and safety are to be confirmed against eight kinds of cancer, including stomach cancer, skin cancer, brain tumors, breast cancer, lung cancer, and three kinds of of virus diseases including hepatitis B and viral eye diseases. The trials are planned for two years. The phase-2 stage, to assess efficacy in the whole country, will be a large-scale operation in more than 100 institutes and hospitals.

Both Roche and Takeda have met the standards of the Ministry of Health and Welfare's "Integrated Research Unit for Clinical Assessment of Interferon" for the refining purity, etc., of the gamma form. Roche is to produce the gamma form in quantity in the Kamakura, Kanagawa Prefecture research laboratory in large, 300-litre culture tanks used for alpha-interferon. (Extracted from Nikkei Sangyo Shimbun, 9 January 1984, 2 February 1984 and 16 April 1984)

C. Itoh & Co. has entered into the seed business through technical co-operation on matters related to feed crop seeds with Denmark's major seed firm, Denfelt (Odense), and its subsidiary, Denfelt USA (Oregon). C. Itoh will develop new varieties of seed suitable to the Japanese climate at an experimental farm in the USA and will sell seeds in Japan through related firms. Moreover, C. Itoh and Denfelt are expected to form a joint corporation specializing in seed-related technologies to develop new varieties through the application of biotechnology for distribution in South East Asia.

Denfelt has considerable experience in developing various types of seeds, including feed crops, vegetables and flowers, and is one of the leading European enterprises in this field. With the help of Denfelt, C. Itoh aims to develop "all-weather seeds" through research carried out in the USA under similar Japanese climatic conditions, with emphasis on improving heat, moisture and disease resistance. (Extracted from Nikkei Sangyo Shimbun, 16 April 1984)

Biotechnology prospects in pulp and paper manufacture

It is likely that biotechnology will radically change the paper-pulp manufacturing process in 10 years. This is the analysis found in the "Report on the Utilization of Micro-organisms in the Pulp-paper Making Process" compiled by the Japan Machinery Industry Federation's Micro-organism Applied Research Association (chief examiner, Yoshiaki Fujii, managing director of Sumitomo Heavy Machinery Envirotech). The application of micro-organisms in the paper-pulp making process has been anticipated as trump card in the conservation of resources and energy. A comprehensive survey of this kind is a first and it would seem likely that this will spur the co-operative efforts of manufacturers and users to develop new equipment that applies biotechnology. (Extracted from Nikkei Sangyo Shimbun, 24 January 1984)

Research activities reported

Fujisawa Pharmaceutical Company Ltd. revealed that it successfully developed a human HLA monoclonal antibody used for tissue compatibility tests for organ transplants. The developed product is a human HLA-A2 monoclonal antibody for a type of HLA, a major tissue antigen in man. In the past, polyclonal (antiserum) HLA antibodies were used both at home and abroad. However, this is the first uniform and highly specific (high recognition accuracy) monoclonal antibody developed.

The company has also developed a monoclonal antibody "human IFN-alpha monoclonal antibody bound to sepharose" for the purification of cultured IFN-alpha and has begun marketing it in earnest. In the past, a British product was imported for sale, but this is the first domestic product to be marketed. IFN-Alpha has entered the time of full-scale cultivation on large and smallscales, and production as anticancer agents is scheduled in about one year. For now, the marketing focus is on industrial demand. At the same time, they developed the first domestic human IFN-alpha assay kit based on the enzyme-linked immunoassay (EIA) technique that can measure the amount of IFN-alpha contained in blood or various solutions, which they will begin marketing.

Fujisawa Pharmaceutical Company uncovered a new immune response regulator which restores the original state of immunity after it is lowered due to cancer, and at the same time, succeeded in its total synthesis. It is a type of alkaloid (a basic substance containing nitrogen) called "swainsonine". It was known previously as a substance, but it was totally unknown that it had an immunity restoring function. It is still in the animal experimental stage, but a marked immunity restoring effect has been confirmed and the company's laboratory contends, "there is no other substance for the moment that is as effective."

Immune response regulators (BRM=biological response modifiers) are fiercely sought after worldwide as new types of cancer therapeutics. According to a related source, the company has already begun collaborative research with a certain overseas firm, and future developments are being watched.

In 1979, an Australian scholar extracted swainsonine for the first time from legume forage. Having absolutely no knowledge of that fact, Fujisawa Pharmaceutical discovered a substance having immune response regulatory action from a fungus. This was swainsonine, and it reacts to increase the number of antibody producing spleen cells in a cancerous mouse up to a normal value in a short period of time.

The experiment consisted of injecting swainsonine for a total of five times, at a frequency of once a day at 3.3 mg per 1 kg weight to mice having spleen B cells reduced to about one-third of the normal level due to cancer. On the 12th day, the number of B cells were counted, which revealed a rapid recovery of cells to the normal level. There is no other substance that has such fast efficacy. Furthermore, one of the characteristics is that the B cells do not proliferate once a normal level was regained. When an immune response exceeds required levels, side effects such as an autoimmune disease develop. However, with this substance, there is little of that risk. (Extracted from Nihon Kogyo Shimbun, 2 February 1984, 3 February 1984 and 22 March 1984)

Patented Microbe Deposition Center to be expanded

The Patent Office and the Agency of Industrial Science and Technology will expand the Patented Microbe Deposition Center of the latter agency's Fermentation Research Laboratory, strengthening the base of the microbe deposition system of which the Center is the hub. Their purpose is to deal with patent applications which make use of microbes. With the rapid spread of genetic manipulation and of seed and seedling technology, such applications are more numerous each year. The nature of the new facilities is to be investigated and considered in 1984; the facilities will be completed by about 1986. (Extracted from Nikkei Sangyo Shimbun, 2 February 1984)

First experiment on alcohol fuel from biomass reported

The first experimental unit for the production of alcohol from biomass will be completed in Okinawa. The project was commissioned by the New Energy Development Organization (NEDO) to the Fuel Alcohol Development Technology Research Association. Unlike the conventional method of alcohol fermentation from yeast, this process uses bacteria giving a high yield. At this point, waste molasses from sugar cane will be used, but eventually the technology will be directed toward the production of alcohol from cellulosic material, including rice straw, rice hulls, and scrap wood, which are in abundance in Japan.

NEDO's fuel alcohol development plan has two parts: (1) the search for and cultivation of the most adaptable bacteria, and (2) the development of the fermentation process technology needed for utilizing these bacteria. The first stage in the fermentation process is the development of a new apparatus, which is the core of the fermentation process, and the use of bacteria-medium method. This uses the bacteria fixation technique, whereby the bacteria will not be discharged with the flow of the alcohol stream from the fermentation apparatus. The bacteria are loaded on a medium such as mica, and then a liquid starting material is continuously fed into the fermentation tank to produce alcohol continuously.

Wine or sake is produced batchwise and needs no bacteria media. In the production of fuel alcohol, the yield must be high enough to compete against gasoline, and the key to this is the continuous production of alcohol. NEDO will improve this technology.

The apparatus was constructed at the Nagoya Plant of Nippon Shipbuilding Co. Ltd. and will be installed in the suburbs of Naha, Okinawa. (Extracted from Nikkei Sangyo Shimbun, 8 February 1984)

National Institute of Genetics re-organized

The Ministry of Education reorganized the National Institute of Genetics into an organization for community use by national universities as of 1 April. Accordingly, the previous ten research departments will be organized into five systems, i.e., four research systems for molecular, cellular, individual and population studies, and a general genetics system that encompasses the above four. In the three research systems for molecular, cellular and population studies a visiting staff department will be established in order to invite outstanding researchers from both home and abroad and to advance collaborative research. (Extracted from Kagaku Kogyo Nippo, 15 February 1984)

Ministry of Agriculture establishes Office of Biotechnology

The Ministry of Agriculture, Forestry and Fisheries (MAFF) has established a "biotechnology office" in the bureau of the Agriculture, Forestry and Fisheries Research Council and has embarked in earnest on drafting overall policies and implementing measures related to biotechnology. In addition to making plans and regulating various measures and related budgets for the purpose of efficiently promoting the development of biotechnology, this office is also to play the role of a biotechnology "headquarters" belonging to the MAFF and will be in charge of a wide range of activities, including gathering, analyzing and disseminating relevant information, promoting international exchanges, conducting public relations, and negotiating and co-ordinating with other concerned ministries and agencies. It will be dealing with a variety of themes, including improving breeds, cultivating seedlings, and securing biological resources. There are great expectations for biotechnology, because it holds the key to the solutions of a number of problems such as food, energy, and the environment. (Extracted from Nihon Kogyo Shimbun, 9 May 1984)

Halved fertilized egg transplanted successfully

The split halves of a fertilized cow's egg have been successfully transplanted into two other cows, according to an announcement made by the Ministry of Agriculture. Foreign researchers have already transplanted cows' eggs, but the Japanese process is reportedly simpler. A young Holstein cow was given an ovulation-inducing drug, and sperm was introduced via artificial insemination. Five days after fertilization the egg was removed and split with a thin glass blade. Half of the egg retained its transparent membrane, but the splitting process removed the membrane from the other half. Researchers in the US, France and the United Kingdom usually wrap the naked half in a membrane from another egg before implanting it when making such experiments, but the Japanese have succeeded without taking this step. Sixty days after the transplant, an inspection of both cows showed that both twins were developing. (Source: Japan Economic Journal, 8 May 1984)

ATP protein separated and purified

A protein that plays a major role in the cell's production of adenosine triphosphate (ATP) has been separated and purified by researchers at Tokushima University. The protein, named 'chargelin' by its discoverers, is thought to convert food energy into a form that can be utilized by the body. Chargelin is abundant in the mitochondria membrane and ordinarily resembles any other protein, but when an electrical field is formed around the membrane the protein polarizes into a minus end outside the membrane and a plus inside it. Chargelin converts electrical energy into chemical energy, stores it, and turns it over to the ATP during the last stage of ATP synthesis. ATP is the source of energy for all life forms. (Source: Japan Economic Journal, 15 May 1984)

Government promotes co-operation on cell fusion technology

The Japanese Government is promoting co-operation between the public and private sectors in the development of cell fusion technology. The Ministry of Agriculture has set up an Agricultural, Forestry & Fishing Technology Information Association with 14 companies divided into three groups. One group including Meiji Milk Products and Kubota, will develop cell fusion for lactic acid bacteria. Another, including Kirin Brewery and Mitsui Toatsu Chemicals, will develop hybrid vegetables. The third group, led by Asahi Chemical Industry and Hitachi, will develop new strains of rice and soybeans. The Ministry's five-year project will cost Y49 billion in its first year, with the Government providing 50 per cent. It believes that co-operation between different groups with similar goals will become increasingly necessary if Japan is to stay ahead in the biotechnology race. (Source: Japan Economic Journal, 17 July 1984)

Spain

Biotechnology centre

The Spanish Government is to set up a National Centre for Genetic Engineering and Biotechnology in Madrid.

The idea arose last year before the Madrid meeting of the committee of the United Nations Industrial Development Organization (UNIDO) on the foundation and location of an international biotechnology centre. Officials from different ministries agreed to contribute funds from their respective budgets to support Spain's candidacy, but when the UNIDO committee decided to locate the international centre in India and Italy, the commitment of the Spanish authorities to create a biotechnology centre in Madrid persisted. A committee including government officials, industrialists and scientists has been at work for the past year, and a planning document has been approved and released. The committee has also approved the creation of a Centre for Microelectronics, to be split between Barcelona and Madrid.

The National Centre for Genetic Engineering and Biotechnology will have a staff of 220-260, including about 40 scientists. The initial group of scientists will come from laboratories already working in related areas, mainly in institutes of the Consejo Superior de Investigaciones Cientificas (CSIC, the Spanish science research council). Because of the lack of experience in some of the fields covered, other scientists will be recruited from elsewhere. It is likely that this and related projects will absorb many of the new positions to be created in CSIC. The lines of research to be followed at the new centre will include molecular genetics, immunology, plant molecular biology, biochemical engineering and industrial microbiology. The total cost of the project is estimated at about 3,000 million pesetas (US$20 million) over the next three years. (Extracted from Nature, 16 August 1984)

Sweden

Company started to develop carbohydrate technology

The concept of the specificity of carbohydrates, which the layman finds rather meaningless, not to say incomprehensible, is the very foundation of the recently established research and development company known as BioCarb, a firm that was started by four researchers and is financed by two private individuals. In co-operation with partners in industry, it is going to manufacture products involving carbohydrate technology. What the research demonstrated was that cells in mucous membranes, for example, have small "arms" - receptors - that trap various substances. The substances may be produced by the body itself - hormones, for example. Those receptors are carbohydrates, and they are very specific - they trap exactly the "right" substances.

This means, for example, that it would be possible to use carbohydrate technology to get at a specific bacterium. As it is now, one often knocks out all the bacterial flora to get at a single bacterium. Carbohydrates can also act as anti-biotics. Since the bacteria are trapped on the receptors, the concentration is reduced and the body's own defenses can do the rest. For example, piglet diarrhoea, a disease that attacks baby pigs, could be cured by adding certain carbohydrates to the animal's feed. The receptors can be used, for example, to diagnose infectious diseases or cancer. Inversely, they can be used to supply the desired bacterial flora."

The four researchers - Professors Sigfrid Svensson, Alf Lindberg, and Per-Anders Mardh and Associate Professor Arne Lundblad - had already co-operated on various projects before deciding to establish BioCarb.

BioCarb, located at the Ideon R&D Park, Lund, is currently owned by the four researchers (60 per cent), the two financial backers (25 per cent), and four consultants (15 per cent). Considerable time was required to actually establish the firm because all those involved were anxious to find the right form of organization. The firm is now at work on most of the projects selected in connection with the financing. It is well ahead with its technology and has also found new ways of operating from a purely business standpoint. The firm acts as an intermediary and undertakes various projects - often on a 50-50 basis - with partners (often large firms). But unlike many other firms, BioCarb does not relinquish the business possibilities. If it invests 50 per cent, it also owns 50 per cent of the results.

Exactly what products it is working on BioCarb does not want to reveal, but carbohydrate technology opens up possibilities in both diagnostics and pharmaceuticals. It can be used, for example, in looking for new birth control pills or, inversely, for improving the possibilities for conception. Toothpaste and deodorants are products to which carbohydrate technology could be applied in the long run. (Extracted from Veckans Affarer, 4 May 1984)

United Kingdom

Biotechnology innovation support

Support for innovation in biotechnology may be cut from 33 to 25 per cent. Critics say the Department of Trade & Industry (DTI) has given most of the development money to large firms such as ICI, instead of to small ones. Others say the DTI spends its money on government research laboratories instead of private industry. The DTI says that 70 per cent of the projects it supports are from small companies (employing under 500 people). Meanwhile, according to J. Teasdale of University College Cardiff, the UK is not spending enough to educate its children about biotechnology. Students do not have enough knowledge to appreciate the importance of biotechnology and base their opinions of the science on stories in the mass media. Only 5 per cent of students can give an acceptable definition of biotechnology. Students are generally in favour of medical biotechnology research, but are against industrial applications. (Source: New Scientist, 29 March 1984)

New test for Down's syndrome

A new test for pregnant women may reduce the number of Down's syndrome children. Medical researchers are becoming more confident they can detect many more babies with Down's syndrome by a test, not only for mothers in their late 30s, but for younger women too. The amniocentesis test now given to women over 35-38 years to detect any chromosomal abnormality works but reduces the overall number of Down's syndrome cases only slightly, because only 20 per cent of afflicted babies are conceived by women in this age group. The new simple screening test identifies younger women at enough risk of bearing a Down's syndrome child to justify amniocentesis. Research by Professor N. Wald of St. Bartholomew's Hospital in London examines the correlation between the incidence of Down's syndrome babies and low maternal protein levels. The safe testing procedure could double current detection rates. (Source: The Economist, 22 June 1984)

UK patent for rennin

Collaborative Research has a UK patent for a genetically engineered form of rennin, the milk-curdling enzyme used to make cheese. Natural rennin is currently in short supply because it must be obtained from unweaned calves. Collaborative Research is working with Dow Chemical, which uses CRI's rennin-producing yeast strains in pilot plant fermentors to maximize production of the enzyme. (Source. Reprinted with permission from Chemical and Engineering News, Vol. 62, No. 39, page 18, 24 September 1984, copyright 1984, American Chemical Society)

USA

USDA biotechnology plan

This was to be the year for launching a biotechnology programme in the U.S. Department of Agriculture (USDA), but the plan may have been set back last May, when the House Appropriations Committee voted out the USDA budget. It cut funding for biotechnology from the proposed sum of $28 million to $10 million and saddled the new programme with one particular $250,000 task: investigating Hawaiian sugar cane. The committee also provided $15.5 million in new money for competitive research grants (to be added to the $17 million already allowed). But at the same time it imposed a new list of items to be studied in the grant programme, including such things as soybeans, alcohol fuels, acid precipitation, brucellosis, aquiculture, gypsy moths, boll weevils, and pine bark beetles.

The administrator of the competitive grants programme, Edward Kendrick, says: "It will be difficult to maintain current enthusiasm and participation in the programme" if funds are divided into special fields. The reason for creating the competitive programme was to get away from this kind of top-heavy, categorized research management for which USDA has been criticized in the past. The aim was to invite proposals from those best able to identify new ideas: the researchers themselves.

The US Agricultural Research Service will shift its focus to genetic engineering and related biotechnologies from conventional plant and animal breeding programmes and will raise R&D for gene cloning and splicing, embryo transfer, regeneration of plants from tissue culture, synthesis of hormones and the use of monoclonal antibodies. Potential applications of biotechnology include new hormones to produce pigs and cattle with less fat, fostering soil microbes that break down toxic farm chemicals before they contaminate groundwater, adjusting photosynthesis to multiply the edible yield of fruits and vegetables, and enhancing the nitrogen-fixing properties of plants to minimize the need for fertilizers. (Extracted from Science, vol. 224, 15 June 1984 and New York Times, 29 May 1984)

Commercialization of useful plants

The Critical Materials Act will encourage commercialization of crop plants that yield chemicals, setting up a new office at the USDA to encourage commercialization of useful plants. An existing programme to encourage development of guayule will be expanded, along with encouragement of jojoba, buffalo gourd and meadow foam, which yield oilseeds, and gopher weed and Chinese tallow which could produce chemical feedstocks. No funding level has been determined for the new office or the new Joint Commission on Research & Development of Critical Agricultural Materials which will have representatives from the USDA, the State and Defense Departments and the Federal Emergency Management Agency. (Source: Chemical Marketing Report, 4 June 1984)

Study on competitive position in biotechnology

"Study of the U.S. Competitive Position in Biotechnology", written by Emily A. Arakaki of the International Trade Administration, warns that the biotechnology industry in the U.S. could lose its front-runner status in the rapidly developing worldwide competition, largely because of a myriad of potential regulatory problems. U.S. companies face serious challenges from biotechnology companies in Japan, Fed. Rep. of Germany, Great Britain, Switzerland, Sweden and France.

The issues the study says American strategists must consider are: support for basic and applied research and development; the training of scientists and engineers in the interdisciplinary fields of biotechnology; and policies on regulation, patents, export control, trade, tax incentives and antitrust matters.

The report acknowledges industry complaints by noting that although the government supports basic research, it "has no specific policy to foster research related to commercial development". The report notes as well that the U.S. has fewer than a dozen interdisciplinary training programmes, causing "an acute shortage" of biochemical and chemical engineers who have backgrounds in biochemistry and microbiology. The study also calls for clarification "on who will regulate the products of biotechnology".

Japan and the nations of Western Europe, determined to avoid such problems, have, in many cases, targeted biotechnology for priority development. (Extracted from Chemical Week, 31 October 1984)

Venezuela

Decree No. 240, dated 15 August 1984, of the Republic of Venezuela, decrees that under the powers conferred by articles 7 and 8 of the Organic Law of the Central Administration, and in consideration that genetic engineering and biotechnology are becoming increasingly relevant for the technological independence of the country in areas such as agriculture and stock breeding, biomedicine and industrial development, it is necessary to encourage research in the basic sciences, genetic engineering and areas related to biotechnology, such as, microbiology, molecular biology, genetics and immunology as well as the development of technical and professional human resources in these fields. It is also necessary to strengthen communication between the scientific and technological research and production sectors in order to stimulate new investment and industrial development. The National Executive is determined to promote the scientific and technological development of the country, and therefore the Decree reads as follows:

Article 1. The National Commission for Genetic Engineering and Biotechnology, is established as an advisory body for the President of the Republic, in matters relating to the planning and formulation of policies whose aim is the promotion and development of genetic engineering and biotechnology, within the guidelines laid down in the national plans.

Article 2. The Commission shall be composed of a President and eight members appointed by the President of the Republic. Each member shall have an alternate, who shall deputize for him during temporary or permanent absences.

In the case of permanent absences, the Minister of State for Science and Technology, or, in his absence, the government department responsible for science and technology, shall designate a new alternate.

Article 3. The President of the Commission shall designate one of the members to deputize for him during temporary absences. In the event of resignation or permanent absence, the Minister of State for Science and Technology, or, in his absence, the national executive organ responsible for science and technology, shall designate his successor.

Article 4. The quorum necessary for deliberation shall be five members and the meetings shall be valid only when the President or his alternate is present. Decisions of the Commission shall be adopted by a simple majority. In the event of a tie the President shall have the casting vote.

Article 5. The National Commission for Genetic Engineering and Biotechnology will have the following functions:

1. To promote scientific and technological research in the fields of genetic engineering and biotechnology;

2. To co-operate with bodies responsible for fostering, planning and financing the scientific and technological development of the country in the aforementioned fields;

3. To establish links between those involved in reseach in the aforementioned fields and the production sector of the country;

4. To bring about the creation of a network of scientific and technological information in the fields of genetic engineering and biotechnology;

5. To co-operate with the bodies responsible for the international action of the Republic as regards relations in the fields of genetic engineering and biotechnology;

6. To promote the training of human resources in the aforementioned fields;

7. To establish its own rules of procedure.

Article 6. The Commission shall create four sub-commissions in the fields of agriculture and stock breeding, biomedicine, industrial development, and the environment and renewable natural resources, each composed of five to seven members who may or may not be members of the Commission. The Commission shall determine what activities shall be undertaken by the sub-commissions.

Article 7. The Commission shall have a Technical Secretariat located at the Headquarters of the National Council for Scientific and Technological Research. The Secretariat shall be headed by a Technical Secretary elected by the Commission, who shall co-ordinate the activities of the Secretariat, as well as those of the sub-commissions.

Article 8. Government agencies shall afford the Commission whatever co-operation is necessary for the fulfilment of the activities assigned to it in this Decree.

Article 9. Expenditure relating to the operation of the Commission shall be charged to the heading for the National Council for Scientific and Technological Research of the budget covering the Ministry of the Presidential Secretariat.

Article 10. The Ministers of Development, Health, Agriculture and Stock Breeding, Environment and Renewable Natural Resources, and the Presidential Secretariat shall be responsible for the implementation of this Decree.

Under Decree No. 241 dated 15 August 1984, the National Commission for Genetic Engineering and Biotechnology shall be composed as follows: citizen Jacinto Convit, President; Carlos Palacios, Jorge Flores, Victor Carrizales, Angel Hernández, José Azócar, José L. Ramírez, Néstor González Cadavid and Luis Enrique Núñez, members; and citizens Manuel Rieber, José Esparza, Juan Mendible, Oscar Valbuena, Raúl Walder, Livio Revel, José Luis Avila and Carlos Fuenmayor, alternates to the members.

C. RESEARCH

Research on human genes

Immune response gene identified

A gene that controls the body's immune response to foreign substances was identified by M. Davis and a research team at Stanford University. The discovery could help doctors understand more about how the immune system fights invading agents and may one day provide clinical benefits for cancer therapy by aiding tumor identification. The isolated gene contains the code for a T-cell receptor, enabling T-cells to recognize and destroy foreign substances in the body. The team isolated the T-cell receptor in mice, and said it is almost identical to the human gene. (Extracted from Wall Street Journal, 3 August 1984)

Transcription rate increased

TCDD increases the rate of transcription of the gene for cytochrome P1-450, according to Doctors Whitlock Jr. and Israel of Stanford University. The cyctochrome P-450 family of enzymes detoxifies many hydrophobic compounds. Using RNA synthesized in isolated nuclei, TCDD increased synthesis of cytochrome P_1-450 mRNA 20 times within 30 minutes in wild-type mouse hepatoma cells. TCDD receptor complexes may activate gene transcription in a way similar to that of steroid hormones. (Extracted with permission from Chemical and Engineering News, Vol. 62, No. 21, page 30, 21 May 1984, copyright 1984, American Chemical Society)

Swedes engineer cells to make tryptophan and phenylalanine

The Swedish company AC Biotechnics, AB, of Malmö claims to have developed the world's first commercial process for making the amino acids tryptophan and phenylalanine using genetic engineering. Tryptophan is the basis for many pharmaceuticals; phenylalanine is a building block for aspartame, the synthetic sweetener. The company claims their process can be scaled up to any size for animal feedstuffs. Their genetically engineered microbes save money by not requiring expensive chemical precursors, such as indole for tryptophan, and by increasing yield and reaction rates. (Source: McGraw Hill's Biotechnology Newswatch, 4 June 1984)

Cloned enzyme inhibitor seen as emphysema treatment

Dr. Alex Bollen, of the laboratory of genetics at the University of Brussels, reports that his groups has cloned alpha 1 antitrypsin in bacteria and yeast. Antitrypsin is an inhibitor of elastase and a promising treatment for emphysema. While yield is still low, Bollen is confident this can be increased after development of more efficient vectors. Bollen is collaborating with the Belgian subsidiary of Smith Kline Beckman, which will "optimize" the process. He says Zymos Corp., Seattle, Wash., and the Paris-based Transgène have also cloned the antitrypsin gene in yeast and E. coli respectively. (Source: McGraw Hill's Biotechnology Newswatch, 4 June 1984)

Leprosy vaccine possible

An effective vaccine against leprosy may soon become available. Existing anti-leprosy drugs have not only failed to wipe out the disease, but in some parts of the world, leprosy is actually on the increase. Obviously, the cost of immunising the enormous number of people

at risk would be formidable, yet the rewards could be huge The disease has no natural host except man, and thus a really effective vaccine could eradicate this ancient and terrible affliction once and for all.

The odd thing about leprosy is that only a fifth or so of those infected develop any sign of infection. What is more, those who do represent a clinical spectrum, ranging from a relatively mild ("tuberculoid") version to a truly horrific ("lepromatous") form in which the bacteria multiply inexorably in nerves and within the skin's cells. These differences result from the way the body's immune system responds to the bacteria. In patients with tuberculoid leprosy, specialised scavenger cells, called "phagocytes", engulf the bacteria and eventually digest them, but in lepromatous victims, the bacteria remain undigested and multiply inside the phagocytes as readily as outside, indicating that lepromatous patients have a flaw in their immune defence system. It is not that their phagocytes are defective; they can respond perfectly well to the closely related tuberculosis bacterium. It seems, in this case, that the leprosy bacterium has evolved an ingenious way of fooling the immune system - by signalling to regulatory cells which prevent the phagocytes from digesting the bacteria.

The key mechanism in this process has recently been pinpointed by Dr. Barry Cloom and his colleagues at the Albert Einstein School of Medicine in New York. It is almost certainly a fatty molecule with three sugar partners attached to it, which forms part of the leprosy bacterium's surface. When this molecule is added to white blood cells from lepromatous patients, the cells then suppress the response of other "helper" cells which normally switch on the phagocytes. However, no suppression is seen when the molecule is added to white blood cells from tuberculoid patients or normal donors. The New York group has shown it is the sugars that switch on the "suppressor" cells.

The World Health Organization is supporting a research drive to develop a vaccine against leprosy, but the trick played by the leprosy bacterium on the immune system would imply that a vaccine should not be much of a help to those who need it most. After all, a vaccine works because the immune system has a memory: once the cells that recognise a particular shape on the surface of a foreign invader have been activated, they are primed to spring into action quickly and effectively the next time they meet that shape. Traditional vaccines prime the system with appropriately-shaped bacteria or viruses but which are no longer virulent - because they have been either killed ot mutated to a harmless variety.

Against all the odds, the result of the first trials of the leprosy vaccine are much better than pessimists feared. The scientists seem to have outwitted the leprosy bacterium by bypassing the suppressor cells altogether - using a combination of killed leprosy bacteria and a live, but harmless, mutant of the tuberculosis bacterium (BCG) routinely used to vaccinate against TB.

There are a number of good reasons for including BCG. Since the tuberculosis bacterium and the leprosy bacterium are closely related, their shapes are similar. And live bacteria (if safe) are always preferable to dead versions because they remain longer in the body and migrate to the same tissues as their virulent relations. So one would expect BCG to help the majority of people who have effective immune responses against leprosy - but surprisingly it helps lepromatous patients as well.

Field work in Venezuela has been most encouraging. When lepromatous leprosy patients were given the vaccine, their phagocytes - which had been completely unaware of the bacteria multiplying in their midst - suddenly woke up and started to digest the harmful bacteria. If these preliminary results hold up, a leprosy vaccine could become a real possibility. There is, of course, no way of knowing yet whether it will be possible to provide long-lasting immunity for those most at risk. For the first time, however, there are grounds for hope that this generation of lepers could be the last. (Extracted from The Economist, 23 June 1984)

Sex determination technique

A new technique enhances the chances of sex determination. Dr. R. J. Ericsson developed the procedure, which involves washing semen in a tissue medium. The sample is then run through two glass columns containing increasing viscous layers of human serum albumin. Sperm cells containing the Y chromosome, which have the genes for masculinity, are heavier, stronger and swim faster than sperm containing the X, the female chromosome. The female egg contains only the X chromosome. Since the Y chromosome is necessary for the conception of a male, the chances are enhanced by an artificial concentration of Ys. After the sperm descend to the bottom of the second glass column, they are withdrawn, separated from the liquids surrounding them, concentrated and injected directly into the woman's cervix shortly after ovulation. Sperm that are immature or abnormal in some other way are almost completely screened out through the use of this procedure, reducing the eventual risk of spontaneous abortion and the birth of babies who are physically deformed or mentally retarded.

As sex selection comes into wider use, questions about the medical, social and religious implications of the practice are increasing. Parents requesting the technique have shown an overwhelming preference for male babies. Over 200 sex-linked diseases in the US have been identified and linked to several thousand deaths/year of newborn babies. (Source: New York Times, 29 May 1984)

Cancer detecting monoclonal produced

Two New England Nuclear (NEN) researchers, Drs. May-Kim Ho and Paul J. Durda, have produced a cancer-detecting monoclonal by 'immunizing' spleen cells in culture. NEN is now characterizing the antibody which detects a breast-tumor-specific cell-surface antigen and is producing other antibodies in both mouse and human in-vitro immunization systems.

Advantages of NEN's in-vitro route include:

- 10-to-100-fold less soluble antigen is needed than for in-vivo immunization in mice;
- the sensitization process takes only five days as opposed to months for in vivo injections;
- human monoclonals can be produced, including antibodies to potentially toxic or tumorigenic compounds.

The researchers make their anti-breast-cancer monoclonals by culturing normal BALB/c mouse spleen with a preformed monolayer of human mammary tumor cells. Spleen cells are multiplied by adding interleukin-2 and growth factors and then conditioning the medium with thymocytes. After five to seven days of joint spleen-breast-cell culture, the sensitized lymphocytes are fused with myeloma cells by conventional techniques to produce the monoclonals. The antibodies characterized are IgM-type, sometimes IgG type as well. (Extracted from McGraw-Hill's Biotechnology Newswatch, 18 June 1984)

InterPharm scales up interferon-β in hamster cells

Israel's InterPharm Laboratories Ltd. is scaling up for industrial production of fibroblast inteferon (INF-β) cloned in mammalian host cells. The proprietary production process was developed for InterPharm by Dr. Michael Revel at the Weizmann Institute of Science. The method, on which patents are pending in the US and Europe, the coding sequence of the human INF-β 1 gene, fused 60 bp after the RNA start of the SV40 early gene, was transfected into dihydrofolate-reductase-deficient (DHFR) Chinese hamster ovary cells together with a selectable DHFR gene to achieve constitutive production of human INF-β. It is hoped that enough material will be on hand by the end of 1984 to start clinical testing of the hamster-cell-synthesized human interferon as an antiviral therapeutic.

In-vitro tests were encouraging; the interferon produced reacted as the conventionally produced material. The advantages were that it permits continuous recovery of high-purity INF-β at 500 times higher yields than from ordinary tissue culture with less risk of contamination. The molecule is claimed to be identical to the native substance - unlike that produced by cloning in Escherichia coli. The mammalian host, being eukaryotic, yields a glycosylated protein, which prokaryotic bacteria cannot do. Moreover, E. coli interferons contain a terminal methionine residue of unknown effect on the finished product. (Extracted from McGraw-Hill's Biotechnology Newswatch, 18 June 1984)

Another gene isolated

A gene that helps activate the eubacteria actinomycetes to produce antibiotics has been isolated by researchers at Tokyo University. The gene 'awakens' the dormant antibiotic synthesizing gene, and its manipulation could result in the discovery of new antibiotics. The research team recently succeeded in extracting the gene that synthesizes A-factor, which promotes the production of streptomycin. During this project they encountered a previously unknown gene that regulates the activation of the A-factor gene. The new gene, called afsB, has about 800 nucleotide bases. It was placed in a different kind of actinomycetes and the host bacteria began making two types of antibiotics it does not ordinarily produce. The researchers believe other regulatory genes resembling afsB could be discovered in other actinomycetes. (Source: Japan Economic Journal, 3 July 1984)

P210 protein isolated

Researchers at the University of California have isolated a protein that could trigger abnormal cell growth in patients with chronic myelogeneous leukemia. P210 protein is produced by a hybrid gene derived from a chromosomal translocation. Part of the hybrid gene

is obtained from the abl oncogene, which is triggered by the protein to begin a kind of enzymic activity believed to have a role in the growth regulation of cells. (Extracted with permission from Chemical and Engineering News, Vol. 62, No. 30, page 21, 23 July 1984, copyright 1984, American Chemical Society)

Mental illnesses may be genetically transmitted

A genetically transmitted abnormality of body chemistry may predispose cerain persons to suffer from manic depression, according to researchers at the National Institute of Mental Health and Wayne State University. However, even though discovery of an apparent genetic marker suggests that specific chemical abnormalities predispose people to manic and depressive symptoms, it should not be concluded that the cause of mania and depression has been uncovered. The defect can be identified in cultured skin cells, which may make it possible to test members of families with a history of manic depressive disorders for their own susceptibility. The special property of skin cells peculiar to victims is an abnormal affinity for acetylcholine. A higher than normal level of muscarine cholinergic receptors, which capture substances such as acetylcholinem, was found in the skin cells of all 18 patients with severe mania or depression, as well as in 18 of their relatives with symptoms of other mental disorders. Receptor levels were not significantly elevated in five other relatives who displayed no symptoms and in 18 normal volunteers. (Source: New York Times, 26 July 1984)

rDNA techniques used to reproduce gamma-hANP

Suntory and Miyazaki Medical University of Japan have successfully used rDNA techniques to reproduce the human atrial natriuretic peptide hormone gamma-hANP, believed to cause the kidney to excrete uric sodium. It also helps lower blood pressure. The substance is found in the heart's atria in quantities of only a few micro-g, which severely limit the study of its physiological function. The Suntory-Miyazaki team used biochemical analysis to establish that it consists of a chain of 126 amino acids. By determining the nucleotide organization and the amino acid sequence and synthesizing an artificial copy chain, it was possible to clone gamma-hANP. (Extracted from Japan Economic Journal, 17 July 1984)

Efficiency of antibody production improved

A technique that improves production of human monoclonal antibodies has been developed by Genetic Systems Corp., Seattle. The technique, according to the company, increases the probability of finding large numbers of the correct type of cell. Combined with an enhanced cell culture and antibody harvesting process developed by Cutter Biological, Emeryville, Calif., the technique also opens doors to making amounts of antibody large enough for therapeutic use.

The new technique uses Epstein-Barr virus to transform human B lymphocytes, rendering them immortal in cell cultures. Previous methods depended on fusing a cancer cell with a spleen cell to produce an immortal antibody-producing cell. Such fusions have a low rate of success with human cells. High yields of virally transformed B lymphocytes increase by 1,000 times the chances of finding cells that make the desired antibody. After they have transformed the lymphocytes, Genetic Systems scientists divide the cell culture among wells of a microtiter plate. Wells are coated with a fluorescent-tagged antigen for the desired antibody. A fluorescence-activated cell sorter detects cells whose antibodies have bound to the antigen.

The first therapeutic antibody to come out of the Genetic Systems advance may be that against Pseudomonas aeruginosa. Skin infections by this bacterium cause the second largest number of deaths among burn victims after the burn injury itself. This microbe also is a frequent cause of pneumonia in cancer, cystic fibrosis, and weakened, elderly, hosptalized patients. (Extracted with permission from Chemical and Engineering News, Vol. 62, No. 35, page 4, 27 August 1984, copyright 1984, American Chemical Society)

Cloning of AIDS genes brings vaccine near

Scientists from Chiron Corporation of Emeryville, California, announced this week that, together with the University of California, they had cloned the full sequence of genes for the virus believed to cause Acquired Immune Deficiency Syndrome. This opens up the possibility of obtaining the viral protein that is needed to make a vaccine for AIDS and to establish a diagnostic test. However, scientists have not yet proved that the bacteria containing the genetic material will manufacture the viral protein. They must get the bacteria to make the viral protein that is coded in the viral genome or genetic material they have cloned. Nonetheless, Chiron is confident that this can be done in a matter of months, or even weeks, because of a recent success it has had in producing a vaccine for feline leukaemia virus which is similar in structure.

Chiron's claims come within three months of receiving a suspected AIDS virus isolated by Dr. Jay A. Levy from the University of California, San Francisco. It is called ARV for AIDS-associated retroviruses and is the third AIDS virus to be announced by different laboratories. No comparative data has been published, but the three are thought to be either the same virus or very similar to one another. The other viruses were isolated by Robert Gallo, from the National Cancer Institute in the US and Dr. Luc Montagnier, from the Pateur Institute in Paris.

Levy was able to grow large amounts of the ARV virus in tissue culture. This enabled Chiron's scientists to isolate the genetic material from the virus. However, being a retrovirus, core genetic material of the ARV was ribonucleic acid (RNA) rather than the more common deoxyribonucleic acid (DNA). To clone the genes for the virus, the scientists needed DNA, so purified RNA was used as a "template" to synthesise complementary DNA molecules. The complementary DNA was inserted into bacteria and clones containing viral sequences were obtained. (Extracted from New Scientist, 13 September 1984)

One-armed antibodies against cancer

Drs. Steve Cobbold and Herman Waldman of Addenbrookes Hospital in Cambridge believe they may have found a way to make monoclonal antibodies deadly enough to use without attaching toxic drugs to them. They have shown that removing one of the two arms with which an antibody fastens itself to an antigen makes the antibody much more efficient as a selective cell killer. Antibodies normally bind to certain proteins (antigens) at two sites on the surface of the foreign cell to form antibody-antigen complexes. The next stage in the process of killing foreign cells involves the activation of a number of blood proteins, collectively called complement, by the antibody-antigen complex. Once complement is activated, the foreign cell has little chance of survival. Foreign cells try to evade destruction by shifting the proteins on their surface so that the antibody-antigen complexes have no chance to activate complement.

Cobbold and Waldman made hybridomas from cells of rat spleen fused with myeloma cells. They picked out only those cells from the descendants of the hybridomas which were producing antibodies in which one arm was derived from a rat spleen cell and the other arm from a myeloma cell. So while one arm of the antibody can bind to a target antigen the other arm would be unable to bind to anything. They found that cells against which this "one-armed antibody" was directed did not alter the positions of proteins on their surfaces, presumably because, never having encountered a one-armed antibody in nature, they did not recognise it as an antibody at all. The one-armed antibodies were, however, as good as two-armed ones at inducing complement to attach itself to a foreign cell and kill it by breaking down the cell's membrane and dissolving the contents. Moreover, one-armed antibodies appeared to be better at inducing complement to kill cells than normal, two-armed antibodies. One reason for this, the researchers believe, is that one-armed antibodies are not thrown off; there are lots more of them to act as markers for complement.

Antibody-ricin conjugates have previously been used to remove T-cells from bone marrow destined for transplantation into people with leukaemia. T-cells are responsible for regulating the production of antibodies against foreign cells. If the T-cells of grafts are not removed, the recipient will suffer "graft-versus-host disease", essentially an attack by the graft on the patient's cells. Tests at Addenbrookes have shown that one-armed antibodies are as effective at removing T-cells from bone marrow as antibody-ricin conjugates. (Source: New Scientist, 13 September 1984)

How the brain defends itself

The body's immune systems depends on being able to recognise cells that belong to the same body. To make this possible, a set of genes known as the major histo-compatibility complex (MHC) programmes the manufacture of MHC antigens molecules that are unique to each individual and sit on the surface of every cell. However, cells in the brain are apparently an exception to this rule; they appear to lack the usual complement of MHC antigens, and is one of the reasons the brain has become known as an "immunologically privileged site" for transplantation. In theory, cells without MHC antigens cannot initiate the immune processes that are responsible for graft rejection. But in practice, grafts of foreign tissue in the brain are rejected, although slowly; and brain cells infected by viruses are attacked by T-cells which can recognise the virus only if it occurs in association with appropriate MHC antigens.

Maybe the antigens (their manufacture according to a genetic programme) can be "turned on" under some circumstances. Grace Wong and colleagues at the Walter and Eliza Hall Institute of Medical Research in Victoria, Australia, found that gamma-interferon could induce a dramatic increase in the number of one variety of MHC antigens, the class I

antigens, on brain cells. In suspensions of brain cells from young mice, they found that the proportion of cells expressing class I antigens was less than 1 per cent. After being cultured for 24 hours with gamma-interferon, 99 per cent of the cells had detectable levels of antigens. They also injected gamma-interferon directly into the brains of mice, and found that 50 per cent of cells from the injected mice expressed the antigens, whereas less than 2 per cent of cells from control mice did.

If Wong and her colleagues are correct, gamma-interferon may have another role in turning on antigen expression so that T-cells can go to work in the brain. (Source: New Scientist, 13 September 1984)

New evidence links cancer to 'normal' genes

Scientists now have the first concrete evidence that cancer can be caused by the manipulation of normal genes contained in the chromosomes of normal cells. Although the evidence arises from experiments on mice, it supports the idea that most human tumours develop when something goes wrong with oncogenes, which are contained in all our cells. Moreover, the results show clearly that the propensity for developing cancer can be transmitted from generation to generation.

Philip Leder, Professor of Genetics at Harvard Medical School, announced the results at a meeting on the molecular biology in Boston during September. Leder, together with Tim Stewart and Paul Pattengale, also at the Harvard Medical School, experimented with a normal cellular oncogene called C-MYC, which is known to play an integral part in the development of Burkitt's Lymphoma. They replaced the promoter region of C-MYC with that of a mouse mammary tumour virus (MMTV). They then injected the oncogene promoter unit into fertilised mouse eggs and placed the eggs into the womb of a female mouse.

Thus every cell of the developing embryo contained the oncogene. The researchers allowed the female offspring to mate and become pregnant. As the mice became pregnant, they started to make the hormones necessary for lactation. These hormones switched on the MMTV promoter which activated the C-MYC gene adjacent to it. All the pregnant mice developed breast tumours.

The experiment is important because it shows that a normal gene can be altered to behave as "activated" oncogenes.

It also shows that a single oncogene may be necessary but not sufficient to produce a tumour. Every cell in the mouse embryo received a copy of the C-MYC gene but only some cells produced tumours. This supports the idea that the development of cancer involves more than one step. (Source: New Scientist, 20 September 1984)

BioTechnica claims to boost yield of recombinant protein

BioTechnica International, of Cambridge, Mass. has announced the development of a new genetic engineering technique which, the firm says, permits the regulated production of recombinant DNA proteins in large quantities. The company's scientists were able to make T4 DNA ligase, an essential enzyme in gene splicing activities, using a promoter-gene construction whose expression of protein could be synchronized and controlled in bacteria. The advantage of the new technique lies in its ability to use a strong promoter that does not interfere with cell growth. The disturbance of cell growth limits product (protein) yield, a major problem with many of the current protein-producing methods.

The basic drawback of existing protein expression technologies that rely on a promoter-gene construction is the nature of the construction itself. Currently, a strong promoter (a DNA site where RNA polymerase can bind securely to make large numbers of messenger RNA copies) is put right next to a gene for a desired protein and this complex is spliced into a plasmid for subsequent cloning in Escherichia coli. Unfortunately, the strong promoter is so effective in getting the gene to elicit large amounts of protein production from the cell that the cell exhausts itself. As there is no effective way to control this production, the cell depletes so much of its energy that its growth is impaired. This translates into a limited overall product yield. (A "weak promoter" that can be regulated by environmental factors such as temperature and nutrient supply could offer some control, but product yield would still be limited because weak promoters do not bind RNA polymerase very well). Rather than putting a strong promoter alongside a particular gene, BioTechnica scientists place the promoter at such a distance from the gene that no protein is produced initially in the bacterial hosts.

At this point, BioTechnica researchers have learned how to get the cell to recombine its DNA on cue so that the promoter and gene are brought next to each other to begin protein production.

The proprietary process involves exposing the host bacteria to a higher temperature to bring about the genetic recombination involving the promoter and gene.

BioTechnica plans to use its protein-producing technology to find strong new promoters for the company's proprietary use and may commercialize the novel process through licensing the technology, licensing the particular bacterial strain used for ligase production, or producing ligase for bulk sale. (Source: Genetic Engineering News, October 1984)

Research on animal genes

Genes from extinct species

Fragments of genes from an extinct animal, the quagga, have been found and reproduced in the laboratory, according to University of California (Berkeley) scientists. The DNA was extracted from a scrap of dried muscle tissue found inside the skin of the quagga, a relative of the zebra and horse. The skin, preserved 140 years ago, has been kept at the Mainz Museum of Natural History. The species died out about 100 years ago. The discovery that portions of genes from animals can survive for over a century may provide a new tool to study the evolutionary links between extinct animals and living ones. The initial success may open the way to recover intact genes from muscles, bones and teeth of species that died out millions of years ago.

The research group has about 25,000 clones of DNA fragments from the quagga tissue. Mitochondrial genes will be studied, since they evolve at a faster pace than most other genetic material and could be valuable in gauging the differences between quagga, horse and zebra, and also ensure that the DNA was really from the extinct animal and not a contaminant. The preserved animal skin has not been satisfactory as a source of DNA. A sample of tissue from a mammoth found in the USSR has not yet yielded detectable pieces of DNA, partly because the tissue was heavily contaminated by modern bacteria. Research leader A. Wilson hopes to obtain DNA from tissues of an extinct species of bison, the steppe bison, found recently in Alaska. The animal was kept frozen after it was removed from permafrost, and may offer well-preserved, uncontaminated tissues. If scientists can ever extract the total complement of DNA from a cell of any extinct animal, they would have the animal's complete blueprint of heredity. (Source: New York Times, 5 June 1984)

Shipworm bacteria that can digest cellulose as well as fix nitrogen

The shipworm is a kind of mussel that bores into wooden hulls. In working out how it survives on this seemingly indigestible diet, scientists have stumbled on a new kind of bacterium with a potentially important future in biotechnology. Inside the shipworm's gill is a brown lump called the gland of Deshayes; inside the gland is a mass of bacteria. Dr. John Waterbury and colleagues at the Woods Hole Oceanographic Institution in Massachusetts isolated some of the bacteria, christened them Teredinobacter and grew them in the laboratory. They found that the bugs combined two special and rare tricks: they could digest the carbohydrate cellulose, and they could "fix" (i.e., extract) nitrogen from the air. There are bacteria that can digest cellulose and others that can fix nitrogen. But this is the first time that both jealously guarded secrets have been found in the same organism.

To build a body, a creature needs plentiful supplies of carbohydrate (largely to burn as fuel) and nitrogen (to make proteins from). Wood is pure carbohydrate and air is 80 per cent nitrogen. But in both cases, tapping these supplies requires special enzymes which are only found in certain bacteria. The answer is a joint venture: such animals as termites employ cellulose-digesting bacteria in their guts and such plants as clover have nitrogen-fixing bacteria in modules on their roots. Shipworms have both in one. (Extracted from The Economist, 30 June 1984)

Research on plant genes

Pollen vector expresses anti-rust genes in corn

A new technique that puts genes directly into seed will rival the Ti plasmid, according to its developer. Dr. Johannes M. J. de Wet of the Genetic Engineering Center, University of Illinois, Urbana, fertilized corn with pollen dosed with DNA from another inbred corn line, yielding plants in the next generation that show new disease-resistance and cob-colour phenotypes. The pollen-vector technique bypasses the problems of regenerating functional plants from transformed protoplasts. The key to the method, states De Wet, is germinating the corn (Zea mays) pollen cells until some 10 per cent of them form pollen tubes and then adding total-cellular DNA extracted from the leaves of the donor plant. (Extracted from McGraw-Hills's Technology Newswatch, 4 June 1984)

Foreign gene expressed in soybean cells

The first expression of a foreign gene in soybean cells transformed by recombinant DNA techniques has been achieved. The work was described at the recent World Soybean Research Conference in Ames, Iowa. Research carried out by Calgene Inc. at Davis, Calif., fused the promoter from a light-inducible soybean gene and the Escherichia coli gene that confers resistance to the antibiotic kanamycin. The product was used to transform a suspension culture of soybean cells. In the transformed cells, kanamycin resistance was light-inducible, demonstrating that the foreign gene was expressed normally.

Calgene and Nestlé are in a joint venture to introduce herbicide resistance to soybeans using genetic engineering techniques. Though some plants, such as tobacco, have proved to be relatively easy to regenerate from single cells or suspension cultures, major crop plants such as corn and soybeans have proved much more difficult to deal with. Efforts are now under way to integrate the Calgene and Nestlé technologies so that whole plants may be regenerated from transformed cultures. (Extracted with permission from Chemical and Engineering News, Vol. 62, No. 35, page 5, 27 August 1984, copyright 1984, American Chemical Society)

Research on yeast and fungus genes

"Killer toxin" cloned

Researchers at the molecular genetics section of the National Research Council (NRC), Ottawa, Canada, have expressed cloned "killer toxin", an important contaminant fighter for use in brewing. Dr. David Y. Thomas and co-workers at NRC, McGill University and Allelix, Inc., Mississauga, Ont., also confirmed the location of the immunity factor for the toxin on the same cDNA segment copied from an M1 virus-like, double-stranded RNA plasmid. Thomas and his group have created two slightly different toxin clones by inserting reverse-transcriptase killer gene copies into yeast vector pYT760. The vectors were used to transform baker's yeast (Saccharomyces cerevisiae) into immunized, killer strains. One of the inserts produces glycosylated toxin, which is exported from the host cells at higher efficiency than the strain that produced toxin lacking the sugar moieties, notes Thomas. The newly created plasmids - are claimed to be suitable for the insertion of other genes at various positions in the preprotoxin gene in order to obtain secretion and proteolytic processing of foreign gene products in yeast. (Extracted from McGraw-Hill's Biotechnology Newswatch, 4 June 1984)

Tumour cells can grow without growth factor

The first clear understanding of how oncogenes cause cancer occurred last year when British and US researchers simultaneously discovered what it was that one of the best-studied oncogenes coded for. The oncogene product was a protein called platelet-derived growth factor (PDGF). Researchers proposed that, in cancer cells, the normally inactive gene for PDGF is permanently switched on. The cells produce and respond to their own growth factor and so are trapped in a never-ending cycle of growth. Previous experiments had shown that certain T-cell cultures could be grown from cells infected with human T-cell leukaemia-lymphoma virus (HTLV) without adding T-cell growth factor (TCGF) to the culture medium. But it was questionable whether the cells were really independent of TCGF and able to grow happily without it, or could it be that the cells produce minute quantities of growth factor - just enough for each cell to secrete and respond to, but not enough to be detected.

Researchers therefore looked for evidence of TCGF machinery at work in the particular HTLV-infected cell lines. To make TCGF, a cell must first transcribe the relevant piece of DNA (the TCGF gene) into messenger RNA (mRNA), which then directs the synthesis of the protein. If the mRNA for the growth factor could be detected in actively dividing T-cells, then this would explain why certain HTLV-infected T-cells lines can grow without exogenous TCGF. A gene probe of TCGF-DNA to search for TCGF-mRNA was used. Although it was found that some of the cell lines contained TCGF-mRNA, some cell lines contained none at all. It is suggested that the cells may produce another molecule, similar in structure to TCGF. The molecule could, conceivably, bind to TCGF receptors on the cell membrane - in effect mimmicking the actions of TCGF. Alternatively, the cell membrane of infected cells might change in a way that is similar to the changes produced by the binding of TCGF with normal T-cells. (Source: New Scientist, 22 March 1984)

Drugs to help cancer cells grow up

As the ideas about the causes of cancer become more sophisticated, so do the ideas of how to treat the disease. John Hickman, a co-director of the Cancer Research Campaign's Experimental Chemotherapy Research Group at the University of Aston in Birmingham, is attempting to bring cancer chemotherapy up to date with theory.

The products of more than 20 oncogenes have been identified so far and about a dozen of these proteins have been found in the membranes of cells. Scientists have now begun to find out what the roles of oncogene products are, both in normal cells and in cells that have become cancerous. Two such proteins have recently been the centre of much excitement; platelet-derived growth factor and epidermal growth factor. But how the products of an oncogene are involved in a cancer is not always so clear-cut. Some of the proteins, for example, are known to bind to guanosine triphosphate (GTP), a high-energy compound involved in using and making energy from glucose, and in protein synthesis. Other surface proteins that oncogenes code for are known to affect the flux of certain ions across the cell membrane, and others still, to phosphorylate proteins. Both are well-recognised phenomena in the minute-to-minute running of a cell. Take the so-called second messenger hormone system, for example. Here a hormone binds to a receptor on the surface of the target cell. The binding stimulates the production of adenylate cyclase. This enzyme catalyses the production of the "second messenger", cyclic adenosine monophosphate (cAMP), which influences a vast range of processes inside the cell, from the degradation of storage fuels to the secretion of gastric fluids. Many of the changes brought about by cAMP can occur only if a particular concentration of certain ions has been reached inside the cell.

Phosphorylation of the amino acid, tyrosine, is integrally related to the processes underlying cell proliferation. Like the binding of a hormone to its membrane receptor in the second messenger system, phosphorylation of proteins by other membrane proteins can be likened to turning on he ignition of a car - a whole series of events can ensue.

Since its formation in 1980, the group's most promising product is n-methyl-formamide (NMF), a compound that the group rediscovered. NMF is an industrial solvent, known to chemists since 1869. Hickman and his colleagues have shown that the drug can convert one particular tumour cell into a normally proliferating granulocyte (a specialised type of white blood cell) in-vitro. And the level of one of the oncogene products in the membranes of reformed cells drops as the cell reverts to a normal growth pattern. A patient treated with NMF for a mouth cancer seemed to "grow" a new layer of cells that line the mouth. The drug is about to be tested in a multicentre European trial against colon and lung cancer (two of the cancers most resistant to treatment of any sort) by the European Organisation for Research into the Treatment of Cancer. NMF is not without side effects; it causes nausea and tiredness, but it does seem to be a promising protégé of the "new" chemotherapy.

Hickman admitted that no one knows how NMF works. His group has shown that it does not bind to nucleic acids; however, it is activated by binding to proteins in the liver. By itself, that is, without activation, NMF alters the movement of calcium in and out of cells. (Source: New Scientist, 29 March 1984)

Making cancer cells kill themselves

A new group of anticancer drugs that could, in theory, be made more effective in killing cancer cells than their nearest equivalents in use today is being developed and tested at Essex University, with support from the UK Cancer Research Campaign. The new drugs have so far been tested only on cultures of leukaemia and sarcoma cells, and are being used in preliminary tests on mice.

They work by the established principle of competitive enzyme inhibition. If an enzyme is added to a mixture containing a small amount of its substrate and a larger amount of a substance that mimics its substrate, the enzyme will normally react with both. But the chances are that more of the mimicking molecule will be used up. Enzymes that break down toxic cellular metabolites can be fed molecules that mimic their substrates - the result is that the toxic metabolite accumulates and eventually kills the cell.

Drugs that work by this principle are already widely used. The new twist, developed by Ken Douglas of Essex University's chemistry department, makes use of the fact that substrate molecules pass through several intermediate short-lived stages during catalysis, and the fact that enzymes bind to these intermediate structures far more strongly than they bind to the original substrate molecules. Anticancer drugs that work by competitive inhibition of enzymes would be far more effective if they mimicked the structure of one of the substrate's intermediate stages.

Glyoxalase is an enzyme that breaks down a toxic metabolite, and its inhibition is known to kill cancer cells. Douglas has identified some intermediate stages of its substrate and has constructed about 40 different molecules that mimic them. The molecules have been tested on cultures of cancer cells at the Royal Marsden Hospital's research centre at Sutton in Surrey.

Several of the compounds tested performed at least as well as existing anticancer drugs that work by competitively inhibiting enzymes, but the first tests on animals show that the new compounds need to be more stable for use in vivo. (Source: New Scientist, 29 March 1984)

Synthetic hepatitis B virus produced

Scientists have synthetically produced a small portion of the hepatitis B virus that has potential as a vaccine. When tested in rabbits, the synthetic virus triggered the build up of an immunity to the hepatitis B virus. Although expensive vaccines for hepatitis B are already available, the new synthetic product would be safe and inexpensive. It is not yet known whether the synthetic virus can be used as a human vaccine. Because of the difficulties scientists have had in isolating the virus antigens, most vaccines have been composed of whole viruses that have been weakened or killed so they would not cause disease. Scientists from the New York Blood Center and the California Institute of Technology have isolated two antigens from the hepatitis B virus that contain a common chain of molecules that seem to be the part of the antigen that provokes the immune response. The chain of molecules was then reproduced synthetically. (Source: Wall Street Journal, 20 April 1984)

Viruses may help replace bad genes

An American team has devised a method of replacing a defective gene with a working one, which works in mice. They have persuaded a virus to carry the gene into the cell.

With blood disorders such as thalassaemia, the target has to be the "stem cells" - a small population of bone-marrow cells destined to spawn red blood cells, white cells and platelets. They comprise 0.01 per cent of the whole bone marrow, and have no obvious characteristics to pick them out. A team at the Massachusetts Institute of Technology led by Richard Mulligan, working with David Nathan of the Harvard Medical School in Boston, decidd to construct a helpful animal virus to do the hard work. It was a retrovirus, which naturally infects mice and generates cancer cells, but the researchers removed the genes that code for the coat protein of the virus and added "marker" genes in their place. These markers would reveal whether this virus (called MSV DHFR-NEO) had got into the right blood cells or not.

The virus was inoculated into mouse bone-marrow cells, and after an adequate infection time (two to six days), the cells were injected into other mice which had their own marrow destroyed by X-rays. Without the help of donor bone marrow, irradiated mice died of severe anaemia; but recipients of the cells lived happily, with about 20 per cent of their bone marrow and spleen stem cells containing the "marker" sequence. These virus-infected cells had the retrovirus/marker genes inserted into their chromosomes at a single (but variable) location, and they divided normally, carrying the marker.

It is easy to think that the same might work with the marker gene being one coding for a haemoglobin chain, and the recipient being a thalassaemic child. Obvious problems are devising a safe (non-carcinogenic) carrier virus that will work in humans; and getting the gene to work correctly, producing not too much and not too little "good" haemoglobin. However, when the only choice is abortion before birth, or probable death after it, this new technique using "superviruses" holds out great promise for practical gene therapy, to eliminate the threat of hereditary disease. (Source: New Scientist, 16 August 1984)

Research instrumentation

New fermentor for tissue cultures

A new high-growth fermentor for animal or plant tissue cultures is three to five times more productive than the conventional route of growing cultures on surfaces of plastic bottles that are continuously rotated. The new Opticell 5300 produced by KC Biologicals contains a ceramic matrix honeycombed with continuous channels. After the matrix has been seeded with cells, nutrients, oxygen and other compounds required for cell growth can be continuously supplied. Electronic controls monitor feed levels and other quantities, such as pH, inside the sealed growth-chamber. The firm can produce 10 billion cells per growth cycle. Several units have been sold to firms developing viral vaccines, monoclonal antibodies and other biological drugs The pilot scale Opticell 5300 costs $110,000. A larger production unit will be available by the end of the year. (Source: Chemical Engineering, 14 May 1984)

New computerized microscope gives 3-D chromosome images

Researchers at the University of California, San Francisco, have produced what they term the first three-dimensional reconstructions of the chromosome arrangement inside a whole cell nucleus. Graduate students David Mathog and Mark Hochstrasser, post-doctoral researchers Dr. Yosef Gruenbaum and Dr. Harold Saumweber, and group leader Dr. John Sedat, reported their most recent results in the March issue of Nature.

Working with a computer-controlled light microscope, the group is examining the physical architecture of chromosomes from the salivary glands of Drosophila melanogaster larvae, the common laboratory fruit fly.

The new microscope provides a series of two-dimensional cross-sectional views which can be combined to mimic a three-dimensional image, similar to the images produced by the more familiar CAT scanner. The resulting photographs and computer models may eventually demonstrate how, or if, the 3-D conformation of a chromosome plays a role in determining gene expression.

The microscope focus is computer-controlled to step through the nucleus in 24 stages to bring 24 different planes into view. A video camera turns each view into a 512 x 512 pixel black and white image which is digitized and stored on magnetic tape. A VAX 11/780 minicomputer manipulates the 24 2-D images (a total of about 6 million bytes of information) to simulate three dimensions.

Using Mathog's Interactive Modeling Program (IMP), a researcher traces the five visible chromosome arms. The tracings generate a model which can be displayed as a stereo pair image of individual chromosomes or of the entire chromosome array, and can be rotated around three axes. The image data can also be analyzed for a variety of graphic displays.

The IMP reveals that the Drosophila chromosomes bend and fold in a regular series of loops of definable length and position, often forming helical structures. The centromeres are fused into a chromocenter which adheres to the inner surface of the nuclear membrane. The chromosome arms bend around each other, but they appear to respect topological boundaries and avoid intertwining. Portions of the chromosome arms adhere to the nuclear membrane in what appears to be a non-random pattern.

Various theories suggest that only genes physically attached to the nuclear membrane are active, and that expression is affected by the physical proximity of genes, even though they may be distant from each other in the DNA sequence, or even on different chromosomes. Current knowledge of chromosome architecture has come from stained cell squashes and electron micrographs, both providing a distorted, two-dimensional view of a three-dimensional object. (Extracted from Genetic Engineering News, July/August 1984)

Japanese decode DNA automatically

Automatic analysis of DNA is now possible thanks to a collaborative effort between Japanese industry and universities. The work took three years and was headed by Professor Akiyoshi Wada of Tokyo University. The first two parts of the system to be developed were a machine to automatically extract DNA segments and an automatic process for mass-producing electrophoretic films. The final part of the programme was the development of a package of analysis pogrammes. These went on sale at the end of July.

To determine the way genetic information is arranged in a segment of DNA, the segment must first be tagged with a radioactive isotope, extracted and then separated into its component nucleotides. Manual extraction of segments of DNA is time-consuming and visual analysis is sometimes error prone, which is why the programme to automate DNA analysis was organised by the Science and Technology Agency of Japan (STA). To automate extraction of the DNA segments, Dainj Seikosha, a subsidiary of Seiko, built a computer-controlled microchemical manipulator which can control complex chemical reactions, involving reagents in quantities as small as one microlitre. A computer controls temperature, centrifugal separation and drying. Once the snippet of DNA is extracted it is broken into its component nucleotides for analysis. This is done by electrophoresis, where the DNA segment is placed on top of a specially prepared gel and film sandwich and subjected to a high voltage. Molecules migrate down the gel, the heavier ones moving more slowly than the lighter ones.

Preparing these gels by hand is a slow process, involving many steps. To eliminate the need for most of these steps, Fuji Film developed a method of producing ready-made gel film sandwiches consisting of an 0.3 millimetre layer of acrylamide coated with polyester film. Currently about 1 million films are prepared manually each year; Fuji expects to produce 10 million of its gel films per year. They were announced at the end of May and will cost between £6 and £9.

Finally, the pattern produced by electrophoresis must be analysed. Analysis by computer is both faster and more reliable than by eye. Mitsui Knowledge Industry, in co-operation with STA has developed a package of application programmes. The company expects to sell the programmes, which run on microcomputers, to chemical and pharmaceutical companies, universities and cancer research centres for about £1,500. (Source: New Scientist, 16 August 1984)

General

New extraction technique developed

Mitsubishi Chemical Industries (Japan) has developed a new technique to efficiently extract gene recombination products from E. coli in co-operation with Nagoya University. A major disadvantage in using E. coli for genetic recombination has been the cell's tendency to store the product. The cell must therefore be broken up and its contents sorted out, which is inefficient and expensive. The Mitsubishi process joins the gene of the desired product toan E. coli gene, encoding a cell surface membrane protein. The product is secreted outside the cell, greatly simplifying separation and purification. (Source: Japan Economic Journal, 15 May 1984)

Biotechnology research into materials science

The US Navy Office of Naval Research has awarded a three-year contract involving the application of biotechnology to problems in the materials scciences to the North Carolina Biotechnology Center (Research Triangle Park). The centre will investigate the biocatalytic reduction of carbon dioxide, use of biomolecular models as catalytic mediators on electrode surfaces, and a new class of materials in synthetic organic/ceramic substances. Material sciences is said to be viewed by the Navy as a particularly vital field in which biotechnology must play a role. (Source: Chemical Week, 17 October 1984)

D. APPLICATIONS

Pharmaceuticals and medical applications

Gene therapy

Human genetic engineering may be no more than two or three years away. The recent discovery of oncogenes may mean that there are risks attached to gene therapy - but these risks are likely to be acceptable for treating diseases that are incurable by any other means. This forecast comes from Professor Theodore Friedmann of the University of California in San Diego, a leading researcher in genetic engineering who is currently working in Oxford.

Friedmann recently created a sensation when he and virologist Inder Verma of the Salk Institute succeeded in "curing" human cells in laboratory culture of a previously incurable disease caused by a defect in a single gene which leads to the lack of an enzyme - Lesch-Nyhan syndrome.

Friedmann and Verma isolated the gene and cloned it - inserted it into bacteria and used them to multiply the gene millions of times over. Then they inserted the gene into a retrovirus which naturally infects human cells, and used the doctored virus to carry the gene into human cells taken from a Lesch-Nyhan patient and cultured in the laboratory. Because retroviruses naturally integrate themselves into and become part of the genetic material of cells they infect, this proved an ideal means of getting the correct version of the gene into human cells lacking it. Defective human cells treated in this way soon began to produce normal quantities of the missing enzyme. However, Friedmann thinks it will be some years before he and others can extend the technique to treat human victims of Lesch-Hyhan syndrome.

But well before Lesch-Nyhan syndrome may become treatable two other conditions are virtually certain to be attacked by gene therapy. These are conditions in which the human body loses its natural resistance to infectious disease. They are caused by deficiencies of two enzymes, called PMP and ADA. Lack of either causes serious defects in the white blood cells which normally defend us against infections. At present both conditions can only be treated by repeated injections of the missing enzymes or by complete bone marrow transplanted after the patient's own bone marrow has first been killed by drugs or radiation.

The human genes coding for PMP and ADA have now been cloned and inserted into retroviruses, using the same procedure as for Lesch-Nyhan syndrome. Several research teams in the USA are now working towards the target of using these doctored retroviruses to infect samples of bone marrow taken from people suffering from PMP or ADA deficiency. When bone marrow treated in this way is reimplanted into patients - a simple procedure - it will form healthy white cells without defects.

The treatment of PMP and ADA will provide a model for how to treat many more of the 2000-odd human diseases. Sickle-cell anaemia and forms of thalassaemia may be among them. The ability of a retrovirus to "swallow" a complete human gene without affecting the virus's ability to target itself right into an infected cell's DNA makes it highly superior to other systems being tested as possible means of human genetic engineering.

The possibility that such viruses may pick up and activate oncogenes does pose a threat to gene therapy. But Friedmann - who is Professor of Medical Ethics at San Diego - thinks the risks will be highly acceptable, in the context of treating otherwise incurable and fatal conditions. (Source: Sunday Times, 18 March 1984)

Biotechnology

New enzyme in fish tissue

The Pacific Institute of Bio-organic Chemistry of the DVNTs (Far Eastern Sciences Center) of the USSR Academy of Sciences proposes an endoribonuclease obtained from waste products of the fish processing industry. The enzyme specifically splits, in the RNA molecule, the internucleotide phosphodieter bonds in the A, G and U, but not the C, nitrogen bases, and is analogous in specificity to the RNAase Phy I from Physarum polycephalum. The enzyme may be used for study of structure and purification of RNA, obtaining nucleotides and nucleosides from RNA and, also, as a medical preparation. It is produced in the form of alyophilized dried powder which may be stored for a year. The price is 50 rubles per milligram. (Source: Khimiya I Zhizn, April 1984)

Possible hepatitis B vaccine developed

A small synthetic peptide that reacts strongly with human hepatitis B virus antibodies could be a safe, inexpensive vaccine against the disease, according to researchers at the New York Blood Center and the California Institute of Technology. Nearly identical proteins found in the virus surface coat, P33 and P36, reacted with human antibodies for hepatitis. A synthetic peptide consisting of 26 amino acids found in the intact protein produced a strong immune response in rabbits and a high level of antibodies, which react with the virus in blood samples from human hepatitis carriers. The peptide is useful as a diagnostic test and animal studies are being conducted to test the peptide as a vaccine against hepatitis. The existing hepatitis B vaccine, derived from the blood of human carriers, is scarce and expensive. (Source: reprinted with permission from Chemical and Engineering News, Vol. 62, No. 17, page 15, 23 April 1984, copyright 1984, American Chemical Society)

Collaboration on bone regeneration research

Monsanto (St Louis, MO) and Collagen (Palo Alto, CA) have jointly announced a bone regeneration research agreement. The research will focus on the production of growth factors, naturally occurring proteins that direct cells to synthesize new bone tissue. The collaboration will be on the development and application of recombinant DNA techniques for the manufacture of these proteins and will augment Monsanto's activities in human health care and Collagen's programme for developing collagen-based materials for the repair and reconstruction of damaged bones and joints. (Source: Chemical Week, 25 April 1984)

Hepatocellular carcinoma

An infant vaccinated with hepatitis-B antigens and antiviral antibodies within 48 hours of birth can be protected against becoming a carrier of hepatocellular carcinoma caused by hepatitis-B virus, generally transmitted when maternal blood is swallowed at birth. The vaccine must currently be purified from the blood of infected humans, and costs $100 per dose. In China, where 20 per cent of the population are hepatitis carriers, efforts are underway to produce a vaccine for 50 cents a dose. Such a vaccine could be made more effective if the antigens were clustered in aggregates. (Source: New Scientist, 26 April 1984)

EPO purification method

Snow Brand Milk Products (Japan) has developed a method for achieving high-level purification of erythropoeitin with a monoclonal antibody in a joint effort with the University of Kyoto. Toyobo has agreed to produce and market EPO for use as a test drug in anaemia treatment. The monoclonal antibodies used by Snow Brand selectively adsorb the EPO from urine derived from anaemic patients. The process has an activation rate of 80,000-88,000 units/mg, versus 50 units/mg for currently available EPO. (Source: Japan Economic Journal, 8 May 1984)

Calcium metabolism regulation

California Biotechnology (Mountain View, CA) and Massachusetts General Hospital (Cambridge, MA) have agreed to develop compounds for regulating calcium metabolism. The compounds are inhibitors of parathyroid hormone, which regulates bone metabolism and controls calcium levels in the blood. The compounds have shown some activity in animal tests, and will be tested for possible uses in a number of conditions associated with some cancers, such as hypercalcemia, which in many cases is linked with elevations of a substance that may function like parathyroid hormone. (Source: Chemical Week, 23 May 1984)

Recombinant interleukin-2 tested on AIDS patients

Biogen (Geneva, Switzerland) is testing recombinant interleukin-2 on AIDS patients in Western Europe. The tests use bacteria that have been genetically altered to produce a form of interleukin-2 similar to that produced by white blood cells in the human body. The bacteria stimulate the growth of cells that control and regulate the human immune system leading to speculation that the product could be used to treat diseases caused by malfunctioning of the immune system such as multiple sclerosis, rheumatoid arthritis and systemic lupus erythema-osus. Biogen will apply for regulatory approval of the product in Europe, the US and Japan. (Source: Wall Street Journal, 6 June 1984)

New anticancer agent

Genentech has produced a new type of anticancer agent that destroys malignant tissue. Lymphotoxin can selectively kill cells by breaking apart the cell membranes. The agent is a protein normally produced by the immune system, but is exceedingly difficult to obtain in purified form because it is so rare. Genentech is now producing the drug through recombinant DNA technology. Lymphotoxin can distinguish between healthy and malignant tissue, and so can eradicate tumors without harming normal cells. (Source: Chemical Marketing Report, 11 June 1984)

Alternative drug therapy

The biological control of disease-causing bacteria is being researched as an alternative to drug therapy. Dr. K. Sprunt, a pediatrician at New York Babies Hospital, has used the idea of confronting dangerous bacteria with competing and harmless species of bacteria to control the sweep of disease through an intensive care nursery. A benign strain of streptococcus was implanted in premature infants at risk; the implants took hold in an impressive 89 per cent of instances and replaced dangerous germs with harmless bugs within 72 hours. Evidence shows that this type of strategy would work with several species of bacteria, perhaps used to combat the bacteria that cause dental cavities and gum disease. Again, the strategy is not to exterminate the enemy, but to buy time to permit the body's own healing powers to take over. (Source: The Economist, 22 June 1984)

Growth factor I produced

Fujisawa Pharmaceutical has produced insulin-like growth factor I, a hormone with various physiological activities. Recombinant technology was used in producing the compound, which is called somatomedin C, and which promotes growth, multiplication of cartilage cells and reduction of blood sugar. The compound can be used to treat pituitary dwarfism and various bone diseases. Genentech (US) is also researching IGF-I. Fujisawa will conduct preclinical tests on animals and begin phase-1 clinical tests in 1986. IGF-I has a molecular weight of 7,649, consisting of 70 amino acids. Colon bacilli containing the necessary DNA plasmid can produce the compound at yields of 1-3 mg/L of incubation liquid. (Source: Japan Economic Journal, 3 July 1984)

Rapid diagnostic tests for interferon and potential cancer gene produce under development

Hazleton Biotechnologies Corporation (Hazleton), of Vienna, Virginia, a subsidiary of Hazleton Corporation and Cellular Products Incorporated (Cellular), of Buffalo, New York have announced a joint project for the production of monoclonal antibodies for diagnostic kits. Cellular's capabilities to provide highly-purified antigens from human blood components will be combined with Hazleton's expertise in tissue culture and hybridoma production.

The first monoclonal antibodies to be developed will be specific for Human Platelet-Derived Growth Factor (PDGF) and Human Immune Interferon. According to Dr. Richard A. Montagna, President of Cellular Products, "PDGF is thought to be involved in the wound-healing process and has also been implicated in atherosclerosis. In addition, the PDGF molecule is very similar to a product of a cancer-causing oncogene. This is the first documented relationship between a growth-promoting protein and a putative cancer-causing product." He further states, "Immune interferon is believed to play a prominent role in the regulation of the immune system and is also being evaluated for its medical efficacy in the treatment of human cancers. Test kits for either of these substances will provide significant diagnostic information to the medical community."

Cellular is a major manufacturer of products derived from human blood components and its wholly-owned subsidiary, Northern Clinical Diagnostics, Inc. will perform and market the diagnostic tests developed as a result of this agreement. While Hazleton conducts research in immunoassay development and provides general services for antibody production, characterization and purification. (Source: Company News Release, 13 July 1984)

Hepatitis B virus surface antigen vaccine

The US Food and Drug Administration has stated that even if a recombinant vaccine mimicks plasma-derived vaccines, its clinical efficacy cannot be assumed. The Merck Institute for Therapeutic Research has announced that its hepatitis B virus surface antigen vaccine is safe and immunogenic in humans. Chimpanzee studies have shown that the recombinant vaccine protects against several subtypes of hepatitis B virus. A vaccine trial will probably require several thousand people and take two to three years, according to Merck. Meanwhile, Genentech is developing a mammalian cell recombinant hepatitis B vaccine. (Source: Medical World, 23 July 1984)

Radiolabeled monoclonal antibody to detect cancer sites

Radiolabeled monoclonal antibody fragments to recognize colorectal cancer sites that conventional detection methods miss are used by Centocor. Subsequent nuclear medicine imaging revealed the labeled fragments in cancerous abdominal lymph nodes. Because the cancerous lymph nodes were normal in size and number, usual detection methods of computer tomography scanning and surgery failed to identify the tumors. An imaging product containing the antibody will be introduced in Western Europe in 1986. (Source: Chemical Week, 25 July 1984)

Test for manic-depressive illnesses possible

A new skin test may allow identification of children genetically susceptible to manic-depressive illness and related mood disorders, according to researchers from the US National Institute of Mental Health. Skin cells of patients and relatives with histories of affective disorders differed from skin cells of normal relatives and unrelated normal individuals. The cells of those with mood-disorder histories contain more receptors sensitive to acetylcholine, a chemical produced in the brain, however the team indicated that more years of studies will be needed before universal validity of the skin test can be proved.

The researchers used biopsy needles to draw fibroblast cells from the hips of all subjects studied. The cells contain some of the same chemicals and receptors found in brain cells. The sixth or seventh generation of cells were used for the experiment to isolate the cells from any medication used by the individuals studied. A radioactive tagging procedure was used that found that in 18 patients and 13 of their relatives with a history of affective disorders, the fibroblast cells had a higher density of receptors. (Source: Wall Street Journal, 26 July 1984)

Three human fertility hormones cloned

Integrated Genetics has successfully cloned all three human fertility hormones using rDNA technology. It recently cloned luteinizing hormone (LH) and follicle stimulating hormone (FSH), in addition to human chorionic gonadotropin (HCG). It applied its proprietary mammalian cell technology to express biologically active human LH by assembling two gene products, each modified by carbohydrates from the biologically active hormone. The two recently cloned hormones are used to treat infertility disorders in men and women. (Source: Chemical Marketing Report, 30 July 1984)

T-PA tested in humans

A blood-clot dissolving chemical passed its first test in humans after tissue-type plasminogen activator, T-PA, was given to seven men in the throes of heart attacks; in six, the blood clots causing the heart attacks vanished in an hour or less, while the blood clot in the seventh man resisted all attempts at dissolution. Gentech supplied the T-PA gene with animal cells. Although all men survived the heart attacks, four of the patients continued to experience severe clogging of their coronary arteries and two suffered second heart attacks. The T-PA researchers said it would take at least two years of controlled testing before it can be determined if the drug is life-saving. T-PA is the most promising of the three clot-dissolving substances being tested with heart attacks; streptokinase and urokinase are already on the market for dissolving blood clots in other situations but are now being tested against blood clots in the heart. (Source: Wall Street Journal, 3 August 1984)

Malaria vaccine

Scientists have identified and reproduced the gene in a malaria parasite ultimately responsible for stimulating immunity to malaria in humans. The vaccine should stimulate immunity against it at least at one stage of the major form of malaria. M. P. McPherson of the Agency for International Development believes that a vaccine would be ready for trial in

humans within one or two years, and widely available worldwide within five years. WHO estimates that there are 150 million new cases per year of malaria, with one million children per year dying from the disease in Africa alone. In the past 10 years, the number of malaria cases has doubled. A. Lucas, director of the UN programmes of research in tropical diseases, attributes the resurgence in malaria incidence to the fact that mosquitoes carrying the parasite are becoming resistant to insecticides, and the malaria parasite itself is becoming resistant to the drugs used to treat the disease. The vaccine would block the first stage of the disease by preventing new infections, primarily benefiting people who have never been exposed to malaria. (Source: New York Times, 3 August 1984)

Enzyme immuno-assay test for hepatitis B infection

Centocor will introduce a new enzyme immunoassay test for hepatitis B infectin which features polystyrene beads coated with mouse monoclonal antibodies against hepatitis B surface antigen. The beads are incubated with serum or blood plasma, and with a solution of biotin-linked monoclonal antibodies against the surface antigen. The surface antigen joins the bead-linked antibody and the biotin-linked antibody if it is present, to form a stable complex. Peroxidase enzyme and the protein avidin are added in later and reacted with another solution to generate a colour that can be directly related to the amount of hepatitis B surface antigen available to begin building the complex chain. The Centocor test is one of two monoclonal antibody-based tests that have received US Food and Drug Administration approval. It is more sensitive that conventional hepatitis tests and features simpler handling and longer shelf-life versus radiolabeled tests. (Source: reprinted with permission from Chemical and Engineering News, Vol. 62, No. 32, page 18, 6 August 1984, copyright 1984, American Chemical Society)

Test for legionnaires' disease

The first US Food and Drug Administration approved monoclonal-antibody based diagnostic test for legionnaires' disease will be marketed by Genetic Systems (Seattle). The test uses a single monoclonal antibody and identifies all species of the legionnaires' bacterium with a sensitivity of 100 per cent and a specificity of 98 per cent. Current tests, based on conventional antibodies, require six different antisera to make the same diagnosis and are said to be less accurate than the Genetic Systems product. (Source: Chemical Week, 22 August 1984)

An Australian monoclonal assay detects blood clots

A monoclonal-antibody-based assay that detects blood clots more quickly, more accurately and at a lower cost than currently available assays has been developed at the University of Queensland (Brisbane, Australia). Alan Whitaker, who leads the blood-clot-assay project, claims the monoclonal antibody can detect low levels of the molecule D-dimer, a byproduct of clot formation. Clinical tests showed that the antibody easily distinguished between normal levels of D-dimer and those found in patients with dangerous clot formation. The assay is said to be simple to perform and can be completed in a matter of minutes, compared with six hours for conventional tests. The Brisbane-based biotechnology company, MAbCo, has developed a kit form of the assay and is negotiating for licensing rights. (Source: Chemical Week, 22 August 1984)

New diagnostic test available for herpes

A new blood test, Simplex-2™, has been developed by Gene-Link Australia, to aid in the diagnosis of genital herpes. The test is specific for herpes simplex virus type 2 (HSV-2), the virus most commonly associated with genital herpes. It can be performed by both private and hospital clinical laboratories and will be offered to physicians as well. The FDA has recently approved the product and it will be marketed by Damon, Metpath, Medical Laboratories Associates, and other major reference laboratories.

Simplex-2 overcomes some of the limitations of herpes virus culturing and provides distinct advantages over other blood tests. This test should be extremely useful in clarifying the diagnosis of genital herpes. Over 98 per cent of all recurrent genital herpes infections are caused by HSV-2. Clinical studies on over 400 patients in both the United States and Australia have demonstrated an accuracy of 93 per cent. It is claimed that unlike other tests, Simplex-2 can effectively detect HSV-2 infections when symptoms are absent. The simple blood test can serve as a valuable aid to doctors, especially those engaged in prenatal screening of pregnant women, and will help identify high risk groups. (Extracted from Press Release, 8 October 1984)

Livestock applications

Sheep/goat chimera

A one-year-old sheep-goat chimera is one of a group that has been bred experimentally by genetic manipulation at an animal research station near Cambridge. The animal, a hybrid of a male sheep and a male goat, behaves like a male goat, has goat-like horn twisted like sheep horns, long, wavy goat wool and its blood contains sheep and goat red cells. But it has proved infertile in natural matings with female goats. Although the semen is of normal density, the spermatozoa have a characteristic tail defect of infertile mammals.

Three series of experiments with hybrid sheep-goats were carried out by scientists at the Agricultural Research Council's Institute of Animal Physiology, near Cambridge. In one experiment, seven animals were born with the general appearance of lambs after their mothers had been implanted with hybrid embryos, but three of them had fleeces characteristic of goats. In another experiment, two new-born animals resembled ordinary kids, except that one had wool considered to be of sheep origin. In a third experiment, six out of nine animals were born resembling ordinary lambs, two had characteristics of both kids and lambs, and one looked like an ordinary kid.

This is not a trick of artificial insemination. The sheep-goat chimera, as the scientists who created it call the hybrid, began as a normally conceived lamb by one set of parents and a normally conceived kid by the other pair. Each of these fertilized eggs was allowed to divide only until they consisted of a microscopic sheep embryo of eight cells and a goat embryo of eight cells. At that stage the cells of the two species were combined by embryo manipulation, and the resulting hybrid implanted into a third parent sheep who hosted the alien animal to birth.

Experiments have shown that these hybrids can be reared in either a parent ewe or nanny. It is suggested that one use for the technique would be in rescuing endangered species by creating conditions in which the embryo of a species at risk could be reared safely in another species.

Hybrid animals have been produced in experiments before, involving mice in one case and frogs in another. However, the breeding of sheep-goats as a hybrid species is seen by scientists as offering new approaches to the study of reproductive incompatibilities between species, and may lead to such incompatibilities being neutralised. (Source: The Times, 16 February 1984)

"Morning-after" antibody blocks pregnancy

With an eye on a multi-million-pet veterinary market and eventually a human market as well, a British researcher and an undisclosed US sponsor are developing a "morning-after" monoclonal contraceptive. The anti-progesterone antibody completely blocks pregnancy in mice after a single intraperitoneal injection, for up to 65 hours, declares Dr. Brian Heap of the Agricultural Research Council's Institute of Animal Physiology in Cambridge.

The monoclonal antibody probably terminates pregnancy by blocking early development and interfering with implantation of the embryo in the uterine wall. Current research focuses on its use as an anti-fertility drug in dogs and cats. Single doses of one to eight nanomoles of monoclonal antibody injected directly into the peritoneal cavity are effective in BALB/c female mice; intravenous injection is less reliable and requires a higher dose. (Extracted from McGraw-Hill's Biotechnology Newswatch, 4 June 1984)

Genetically pure animal breeding facility

Hilltop Laboratory Animals is building a $350,000 genetically pure laboratory animal breeding facility, the first in the US to provide isolation of individual breeding groups. Breeding chambers will consist of sterile cages to protect the animals from airborne viruses and carcinogens. Hilltop hopes to produce the purest strain, the perfect uncontaminated control group. The present facility annually produces two million mice, rats and guinea pigs for research by pharmaceutical firms and the medical community. (Source: Chemical Week, 6 June 1984)

Agricultural applications

Four companies set up joint venture

Sumitomo Corp. and Kyowa Hakko Kogyo Co., Ltd. announced they will co-operate with the U.S. plant biotechnology venture company, NPI, and the Indian financial combine, Tata group, in setting up Plantech International (PIP), a company for the production of seeds and

seedlings through plant biotechnology, in Singapore. The company will embark on the business of supplying seeds and seedlings of subtropical and tropical plants, centering on the Southeast Asian region. The four companies will sign a business co-operation contract. The new company has already been registered.

The new company will apply NPI's technology to make sterilized seeds of useful plants, perform large-scale propagation of seedlings, realize product improvement as well as development of new products, and carry out production and marketing of these seeds and seedlings. Tentatively, business development will be oriented toward Southeast Asia, India, East Africa, and the Pacific Basin states, centering on seeds and seedlings of coffee, cocoa and tea with which NPI established its technology, along with spices, fruits, etc. As for Japan, China and Korea, Sumitomo Corp. and Kyowa Kakko are considering future co-operation with Kaneko Seeds and Seedlings, Nakajima Tenkoen, and others, to commercialize these products domestically. (Extracted from Nihon Kogyo Shimbun, 22 March 1984)

Use of old rubber trees

Old rubber trees are being chemically reprocessed into valuable export timbers and thereby relieving pressure on dwindling forests. Until recently, most of this wood was burned on the plantation because the wood from rubber trees is particularly susceptible to rot, fungus and wood-boring insects. Untreated rubber wood left in the forests for two days or more will be significantly affected. However, new systems involving immediate fungicide spraying, on-site sawing by portable saw mills, dipping into a chemical solution and rapid-transportation have made use of the wood practical for the first time. Special drying kilns are used to reduce the high moisture content of the latex-soaked wood so that it can even be used for high quality flooring and furniture. The smooth cream-coloured wood is in high demand by furniture manufacturers and lumber exporters. (Source: Technology Update, 5 May 1984)

Researchers study pine clones

Scientists at North Carolina State University's Southern Forest Research Center are trying to make one of the greatest resources of the southern USA - the loblolly pine - even more productive. By cloning tissue from a single plant and then treating it with hormones, the scientists have been able to produce anywhere from two to 100 new loblolly trees. The new trees are, in theory, identical to the plant that produced the original tissue.

Many paper companies have become interested in the field of biotechnology in the last several years and 13 companies are funding NC State's research into tissue culture techniques. The aim of the programme is to discover whether cloning can increase forest yield, produce genetically superior trees, and lessen disease. The initial results of the research indicate that trees cloned from a single seed are, in fact, quite similar in height, branch structure, and the appearance of needles. This leads scientists - and paper companies - to hope that certain trees could be made-to-order for specific purposes.

Like any forest research, however, the process is a slow one, measured in terms of decades. This current batch of pine clones will have to be studied for 20 years before the success of the project can be determined.

Right now, the cloned trees are smaller than their natural counterparts, but the researchers are confident that they will eventually catch up. Of more concern is the cost of producing these trees. A regular nursery seedling costs about 1.5 cents; the price for a tissue cultured plant is closer to 75 cents. If pine cloning is to become a viable alternative for the industry, a less expensive method will have to be found. (Extracted from Paper Trade Journal, July, 1984)

Biotechnology-based herbicide

Japan's first biotechnology-based herbicide will be introduced, possibly by the end of the year. The product is effective against any weed and has an extremely low level of residual toxicity. The Japanese Ministry of Agriculture has approved its use only on soil where no edible plants are to be grown, however, and the firm of Meiji Seika Kaisha will apply for permission to expand its applications. The main ingredient of the new herbicide is a compound produced by fermentation technology. The antibiotic inhibits the functioning of a nitrogen-converting enzyme in weeds and thereby destroys them. (Source: Japan Economic Journal, 26 June 1984)

Calgene and Campbell announce agreement to develop high solids tomato using genetic engineering

Calgene, Inc. announced it has entered into an agreement with Campbell Soup Company to develop high solids processing tomatoes using Calgene's plant genetic engineering expertise and Campbell's plant breeding expertise.

Tomatoes, California's number one vegetable crop, are more than 90 per cent water by weight. The objective of the research agreement is to develop a proprietary tomato variety having a 50 per cent increase in solid material as compared to presently available varieties. Increased solids will result in major savings in the cost of production of tomato paste, sauces and related processed tomato products. California currently produces 85 per cent of the United States' requirement for processing tomatoes, with a grower value in excess of $400 million per year.

Norman Goldfarb, chief executive officer of Calgene, points out that the agreement signals an increasing trend among food companies to apply the most advanced genetic engineering technology to their needs. Similar relationships may in future be established to improve potato, soybean, sunflower, and other processed and fresh market crops through genetic engineering and breeding.

According to Campbell's vice president of Vegetable Research, Dr. Alan Stevens, the agreement is part of Campbell's on-going commitment to improve vegetable product quality and production.

Calgene is a leading plant biotechnology company, organized in 1980 to develop and commercialize new crop varieties and plant products. The company utilizes recombinant DNA and cell and tissue culture technologies along with traditional biological methods such as plant breeding. Campbell Soup is a leading supplier of high quality food products and conducts crop research and vegetable seed production through the Campbell Institute of Research and Technology and Campbell Seeds Company. (Extracted from Calgene News Release, 11 September 1984)

Sunlight triggers "natural" herbicide

Some 30 chemical, pharmaceutical and biotechnology companies have expressed interest in licensing for commercial development of an amino acid that induces herbicidal action in plants. The inducer, aminolaevulinic acid (ALA), stimulates the production of excess concentrations of photosensitive compounds that, when activated by sunlight, kill a number of weeds, while having little or no effect against important food crops, such as corn, wheat, barley and oats. ALA is also biodegradable and is believed to be nontoxic. ALA's developer is Constantin A. Rebeiz, plant physiologist at the University of Illinois (Urbana-Champaign).

However, the present cost of ALA, £6-7/gramme, prohibits its use on a commercial scale. Currently, it is used by researchers to study photosynthesis and some species of micro-organisms, but widespread use of ALA as a herbicide would depend on industry developing inexpensive methods of synthesizing large quantities of the compound. Patent application on behalf of the University of Illinois covering the use of ALA as a herbicide has been filed. (Extracted from Chemical Week, 24 October 1984)

Food production and processing

Immobilized lactase

Sumitomo Chemical and Shin-Nippon Chemical Industries have developed high-purity immobilized lactase for use in hydrolysis of milk sugar. The product will be used to produce lactase-decomposed milk. (Source: Japan Chemicals, 3 May 1984)

Cheese makers try r-DNA to preserve plasmid variety

Genetic engineering and screening techniques may turn the art of cheese-making into a science, while preserving the flavour-enhancing complexity of bacterial starter cultures and their resident plasmids.

Lactic acid streptococci are indispensable for cheese-making and a number of critical cheese-making functions are encoded on resident plasmids: proteolysis of caseins that give cheese its texture, transport and metabolism of lactose and lactic acid production that gives "bite", the buttery diacetyl flavour of a ripe Gouda and production of CO_2 from citrate that causes formation of small "cheese eyes". However, some dairy streptococci harbour prophages that become virulent at the elevated temperatures needed for cheese-making.

Dr. Michael Teuber of the Institute für Mikrobiologie, Bundesanstalt für Milchforschung, Kiel, (FRG) stated that the amount of genetic diversity of most European starter cultures is phenomenal and he has been identifying the hundreds of plasmids found in cheese-producing bacteria, using DNA probes, restriction mapping and electrophoresis. He has looked at over 400 dairy strains, and all have at least two to 15 different plasmids that are stable and strain specific and as more and more cheese-makers begin to use defined-strain cultures with only six or seven strains, there is a probability of making less interesting cheese. Dr. Teuber asks cheese makers to at least send him samples of their old cultures so that they may be preserved for study. To preserve the complex character of cheese starter cultures while avoiding the perils of virulent phage infections, genetic engineering of dairy strains is a necessity. (Extracted from McGraw-Hill's Biotechnology Newswatch, 4 June 1984)

Chemical applications

Chemicals and fuels from algae

Many technical hurdles remain before production of chemicals and fuels by algae is economically attractive. Growing algae in open systems, like ponds, suffer from poor growth yields, low and variable cell densities, low photosynthetic efficiencies and difficulties in maintaining pure cultures according to Richard Radmer of Martin Harrietta Laboratories (Baltimore, MD). Radmer notes that only about 20 per cent of light absorved by algae in the 400-700 nanometer range is retrieved in chemicals in algae i.e. the photosynthetic efficiency is only about 20 per cent. Consequently, systems using artificial light are expensive. For example, even with the theoretical yield and electricity costing 16 cents per kilowatt-hour the cost of electricity alone for producing one pound of dry cell mass is four dollars. If the desired product is 10 per cent of the dry cell mass, the cost of just the electricity jumps to $40 per pound of product. Using natural sunlight can reduce the costs of electricity but yields are low, recovery is expensive and large areas are required. Typically cell densities in open systems are about one gramme of dry weight per litre compared to 50 grammes of dry weight per litre reached in fermentors and the highest yield of a product like glucose would be about one mole of glucose per square metre per day.

An attractive way to avoid the low photosynthetic efficiency problem is to grow algae heterotropically, i.e. to substitute nutrients as carbon sources instead of relying on photosynthesis, thereby allowing the algae to grow in standard fermentors. Unfortunately, only a few per cent of the different types of algae which are attractive for producing chemicals can be induced to grow heterotropically, i.e. without light.

Martin Marietta began an intensive effort about six months ago to develop economical methods of producing chemicals using algae.

Genetic engineering of algae is hampered because knowledge of the genetics, physiology and biochemistry of algae is very limited compared to that of bacteria. Further, it appears that only one or two genes rather than whole clusters of genes can be cloned in algae. Nonetheless martin Marietta has formed a joint venture with Chiron (Emeryville, CA) and Native Plants Inc. (Salt Lake City, UT) to use genetic engineering and associated biotechnoiogies initially to improv algae and eventually to improve higher plants.

The close relation between algae and higher plants is reflected in the discovery that Agrobacterium tumefaciens, which is used to genetically engineer plant cells, can also be used to genetically engineer algae. Rodney Ausich of Standard Oil Company (Indiana) (Naperville, IL) has shown that the antibiotic resistance carried in the Ti (tumour inducing) plasmid of Agrobacterium tumefaciens and an added transposon, Tn5, can be transferred with high efficiency to the algae, chlamydomonas reinhardtii. After mixing the algae and bacteria, 10 to 40 per cent of the algae cells, depending on the species used, are resistant to normally toxic levels of anticiotic. The transferred algae cells are unusual in that they grow on agar supports but not in solution. The normal or untransformed algae grow in solution. The transformed algae will grow in solution if an aqueous extract of agar is added to the culture media solution. However many of the transform algae cells grown in clumps ranging from a few cells to as many as 30-40 cells rather than the individual isolated cells observed with untransformed cells.

Based on DNA hybrid probes for the Ti plasmid and for the Tn5 transposon, Ausich claims that DNA in the chloroplasts, where photosynthesis occurs, is not altered in the transformed algae. The nuclear DNA is altered and produces less than one copy per genome. Ausich suspects that he has a mixed culture containing some algae with the Tn5 transposon and some without it. Other researchers have reported that cells tend to lose the Tn5 transposon, so Ausich suspects he is observing a similar instability.

While Ausich and others work to develop practical methods of genetically engineering algae, Chase Van Baalen and his colleagues at the University of Texas Marine Science Institute (Port Aransas, TX) are using classical methods to develop improved strains of Anabaena Spp. for producing hydrogen. The researchers have discovered two strains, CA and IF, which produc "hydrogen at 10 to 20 per cent of the rate at which they conduct photosynthesis". The hydrogen production rates, 32 and 24 microlitre per milligramme of dry weight per hour for CA and IF respectively, are the highest levels ever obtained under normal, aerobic growth conditions. The algae are grown under conditions suitable for the cells to fixed nitrogen, so some of the hydrogen produced is consumed by the algae, but less than 30 per cent of the net hydrogen produced is consumed that way according to Van Baalen. A key factor in both the net hydrogen production and the activity of the enzyme uptake hydrogenase, in whole cells is the level of nickel ions in the growth medium.

Using chemical mutagens, the researchers have produced variants of the algae strains which are even greater producers of hydrogen. Consequently, Van Baalen believes "blue-green algae are a very good prospect for renewable, continuous hydrogen production." (Source: Biotechnology News, Vol. 4, No. 8, p.9)

Biotechnology impact on speciality chemicals

One group of companies, in particular, which ought to take a very close look at biotechnology to see how it might influence its business in the future, is the producers of speciality and fine chemicals.

Speciality chemical categories in which bioproducts already have a natural place are diagnostic acids, food additives, laboratory chemicals and thickening agents. Other categories to which bioproducts may probably contribute in the future include adhesives, biocides, electronic chemicals, flavours and fragrances, flotation reagents, oilfield chemicals, paint additives, paper additives, pesticides, surfactants and water management.

Fine chemicals that could be profitably produced using biotechnology include the l-amino acids and possibly other substances with optical activity. Enzymatic processes will also be used in the synthesis of fine chemicals which are otherwise hard to make, needing multistep synthesis or being too unselective.

To many producers, the traditional process of fermentation, using live organisms in large tanks operated batchwise, appears strange and somewhat frightening. Therefore process technologies more similar to the ones used in the chemical industry will be preferred, including the application of continuous fermentation in high-performance fermenters built to meet specified demands in ozygen transfer rate, mixing, heat removal, asepsis, control and regulation. High productivities in such fermentations could sometimes be achieved by retainment of the micro-organisms in the fermenter or by reclying the micro-organsisms to the fermenter after cell harvest.

The fermentation must be followed by efficient product recovery and purification procedures. These may be as important as the bioprocess itself in determining the overall profitability of the system. In the production of speciality and fine chemicals the complexity of the products and the purity requirements are not as high as in pharmaceutical production. The downstream processing technique can still have a decisive influence on the competitiveness of processes for the production of fine chemicals. In addition, enzymes to be used for such productions are proteins and are often available only in very low concentration mixed with other enzymes etc. Their production requires almost pharmaceutical-type recovery and purification methods.

By the use of membrane reactors with immobilized cells or enzymes, in some applications a regular fermentation step can be entirely avoided or handed over to the supplier of the biocatalyst. This will be of particular interest for such bioprocesses that require only one or a few enzymes.

Although many attempts have been made, systems based on immobilized cells or enzymes have not yet found their way to industrial production of speciality and fine chemicals. High cost and low stability of the support materials used initially have restricted such systems to use in analysis and for high value products.

New matrix materials for immobilization of cells and enzymes giving much improved stability of the catalyst systems have, however, been developed. Such systems will very soon be used industrially for the production of fine chemicals, especially amino acids. With biocatalysts that retain their activity over periods of many months, several other applications should become feasible. (Extracted from European Chemical News, 21 May 1984)

New chemical-sensor technology

Chemical Sensors of the USA will commercialize a proprietary technology for medical diagnostic, environmental sampling, industrial process control and other analytical applications using a technology based on the sensitivity of piezoelectric crystals to minute changes in surface mass caused by specific adsorptions of analyte molecules such as proteins and DNA segments. It can apparently employ a variety of active agents, including monoclonal antibodies and DNA probes which respond to submicrogram levels of analytes, and are expected to require no sample manipulation or chemical separations. Performance is expected to be equivalent to, or better than, current diagnostic assay methods, such as radioimmunoassay and immunofluorescence. (Source: Chemical Week, 24 October 1984)

Energy and environmental applications

R+D on energy from biomass

If not currently a source of energy to the extent once thought possible, biomass is nevertheless still an energy option. And work of various sorts on biomass conversion continues to develop the technology.

After several years of severe cuts in funding, R+D on conversion of biomass and wastes to produce energy continues at a subsistence level. Some small-scale commercial successes have cancelled out some failures, leaving proponents of biomass conversion still looking for an unquestioned economic incentive to build on. But, however desirable the technology for conversion of renewable biomass and waste may be, there is also doubt that it can provide a truly significant amount of energy in the near future. Nonetheless, incremental technical improvements continue to accumulate, and the search for suitable plant species appears to be nearing a decisive stage.

Most of the funding for renewables R+D comes from the US Department of Energy, and most of the funds provided by DOE in 1983 were spent by the Biomass Energy Technology Division, the Office of Alcohol Fuels, and the Office of Energy from Municipal Wastes. All three suffered cuts in 1983. These included projects on short-rotation forestry, herbaceous crops, direct liquefaction, and a number of regional programmes.

One of the more practical results of the Department of Energy's activities has been the loan guarantee programme for ethanol-from-grain production. Ten individual proposals have been selected for consideration and one has already been granted to the New Energy Co. of Indiana, which has begun construction of a 50 million gallons-per-year ethanol plant in South Bend, Ind. The output from these plants will be used for motor fuels.

At least 17 countries other than the US maintain programmes for development of biomass and waste conversion. None of them spend what the US does, but several of them spend a larger fraction of their national incomes for this purpose. The most prolific spenders for biomass R+D outside the US are Sweden, Canada, and Italy.

Most of the impact of the work done thus far in biomass and waste conversion has been felt in two areas - ethanol manufacture and tree production. But the impact isn't as great as it might have been, largely because of constant tampering with R+D goals by the government. The US Energy Security Act of 1980 proposed that 60,000 barrels per day of alcohol fuel production reach about 10 per cent of national gasoline production by 1990. That translates into about 8.5 billion gallons of alcohol. Changeable federal attitudes impeded attaining the goals of the energy act, but even so, 57 per cent of the goals proposed for now have been reached, in terms of production. In 1983, plans were changed again because of a belief in Washington that, although the goals of the energy act were technically attainable, they also would produce an economic disaster. The major problem was a fear that production of ethanol in the amounts envisioned by the energy act would drive up corn prices unnecessarily. The final version of the new plan calls for a maximum production of 1.5 billion gallons of fuel ethanol by 1990. This is not expected to greatly affect corn prices.

The current Department of Energy forecast for nonalcohol biomass energy sources is for production of 4 quadrillion Btu (10^{15}, or quad) of wood and wood residues. Most of it would be used in direct combustion. The Department of Energy expects the contribution of biomass energy by 2010 to be about 4.5 per cent of the national energy requirement. Not everyone agrees with this forecast. The Office of Technology Assessment, for example, thinks the biomass contribution will be even greater. It suggests that, depending on the efficacy of some of the newer agronomy programmes, the contribution could be as high as 17 quads.

Elsewhere in the world, biomass contributes up to 80 per cent of local energy requirements. On a global basis, however, several independent estimates place the biomass contribution at about 9.4 per cent of energy needs, and that is expected to rise to about 11.5 per cent by the end of the century.

Two environmental problems have a direct bearing on the production and conversion of biomass for energy. One is the effect of rising carbon dioxide concentration in the atmosphere. Two new reports on the climatic effects of that increase appeared in 1983, one by the National Research Concil and one by the Environmental Protection Agency, both reports making "best guess" scenarios and concluded that carbon dioxide concentration in the atmosphere would double in the next century. That rise was projected to cause, through the so-called greenhouse effect, an increase in average atmospheric temperatures from 1.5 to 4.5 °C by the time carbon dioxide concentration reached 600 ppm. But NRC cautions against overreaction and advises no major policy changes until research provides a clearer picture.

The second environmental effect of interest to biomass converters is that of dioxin. From the viewpoint of biomass technology, the possibility that dioxins are produced in the combustion of materials containing chlorinated phenols and its precursors. Dioxins are also reported to be formed in trace amounts in the fly ash and soot from industrial and municipal incinerators supplied with solid wastes. Just how great the problems is - if it is one at all - is unknown.

A major concern in the development of renewable resources of energy is ensuring sufficient production of the biomass. Simply planting trees in every available place won't do much but clutter up the landscape. The necessity of allocating growing areas for this purpose demands that approriate species be selected for cultivation. For some years, a programme has been under way in the USA directed to tht end. The programme is still under way, and the choice of species is being narrowed down gradually. Not surprisingly, the choices are proving to be site-specific in most cases.

One well-publicized effort that might have benefited from better species selection was a Braxilian project that finally was terminated when it was discovered that the planners had overestimated the productivity of the local trees by 100 per cent. The Brazilian government has taken over the project in co-operation with a commercial consortium. The cost of the fertilizer necessary to bring the local tree production up to that required by the conversion plant was prohibitive. However, there is some indication that a more modest goal will be effective in retaining the plant. It is a barge-mounted module that can be moved to another location if necessary.

Most interest in biomass centres on trees and other woody plants. However, there is considerable work on species selection and production of herbaceous and aquatic plants. Two plants that have shown some ability to produce chemicals are guayule and jojoba, and about 50,000 acres of guayule are expected to be planted in the southwestern US by 1990 as a production test. The Gas Research Institute of the USA has targeted a hybrid sorghum for investigation as a possible source of biomass under intensive cultivation. Most of the R+D on aquatic species appears to be concentrated on microalgae, freshwater macrophytes, and macroalgae.

In the US, the chief contribution of biomass to energy needs is through the direct combustion of wood in residences and industrial installations. There has been a sharp increase of interest in residential consumption of wood fuel in the Northeast and Midwest. Some of this may be a fad, but much of it is a direct response to fuel prices and local availability of wood. There are also some penalties associated with burning wood. In some places the pollution problems from that activity have caused local officials to require immediate cessation of wood burning when pollution levels reach a certain value. In some instances this is enforced by requiring every wood-burning fireplace to be equipped with a sensor that transmits to a central municipal computer. Enforcement is reported to be swift and severe. The largest commercial wood-burning utility is Burlington (Vt.) Power Co., which operates a 50-MW generator powered from local wood supplies.

There are numerous projects dealing with enzymic conversion, digestion by microbes, and chemical conversion of biomass. These are all of scientific interest, and most have eminently practical objectives. However, few of them have been able to demonstrate an immediate economic utility in competition with established sources of energy.

The panic of the 1970s following the Arab oil embargo led to a number of premature projects on questionable systems. It also saw the beginning of numerous projects of great merit. The ever present threat is that funders and planners won't distinguish between the two. In the quest for immediate results, there is always the possibility of unnecessarily sacrificing meritorious work. However one lesson repeatedly demonstrated in the energy

business, and particularly with respect to renewables is that there is no alternative to maintaining a well-directed, long-term R+D programme. (Extracted with permission from Chemical and Engineering News, Vol. 62, No. 10, page 22, 5 March 1984, American Chemical Society)

A sticky end for pollution

Two researchers from the Physical Chemistry Laboratory at Oxford University, Dr. Alastair Dean and Dr. Lynne Macaskie, have discovered that Citrobacter, a tiny bacterium can be used to remove cadmium from industrial effluent. Cadmium is one of industry's most toxic pollutants and is extremely difficult to dispose of safely. In Oxford, the Citrobacter bacteria take about one to two days to grow and are then separated from their growing medium by centrifuge. The pure bacteria are incorporated into a plastic gel, which is shredded into granules. The granules form a filter and any solution passed through them will emerge less its cadmium, which will have adhered to the Citrobacter. Citrate passed over the granules will give a solution of concentrated cadmium and pure Citrobacter again. The scientists are hoping to raise finance from the Department of Industry to continue their research. (Source: Sunday Times, 6 May 1984)

Subterranean plants to purify waste

Multireaktor (Hillegom, the Netherlands) has developed a plant which uses activated sludge to purify both sewage and biologically decomposable industrial effluent. Where the conventional oxidation ditch or basin system would need an acre of ground, the new plant occupies only 90x90 ft. The process employs a rotating riser inside a combined mixing and aeration zone. Waste water enters the reactor at the top and whirls downward through the aerating and mixing chambers in counterflow against rising oxygen or air bubbles. When the sludge-and-water mixture reaches the reactor bottom, it is forced upward through the riser to a separator at ground level, where the water is taken off. Gas is exhausted through a single tall stack. The reactor has been tested at the Agricultural University of Wageningen. (Source: Chemical Week, 10 October 1984)

Extraction industry applications

Microbial oil recovery

Phillips Petroleum has received a patent for use of microorganisms in oil recovery from existing wells. Any microorganism capable of consuming polymeric materials and producing solvents as a byproduct can be used in the process. A mixture of bacteria and polymer is injected into oil reservoirs to facilitate release of oil from rock formations. Suitable polymeric materials include biopolymers and celluloses. (Source: New York Times, 2 June 1984)

Mineral extraction

The Battelle Memorial Institute (Columbus, OH) will examine the feasibility of applying biotechnologies to mineral and coal processing. Biotechnologies have considerable mineral extraction potential through bioleaching of ores, biomodification of mineral surfaces and bioaccumulation of metal ions from solution. The results could help companies reduce production and pollution abatement costs, while complying with environmental regulations. Biotechnologies can be used in mineral processing for recovery of metals or removing undesirable constituents. Most problems preventing widespread application of biotechnologies in minerals processing are due to the lack of information about them. The study will develop important parameters for the proper design of each process and apply them to real ores and waste streams. (Source: Mining Journal, 11 May 1984)

Industrial microbiology

An enzyme may trim papermaking costs

A newly isolated enzyme that degrades lignin, the intractable polymeric component of wood, offers the promise of cleaner, more economical paper production, as well as a low-cost route to many lignin-derived chemicals, according to researchers at the US Department of Agriculture's Forest Products Laboratory in Madison, Wis.

The enzyme, recovered from the wood-rot fungus Phanerochaete chrysosporium by USDA microbiologist Kent Kirk and postdoctoral student Ming Tien, catalyzes the splitting of carbon-carbon bonds in the connecting links of lignin. The enzyme requires small amounts of hydrogen peroxide for activity.

Lignin, which supplies the structural support in wood, is a chemically resistant molecular web that consists mostly of benzene-like structures interconnected by numerous carbon-carbon and carbon-oxygen bonds. But, when some carbon-carbon bonds are split, as by the fungal enzyme, the molecule is left relatively exposed.

Bond cleavage makes the polymer more susceptible to attack by chemicals used to bleach the dark lignin in brown pulp produced by the widely used kraft papermaking process. The enzyme, says Kirk, might allow paper producers to use less of the expensive and noxious bleaching agents such as chlorine dioxide and hydrogen peroxide and might also be used to decolorize lignin effluents from paper plants; to aid in the recovery of phenol, cresols, xylenes, and other chemicals from lignin; and to treat the surface of wood pulp fibers, perhaps leading to stronger paper. (Source: High Technology, November 1983)

Papain-allergenic tendencies

Papain, a proteolytic enzyme, obtained from unripe papaya fruit, has many industrial applications and, in particular, is used as an agent for tenderizing meat and clarifying beer. It is also a common ingredient in cosmetic, food and drug products. There have been several publications describing allergic reactions (expressed mainly as respiratory illness) which have been attributed to papain exposure. However, despite the potentially considerable exposure of the general public to this enzyme, reports of papain allergy outside the workplace are rare. A recent paper by Mansfield and Bowers (J. Allergy clin. Immun. 1983, 71, 371) helps to fill this particular gap and is especially interesting since ingestion, rather than inhalation, was the chief route of exposure involved.

The authors conclude that the severe systematic allergic reaction observed in the patient was mediated by IgE antibody to papain. They also postulate that papain may be a significant unrecognized cause of allergic symptoms in the general public, particularly since papain exposure is probably increasing due to the growing popularity of natural health food supplements and meat tenderizers. (Extracted from BIBRA Bulletin, December 1983)

Biological catalysts

Biochemists at Liverpool University have developed a new, faster technique for isolating, identifying and classifying restriction enzymes.

The work of the Liverpool team, led by Dr. Peter Dean, is finding immediate applications in a local company, P and S Biochemicals which now offers a range of more than 40 restriction enzymes worldwide to drug companies, genetic engineers, other research workers and university teachers.

The new technique has been developed using funds from the Wolfson Foundation and a "co-operative" award from the Medical Research Council. Co-operative awards are for collaborative projects between academic institutions and industry. It enabled the purchase of a fast protein liquid chromatograph from Pharmacia, the Swedish drugs company. Normally, such machines are used as high performance ion exchange columns. The Liverpool team has adapted its machine for affinity chromatography - the field which Dr. Dean pioneered as a means of obtaining pure enzymes for research.

Affinity chromatography works by putting chemical "bait" into a column of liquid, down which is poured whatever substance is to be analysed. If there is an affinity between the bait and particular constituents of the substance under analysis, those constituents are drawn to the bait like iron filings to a magnet.

The trick that Dr. Dean and his team had already mastered was finding the right bait to isolate restriction enzymes from solutions of bacteria. In 1982, this led to the means by which an enzyme called Aha III could be isolated in commercial quantities from a blue-green algae that flourishes in the Sinai desert. Aha III's importance is that it can recognize and snip out the pieces of genetic material that promote cloning.

What made the process laborious, however, was that it might take two days or more for the substance being analysed to travel down the column, with unstable or short-lived enzymes likely to be missed. Realistically, only three runs could be carried out per week.

The adapted Pharmacia machine pushes solutions down columns under four atmospheres' pressures. A controlling microprocessor spots any indications of unstable enzymes and highlights them. Most important, however, it takes only 15 minutes to deal with each.

The machine's speed has enabled Dr. Dean to start setting up a national screening system whereby biochemists and biologists send likely cultures and samples for testing. The basis for this existed already but was hampered by the speed of testing.

A new enzyme, Rsr II, was discovered recently in sludge dredged from the bed of the River Tamar. So far, scientists contributing material for the screen have been based in the universities of Aberystwyth, Lancaster, London, Cambridge and Bristol.

If a new restriction enzyme is found, the scientist who discovered the bacteria which yielded it stands to get royalty payments. The enzymes sell for between 20p and £10 per unit, depending on rarity and demand. Since a unit is only one microlitre, commercial quantities need only be minuscule.

Dr. Dean says their only competition in supplying restriction enzymes on a large scale is in the US and no one there can operate a screen as they now can. They are issuing a general invitation to microbiologists to co-operate with them in order to find more new enzymes. (Extracted from Financial Times, 24 February 1984)

Protein engineering yields improved enzyme

Anthony J. Wilkinson and his colleagues at the Imperial College of Science and Technology in London and the Medical Research Council Laboratory of Molecular Biology in Cambridge examined the 3-D structure of an enzyme (tyrosyl-tRNA synthetase) and attempted to predict the effects of changing a single amino acid in the functional part of the molecule. They used a piece of synthetic DNA to modify the natural gene coding for the enzyme, so that the chosen amino acid (threonine) was replaced by a different one.

The researchers produced two mutant enzymes, one containing alanine, which is structurally similar to threonine, the other containing proline, which is structurally quite different and hence distorted the backbone of the enzyme. While both altered enzymes displayed elevated catalytic activity, the proline mutant showed a 25-fold increase. The finding that small changes in enzyme structure can result in large changes in function opens the way to engineering industrial enzymes for improved activity or stability. (Source: High Technology, April 1984)

Genex develops enzymes for cleaning applications

Genex Corp. has been working on a range of hydrolytic enzymes for use in cleaning and other janitorial applications. It has used genetic engineering techniques to construct strains of Bacillus subtilis that express at high levels the hydrolytic enzyme alkaline protease, which is currently used in detergents and laundry pre-soaks. Genex is also interested in alkaline protease for other cleaning applications.

The major objective has been the development of a bathroom drain cleaner, although a separate programme is under way to develop a kitchen drain cleaner. The market for such cleaners is substantial: Genex points out that the products in use at present are noxious and hazardous due to the presence of sodium hydroxide (lye) or hypochlorite (bleach).

Current products function by contracting and clumping hair, the main cause of bathroom drain clogging, allowing the material to be pushed down the drain. Genex's product, however, dissolves the hair. The company has also developed a proprietary method for producing beads of the enzyme and its other active ingredients - which it expects to extend the product's shelf life. (Source: Biotechnology Bulletin, No. 5, June 1984)

Marine monoclonals

Monoclonals specific to the commercially valuable fractions of marine algal polysaccharides promise better thickeners and extenders for the food industry, and improved gels for electrophoresis and chromatography. Dr. Valerie Vreeland and co-workers at the Botany Department of the University of California, Berkeley, have developed three dozen monoclonal antibodies to various portions of the mixed carbohydrates in algal cell walls. In work soon to be submitted for publication, the phycologists identified an antibody against polyguluroniate sequence that gives alginate its most valuable property - gelling.

Some applications that Vreeland's group envisions for their marine monoclonals are the selection of better organisms for algal farming, in conjunction with Dr. Donald P. Cheney's work on red algal protoplast fusion at Northeastern University, Boston; evaluating harvested source material for processing; monitoring batches of thickeners and emulsifiers during processing; purifying agarose for use in electrophoresis gels; identifying expression of useful carbohydrates in cell fusion and genetic engineering of algae.

Preliminary work showed that some antibodies also cross-reacted with a pathogenic Pseudomonas alginate. When this species infects the lungs of cystic fibrosis patients, the secreted polysaccharides add to the congestion. Therefore, these antibodies would be useful in understanding the pathology of this organism. (Extracted from McGraw-Hill's Biotechnology Newswatch, 18 June 1984)

Industrial equipment

Fermentation control

A newly developed instrumentation cartridge to control fermentation contains an immobilized enzyme and a temperature gage has been invented by Klaus Mosbach, professor of biochemistry at the University of Lund, Sweden. When broth contacts the enzyme, the temperature rise is measured and related to ethanol or other product concentration in the reaction broth. The response time (1-3 min) lends itself to continuous measurement and control. (US Patent 4 021 307) (MA) (Source: Chemistry and Industry, 2 April 1984)

Stanford gene patent granted

The US Patent Office finally granted Stanford University and the University of California the second of two patents covering the basic gene-splicing technique developed in 1973 by Stanley Cohen and Herbert Boyer. Letters to more than 100 genetic-engineering companies around the world were sent, asking them to accept the patent and pay annual licence fees of $10,000, plus a percentage of sales resulting from any commercial product using the Cohen-Boyer technique. However, University officials are sceptical that the payments will be made, and that precedent-setting court cases are possible. Millions of dollars are at stake, not to mention the future organization of the genetic engineering industry.

Stanford, which is handling the patent for both universities, believes it now has a strong patent that will survive legal challenge. The universities should be able to sue recalcitrant companies which use the technique but do not pay the licence or hand over the royalties. Also, Stanford is planning to raise its rates next January. At the moment companies pay a $10,000 joining fee and $10,000 a year. The universities also receive annual royalties of 1 per cent for the first $5 million net sales; 0.75 per cent for the next $5 million; and 0.5 per cent for sales over $10 million. Some universities are already asking for royalties of 3 per cent on genetic-engineering inventions.

The industry is watching a court case that is bound to affect the Cohen-Boyer patent. It involves Roche Products and Bolar Pharmaceuticals, a generic drug manufacturer. Roche claims that Bolar used a patented compound in its research before Roche's patent expired. At issue is when patented technology used in research becomes a threat to the patent holder. A lower court ruled in favour of Bolar. An appeals court reversed the decision. Now Bolar is contemplating an appeal to the Supreme Court.

Another important precedent was set when the Patent Office refused to accept that Dr. Robert Helling from the University of Michigan, who was on sabbatical leave in Boyer's laboratory in San Francisco when the technique was developed, was a co-inventor. This will make any legal challenge by Helling that much harder. If he had been decreed a co-inventor of the technique then he would have been entitled to a share of the royalties (Cohen and Boyer have waived their rights). (Extracted from New Scientist, 6 September 1984)

Selection of recent patents

Applicant; country	Purpose, use, or process	Application System/No.
University College, London, United Kingdom	Monoclonals against Rh factor: Production of monoclonal antibodies specific for the human Rnesus D antigen, involved in rhesus disease of newborns, by a lymphoblastoid cell line transformed with Epstein-Barr virus. Monoclonals can be used for prevention of Rh disease and blood typing.	GB 2 127 434
Salk Institute for Biological Studies, La Jolla, Calif., U.S.A.	Synthetic pancreatic GRF and analogs: Synthesis of fragments of human pancreatic growth hormone releasing factor (GRF) and active analogs of them - all of which stimulate pituitary growth hormone secretion in humans and animals - by solid-phase, solution or recombinant DNA techniques.	EPO 105 759 WO 84/01379

Max Planck Gesellschaft zur Förderung der Wissenschaften e.V., Göttingen, FRG.	Hepatitis B surface antigen cloned in vertebrate cell lines: Production of peptides with the immunogenicity of hepatitis B surface antigen (HBsAg) for vaccines and diagnosis in vertebrate cell lines, thus avoiding purification and other difficulties encountered in using bcterial and yeast hosts. The gene coding for HBsAg is expressed in vertebrate hosts such as mouse fibroblasts and African green monkey kidney cells using bovine papilloma virus or Moloney mouse sarcoma virus as a vector.	EPO 105 141
Science and Technology Agency Tokyo, Japan	Hepatitis B surface antigen cloned in yeast: Synthesis in yeast of peptides with the immunogenicity of hepatitis B surface antigen for vaccines and diagnosis. Recombinant plasmids containing DNA coding for hepatitis B virus, the repressible acid phosphatase promoter from yeast and DNA sequences necessary for replication in E. coli and inserted into Saccharomyces cerevisiae for expression.	EPO 105 149
Wellcome Foundation Ltd. London, United Kingdom	Foot-and-mouth disease antigens: Peptides with the amino acid sequence of the VP, antigen of foot-and-mouth disease (FMD) virus useful as vaccines against FMD. Peptides can be produced by synthesis, protein cleavage or reverse transcription of FMD viral RNA and expression of the cDNA obtained in hosts such as E. coli. Text contains DNA and amino acid sequences.	EPO 105 481
The University of Rochester, Rochester, N.Y., U.S.A.	Antibodies against tetanus, diphtheria: Method for "consistently and inexpensively producing high titers" of monoclonal antibodies against bacterial toxins, such as those causing tetanus and diphtheria, by culturing hybridomas of mouse myeloma cells and lymphocytes from humans immunized against the toxins. Monoclonals can be used for therapy, diagnosis and production and purification of vaccines.	EPO 105 804
Takeshi Makitsubo, Nagoya, Japan	Extraction of tumor necrosis factor: Method for obtaining tumor necrosis factor (TNF), a protein that attacks cancer cells but not normal cells, "easily and uniformly on a large scale", without impurities, by collecting and culturing macrophages, then destroying them.	WO 84/01288
Claude Bernard University, Lyon, France	Chemical synthesis of sweeter-than-aspartame molecule: Invention describes a series of 11 derivatives of aspartame-related molecules producing "a fine white powder" with sweetening potency "50 to 100 times that of the highest-performance compounds now on the market", notably, aspartame. The new substance is free of "parasite taste such as the bitter aftertaste of saccharine" and because of its claimed superior potency can be sprinkled sparingly like table salt or used at very small concentrations in foods and beverages.	French Patent Office 2533210

U.S. issuances

Assignee	Purpose, use or process	U.S. Patent No.
Sybron Corp., Rochester, N.Y.	Microbial decolorizing of pulp, papermill effluents: New mutant strain of Pseudomonas aeruginosa, when aerobically cultured in pulp and paper mill wastewater, metabolizes hard-to-degrade "colour bodies .. to provide treated wastewater suitable for discharge after any additional conventional processing".	4,444,888
Murray Moo-Young, Waterloo, Ontario, Canada	Bioconversion of Cellulosic wastes: Production of "safe, digestible and nutritious" single-cell protein using the fungus Chaetomium cellulyticum by aerobically fermenting cellulosic materials such as wood; wastes from making paper, coffee and sugar; and bananas, potatoes, yams and cassava.	4,447,530
Armour Pharmaceutical Co., Tarrytown, N.Y.	Synthetic calcitonin: Peptide analogs of calcitonin, used to treat osteoporosis, hypercalcemia and Paget's disease, with tyrosine at position 21. Analogs, synthesized using solid-phase techniques, have "good potency and quality when compared with known calcitonins".	4,444,681
Genentech. Inc., South San Francisco, Calif.	Isolation of human variant: New human growth hormone (HGH) variant obtained by probing gene bank, cloning gene into host to obtain mRNA transcripts without introns, and reverse-transcribing the mRNA to produce cDNA that can be cloned into vectors and hosts for expression. Variant is "doubtless implicated" in HGH metabolic activities. Text includes nucleotide and amino acid sequences.	4,446,235
The Upjohn Co., Kalamazoo, Mich.	Synthesis of bovine form in yeast: Production in yeast of bovine growth hormone (BGH) - used to increase milk, and possibly meat, production in cows. The gene coding for BGH is inserted into plasmids which are grown in E. Coli and expressed in Saccharomyces cerevisiae.	4,443,539
Molecular Genetics, Inc., Minnetonka, Minn.	Antibodies to treat infectious diarrhea: Monoclonal antibodies against surface antigens - pilus proteins and glycocalyx polysaccharides - of pathogenic bacteria such as E. Coli. Antibodies are useful for preventing and treating diarrheal disease in newborn farm animals, and in humans for diagnosis, research and purification.	4,443,549
Massachusetts Institute of Technology, Cambridge, Mass.	Improved bacterial synthesis of heparinase: Production of heparinase without using expensive inducers such as heparin by culturing Flavobacterium heparinium at higher cell densities and with minimal amounts of sulfur. During dialysis, heparinase removes heparin from circulating blood before it re-enters the body.	4,443,545
Regents of the University of California, Berkeley, Calif.	Microbial synthesis of vertebrate proteins: Method for producing, "for the first time", vertebrate proteins in microbial hosts by isolating MRNA, reverse transcribing it to produce cDNA, inserting the cDNA into a bacterial plasmid, and cultivating the host - for example E. Coli - to produce desired protein - for example, proinsulin.	4,440,859

(Extracted from McGraw Hill's Biotechnology Newswatch, 4 June 1984)

F. BIO-INFORMATICS

UK community seeks new computer link-up scheme

British molecular biologists, frustrated by inadequate computing facilities, are attempting to persuade research councils and cancer charities to finance a new national computer link-up and software support scheme for protein and DNA sequencing. A group of prominent researchers voiced their concern from a feeling in the research community that scientists have to waste too much time in writing or modifying programmes that are system-dependent. It was also felt there was scope for an improvement in access to databases.

Enthusiasts in the research community speak of a network of "maybe 6 or 8" VAX machines at national centres, providing regular updates for databases and allowing the transfer of the latest software. These might in turn be connected to microcomputers for local analysis once the letter crunching had been done by the large machines. One estimate puts a price of "one or two million" pounds on the scheme.

The three research councils involved, the Medical Research Council, the Agricultural and Food Research Council (AFRC) and the Science and Engineering Research Council, all have their own budgetary problems. But, it is pointed out, all of these bodies give a high priority to the new biology, and the cancer charities are thought likely to look favourably on the idea. One of the difficulties is that the subject falls between the concerns of several research councils; however, the existence of the inter-research committee has allowed a quick response. And, it is argued, the advantages of a computer link-up have already been demonstrated by the "Starlink" network used by astronomers. (Extracted from Nature, 17 May 1984)

New software package

Battelle Northwest has a new software package that applies computer aided design (CAD) to genetic engineering. The package offers editorial freedom by permitting scientists to design any genetic engineering experiment without having to resort to other computer files or printouts. It is based on 6-colour graphics vs alpha-numeric stores of information. The programme can call up stored information on the genetic profiles of molecules, count the number of DNA building blocks in genetic material, find homologies between molecules, and map restriction sites in DNA. It can also be instructed to display on the VDU a whole plasmid, that could consist of 4,000 bases, or focus on an 8-unit long section. Pieces of DNA can be inserted or deleted at certain spots, and chunks inverted, at any level of magnification. The software, which will run on VAX and mini-VAX computers made by Digital Equipment, will cost $20,000-40,000.

Molecular modeling software reaches micros

A molecular modeling software package for the Apple II and the IBM PC, costing less than $200, will be released by Academic Press (San Diego) The programme creates and manipulates 3-D ball-and-stick molecular models containing up to 500 atoms. It can depict the functional region of an enzyme and enable a pharmaceutical chemist to "dock" candidate drug molecules with it, facilitating the design of new enzyme inhibitors. Although image quality is limited by the low resolution of the display screen, the software makes drug-enzyme docking studies available for the first time to drug designers, biochemists, and educators who do not have access to costly dedicated computer-based modeling facilities.

The software includes several sample molecules, such as the active site of the enzyme thermolysin and its substrate. In addition, the user can construct new molecules interactively by typing in atomic coordinates or by using a 3-D digitizer to enter the positions of atoms in a mechanical model. (A 3-D digitizer hardware/software package is available from Micro Control systems in Vernon, Conn., for about $2,000.) Molecular models are drawn isometrically, with depth indicated by different colours. Molecules can be rotated around any bond or axis, translated, or scaled, and two models can be moved independently for enzyme docking studies. The software also measures bond lengths, bond angles, tortion angles, and interatomic distances, which can be stored on floppy disk.

The programme was developed by Frank Clark, a research fellow at Ciba-Geigy (Ardsley, N.Y.), and James Henkel, an associate professor of medicinal chemistry at the University of Connecticut (Storrs). (Source: High Technology, June 1984)

National computer system for US universities

Intelligenetics is developing Bionet, a national computer system for university and college genetic engineers, under a $5.6 million, five-year grant from National Institutes of Health. Based on a Digital Equipment computer, the system will provide computation services to analyse the sequences of DNA and proteins. The data base will include a vast amount of new information on genes. Its network aspect will help keep the data as current as possible and available to more researchers. An easily accessible pool of current research will also help speed development of early genetic tests for altered genes that signal possible birth defects. With a computer-managed data base, some 300-400 DNA sequence codes can be read in hours, whereas in the past it took 5-10 man-years to read even a few codes. Bionet features a DEC 2060 mainframe containing an array of established national and international data bases: GenBank and EMBL, nucleic acid sequences, NBRF, a protein data base; and VectorBank, a catalog of genetic information. (Source: Information World, 7 May 1984 and Chemical Week, 25 July 1984)

MRC reveals drug action

Medical Research Council scientists have produced - for only the third time ever - an exact computer graphic representation of how a drug binds to its biological active site. The drug attaches to the haemoglobin in red blood cells and the discovery is expected to give considerable help in the design of new analogues for use in treating sickle-cell anaemia.

The team from the Laboratory of Molecular Biology, under Max Perutz, are working on two drugs which affect in opposite ways the oxygen-carrying capability of haemoglobin. By modifying the oxygen affinity it is hoped to find a more satisfactory treatment for the disease which is widespread in the tropics and becoming more common in the UK and USA. It is caused by a single point mutation leading to the replacement of one of the 274 amino acids in the haemoglobin molecule. Carriers of the disease, with the defect on one of the paired sets of chromosomes, receive some protection against malaria and so the frequency of the mutation has increased in many areas. In Uganda, for example, 45 per cent of the population are carriers. However, those unfortunates with the defect on both chromosomes suffer a debilitating disease, often resulting in fatal kidney malfunction or succumbing to infections in their mid to late 30s.

The defect causes the haemoglobin to form a fibrous gel when oxygen levels are low. This causes the blood cells to stick in capillaries blocking access to the tissues. Using crystals of the drug/haemoglobin complex in X-ray diffraction studies and feeding the information into the LMB computer the exact point of attachment was shown.

The drug, ethacrynic acid, in fact bonds at two sites on each half of the symmetrical haemoglobin molecule, with the crucial bond where two haemoglobin molecules join to form the fibrous material. Previously, the anti-tumour agent methotrexate and a sulphonamide drug have been successfully mapped using computer graphics. (Source: Chemistry and Industry, 6 August 1984)

Biotechnology Software Report published

The first issue of Biotechnology Software Report, a new newsletter published by Mary Ann Liebert, Inc., was published in September 1984. Two issues will be published this year and complimentary copies may be had upon request. In future, Biotechnology Software Report will be published bimonthly. The publication will act as a clearinghouse for information on software designed for genetic sequence analysis, manipulation of data and other molecular biology applications, and will provide the research field with information regarding costs and compatibility of software, its capabilities, language, speed and format.

The contents of the first issue include: Compugene's semi-automatic gel-reading/gene-searching for the IBM; microbiology user group news; Biotechnology Software Report bulletin board, containing programmes for AT&T, Apple, IBM, Zenith, Tandy, TI, and other compatible micros; book and programme reviews, including University of Minnesota Sequence Analysis Programme; and gene sequencing plans.

Aside from news, calendar, book reviews and even occasional source code for special routines, the newsletter will cover:

- Publicly accessible databases and mainframe computing facilities
- DNA sequence management analysis, homology searches, restriction enzyme mapping
- Molecular kinetics, dynamics and structure prediction
- Calculating, analyzing and plotting data - mathematical and statistical evaluation
- Interfacing microcomputers to lab equipment

. Literature searching
. Graphics and molecular modeling
. Calculating the surface areas and other parameters of molecules
(Source: publisher's News Release)

Research and training programme in biomolecular engineering, Progress Report 1983: Vol. 1 - Research

The multi-annual research and training programme of the European Economic Community in the field of biomolecular engineering was adopted by Council on 7 December 1981 for the period April 1982 to March 1986. The main objective of the programme recognised as being of primary importance for Europe's development and competitiveness, is to remove the bottlenecks which prevent applications of modern biochemistry and molecular genetics to agriculture and industry. The programme is executed in two phases with a total budget allocation of 15 Mio ECU.

The present progress report has been prepared after the first year of implementation of the programme and is therefore restricted to a review of the work executed in the frame of the first stage of the programme. It outlines, in a condensed form, the results obtained in 1983 through multi-annual cost-shared research contracts between the Commission and public or private institutions in the Member States (volume 1) and through tripartite training contracts between the Commission, individual scientists and host laboratories (volume 2).

The selection of laboratories participating in the cost-shared research actions and the selection of trainees were carried out with the help of the Advisory Committee for Programme Management (ACPM) (Section II).

Research actions. The funds allocated to the first phase of the programme allowed the conclusion of research contracts specifically designed for promoting new applications of biomolecular engineering to agriculture and to agro-food production. These contracts fall within the six following sectors:

Sector 1: Development of second-generation bio-reactors (multienzymatic, multiphasic or co-factor requiring) for agro-food industries.

Sector 2: Improved production, by means of biomolecular engineering methods, of safer substances important for animal husbandry (vaccines, etc.) and for agro-food industries.

Sector 3: Upgrading of plant products, particularly ligno-celluiose, by means of biomolecular engineering methods.

Sector 4: Development of methods (and, in particular, of host-vector systems) for the identification, transfer, expression and transmission of new genetic information in cultivated plant species.

Sector 5: Improvement, by means of genetic engineering, of symbiotic relations between cultivated plant species and micro-organisms in the soil.

Sector 6: Development of methods which render possible the selective screening of cells and protoplasts and their regeneration into fertile and differential plants.

In 1983, the services of the Commission made visits to the contracting laboratories and organized at Louvain-la-Neuve a multidisciplinary meeting where all project leaders met, discussed their results and established collaboration links. The cooperation between the laboratories participating in the programme is particularly well reflected through:

- The direct association of contracts in joint research programmes (two laboratories for the production of sugar derivatives, three laboratories for gene cloning in dairy industries, four laboratories for gene cloning for pecto-cellulolysis, three laboratories for the molecular analysis of male sterility).

- The constitution at Louvain-la-Neuve, of five working groups which will meet regularly throughout the duration of the programme.

While it is difficult to make a detailed appraisal of results obtained in the framework of a research programme which was initiated only one year ago, it is nevertheless obvious from the reports provided by the contractants, that significant advances are being made in all sectors of the programme.

Training actions. In 1983, 15 training contracts were implemented. The list of contracts ending in 1983 or early in 1984 is provided, together with the final report of the trainees, in colume 2 of the present progress report.

The specific objectives of the cost-shared research contracts and of the training contracts presented in the progress report for 1983 are outlined in a "catalogue of contracts" which can be obtained, upon request, from the services of the Commission. It is hoped that this catalogue, together with the present progress report, will provide a clear cross-section of ongoing Community research in Biomolecular Engineering and will be useful to research workers and to decision-making bodies concerned with the stimulation and the development of modern biotechnology in the Member States.

The report is available from the Office of Official Publications of the European Communities, Luxembourg. Price: $14.00.

World Directory of Collections of Cultures and Micro-organisms, Second Edition: Edited by Vicki F. McGowan and V. B. D. Skerman (Brisbane MIRCEN, Australia), was published in 1982 by the World Data Centre on Micro-organisms at the University of Queensland, Brisbane. It contains updated information and lists of species of micro-organisms in about 356 culture collections in 52 countries. The index of culture collections contains information on: address, curator, staff, main interests and functions and numbers of cultures held in the collection. The cultures include algae, bacteria, fungi, lichens, protozoa, tissue cultures, viruses (animal, bacterial, plant) and yeasts.

The catalogue is an important tool for anyone wishing to obtain information on the availability of a certain species of micro-organism. The information, continuously updated, is stored in a computer at the World Data Center. The Volume (US$25) is available from Thomas Rosswall, Department of Microbiology, Swedish University of Agricultural Sciences, S 750 07 Uppsala, Sweden. (Source: MIRCENET Newsletter)

Cairo-MIRCEN: Catalogue of Culture Collection

This catalogue provides relevant information on the bacterial, fungal and yeast collections maintained at Cairo MIRCEN and also on microbial species culture holdings at the Univeristy of Jordan (Amman, Jordan), the King Faisal University (Hopf, Saudi Arabia), and the Agricultural Research Centre (Cairo, Egypt). Details on culture media, parameters of growth, culture maintenance and preservation are also provided.

The catalogue is divided into six sections: 1. List of bacteria; 2. List of fungi; 3. List of yeasts; 4. List of cultures available at other institutes in the region; 5. Media composition; 6. Numerical index for strains.

Please contact: Prof. A. El-Nawawy, Biotecnnology MIRCEN, Faculty of Agriculture, Ains Shams University, Shobra-Khaima, Cairo, Arab Republic of Egypt. (Source: MIRCENET Newsletter)

Amino Acid Biosynthesis and Genetic Regulation, edited by Klaus Herrmann and Ronald Somerville, available from Addison-Wesley, London, UK at £33.95, contains chapters by 29 contributors and aims to provide the reader with a solid understanding of amino acid biosynthesis, how intermediates are diverted from central metabolism to form the amino acids, how this metabolic flow is regulated, and what experimental strategies are used to identify and bypass control points in biosynthetic pathways.

Organic Chemicals from Biomass, edited by Donald Wise of Dynatech and available from Addison-Wesley at £35.95, contains chapters by 21 contributors and reviews the range of organic chemicals made - or potentially produced - fermentation. It ranges from new insights on classical fermentations such as acetone-butanol, ethyl alcohol and acetic acid, to new work on such areas as suppressed methane fermentation.

Nitrogen Fixation News

NifTAL now also has a wind-powered nitrogen fixing project, developed at the Charles F. Kettering Research Laboratory. See the HNEI Newsletter - Renewable Energy in Hwaii which you can get free of charge by writing: University of Hawaii at Manoa, Hawaii Natural Energy Institute, 2540 Dole Street, Honolulu, HI 96822, USA.

Tree seeds available:

The Commonwealth Forestry Institute has assembled a list of N-fixing trees and seed germplasm. both are available free to researchers who are making trials. Interested persons should write to Colin E. Hughes, Research Officer, Unit of Tropical Silviculture CFI, University of Oxford, South Parks Rd., Oxford OX1 3RB, UK. (Source: MIRCENET Newsletter)

Biotechnology: A New Industrial Revolution by Steve Prentis, published by George Braziller, Inc., New York City, is the title of a slim book which qualifies as a premier primer of biotechnology for the motivated non-scientist. From the basics of molecular genetics through fermentation and monoclonal antibodies, it lays out the technical and industrial hows and whys of the field - with superior diagrams. The author is editor of Trends in Biotechnology. (Price $18.50)

Biofuture: Confronting the Genetic Era by Burke K. Zimmerman, published by the Plenum Press of new York and London. This presents a deeper, broader layman's treatment covering not only the research, development and commercialization of biotechnology in all its ramifications, but also its societal implications and likely future evolution. The author, who holds a Ph.D. in biophysics, was until recently assistant to the chairman of Cetus Corporation and is a consultant to UNIDO. (Price $16.95)

Monoclonal antibodies and DNA probes: Perspective for Medical Diagnostics and Therapeutics by Peter F. Drake, and published by Kidder, Peabody & Co., Inc., New York City. In 36 pages, seven charts and 15 tables, this industry analysis sets out the science, technology, investment and market aspects of two high-potential aspects of biotechnology. The author handles BioMedical Technology for Kidder, Peabody's health care research group and is working on a monograph covering scale-up for publication in the fall. (Price $340)

Opportunities for training in biotechnology in Canada, France, Italy, Japan, Federal Republic of Germany, United Kingdom, published by the International Network of Biotechnology, 1 rue Descartes, 75005 Paris, France. This is a catalogue of curricula in the fields of biotechnology - molecular genetics, microbiology, nitrogen fixation, fermentation, enzyme engineering, etc. - cross-referenced to an address list of universities offering the courses. The booklet, in English and French, includes an application for enrolment and for stipendiary support. (Since no price is quoted, it is presumably free.) (Source: McGraw-Hill's Biotechnology Newswatch, 18 June 1984)

Maintenance of Micro-organisms. A Manual of Laboratory Methods, B. E. Kirsop, J. J. S. Snell (Eds). Academic Press (February 1984). This manual has brought together information on the preservation of a wide range of micro-organisms. Easy to use with general information on culture collection services and over 1,000 references. Price £11.60 - UK/$20.

Recent publications available from Technical Insights, Inc., P. O. Box 1304, Fort Lee, NJ 07024, USA:

Monoclonal Antibodies: Technical Opportunities
Price: $645

Annual Report on Genetic Technology: 1983: The year that was ...
Price: $215
1984: The year to come

Annual Report on Energy and Chemicals from Biomass: 1983:
Price: $205
The year that was ... 1984: The year to come

Biomass Process Handbook, An Updated Production/Economic Guide
Price: $540
to 42 Chemical Processes

Genetic Technology. A Guide to Key R&D Projects
Price: $237

G. MEETINGS

21-23 November 1984	European Biotechnology Conference, Geneva, Switzerland
25 November - 1 December 1984	Fifth International Congress of Culture Collections, Bangkok, Thailand. (Dr. Robert E. Stevenson, Chairman, ICCC-V, American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD 20852, USA)
26-30 November 1984	International Resources for Biotechnology, Bangkok, Thailand (Dr. P. Atthasampunna, Thailand Institute of Scientific and Tech. Research, Bangkhen, Bangkok 9, Thailand)

14-18 January 1985	Hybridoma/Monoclonal Antibody Production, to be held at The Center for Advanced Training in Cell & Molecular Biology. Washington, DC. Contact: Roland M. Nardone, Director, The Centre for Advanced Training in Cell & Molecular Biology. The Catholic University of America, Washington, DC 20064. Call: (202) 635-6161.
19-26 January 1985	Nuclear Envelop Structure and RNA Maturation, to be held at Steamboat Springs. CO. Sponsored by UCLA Symposia on Molecular & Cellular Biology. Contact: UCLA Symposia. Molecular Biology Institute, University of California, Los Angelos, CA 90024. Call: (213) 206-6292.
26 January - 2 February 1985	Monoclonal Antibodies and Cancer Therapy, to be held in Park City, UT. Sponsored by Hoffmann-La Roche and UCLA. Contact: (See January 19).
3-6 February 1985	Fifth Annual Congress for Recombinant DNA Research, to be held at San Francisco Hilton, San Francisco, CA. Sponsored by Scherago Associates, Inc. and Mary Ann Liebert, Inc., Publishers. Contact: Scherago Associates, Inc. 1515 Broadway, New York, NY 10036. Call: (212) 730-1050.
3-6 February 1985	Fifth Annual Congress for Recombinant DNA Research, Fourth Annual Congress for Hybridoma Research, and the Second Annual Congress for Automation. Scale-Up and the Economics of Biological Process Engineering will be held February 3-6 at the San Francisco Hilton, San Francisco, Calif. Contact: Scherago Associates, 1515 Broadway, New York, NY 10036. Call: (212) 730-1050.
3-6 February 1985	Second Annual Congress for Automation, Scale-Up, and the Economics of Biological Process Engineering, to be held at San Francisco Hilton, San Francisco, CA. Sponsored by Scherago Associates, Inc. and Mary Ann Liebert, Inc., Publishers.
11-15 February 1985	The 17th Miami Winter Symposium, "Advances in Gene Technology: Molecular Biology of the Immune System", to be held at the Hyatt Regency Miami Convention Center, Fla. Contact: Sandra Black, Miami Winter Symposium, P.O. Box 016129, Miami, FL 33101. Call: (305) 547-6265.
17-29 March 1985	Recent Developments in Biotechnology. A NATO/ASI Meeting, co-sponsored by the Laboratorio Nacional de Engenharia e Tecnologia Industrial and the Institute for Biotechnological Studies (U.K.). Location - Troia, Portugal. For further information apply to Dr. Jose Duarte, LNETI, Queluz de Baixo 2745 Queluz, Portugal.
25-28 March 1985	Controlled release technology: Polymeric delivery systems for drugs, pesticides and foods, Munich, FRG. (For further information apply to Ms. Maria Clara Suva-Martin, Industrial Liaison Program, Massachusetts Institute of Technology, Cambridge, MA 02139, USA).
1-4 April 1985	SGM Symposium: Viruses and Cancer, Warwick (Meetings Assistant, SGM, Harvest House, 62 London Road, Reading RG1 5AS, UK).
21-23 May 1985	Biotech 85 Europe, International Conference and Exhibition, Palexpo, Geneva, Switzerland (Online Conferences Ltd., Pinner Green House, Ash Hill Drive, Pinner HA5 2AE, Middlesex, UK).

June 1985	Colloquium on Biotechnology. This conference to be held at Szeged, Hungary, will focus on the importance of biotechnology in future economic development. Organized by the United Nations Economic Commission for Europe (ECE), it is aimed at helping governments and officials to give biotechnological development programmes and strategies their place in the various branches of research. Further details may be obtained from Division de l'Industrie et de la Technique, EEC/ONU, Palais des Nations, 1211 Geneva 10, Switzerland.
2-6 June 1985	Thirty-sixth Meeting Tissue Culture Association, New Orleans, USA. (Frederick H. Kasten, Dept. Anatomy, Louisiana State Medical Center, 1100 Florida Ave., New Orleans, LA 70119, USA)
5-6 June 1985	A Meeting for Discussion: Design construction and properties of novel protein molecules, London, UK. (Miss C.A. Johnson, The Royal Society, 6 Carlton House Terrace, London SW1Y 5AG)
27-28 June 1985	SGM Scottish Branch: The Biology and Molecular Genetics of Human and Animal Viruses, Glasgow (Dr. D.E.S. Stewart-Tull/ L. MacInnes, MRC Institute of Virology, Church Street, Glasgow G11 5JR, UK)
7-13 July 1985	Fourteenth International Conference on Medical and Biological Engineering and Seventh International Conference on Medical Physics, Helsinki, Finland. (N. Saranummi, Finnish Society for Medcical Physics and Medical Eng., PO Box 27, SF 33231 Tampere 23, Finland)
1-6 September 1985	Sixth International Symposium on Bioaffinity Chromatography and Related Techniques, Prague, Czechoslovakia. (Dr. J. Turkova, Institute of Organic Chemistry and Biochemistry CSAV, Flemingovo n.2, CS-166 10 Prague 6 Czechoslavakia. Tel. (422 324541, Int. 080)
2-5 September 1985	International Symposium on Chromosome Sorting and Genetic Engineering, University of Nijmegen, The Netherlands. (For further information apply to C. Haanen, Dept. of Hematology or H. Bloemers, Dept. of Biochemistry, University of Nijmegen, The Netherlands)
10-12 September 1985	Tissue Culture Association (37th Annual). Chicago, IL, USA. (Nancy Jo Lewis, Northwestern University Medical School, Center for Endocrinology, 303E Chicago Ave., Chicago, IL 60611, USA)
10-12 September 1985	FEMS Symposium: Natural Antimicrobial Systems, Bath, UK. (R.G. Board, School of Biological Sciences, Universtiy of Bath, Claverton Down, Bath BH2 7AY, UK)
17-20 September 1985	Pathogenic Mechanisms and Vaccine Development Against Bacterial Diseases, Bethesda , USA. (John B. Robbins, National Institute of Child Health and Human Development, Bldg. 6, Rm. 416, NIH, Bethesda, MD 20205, USA. Tel. 301 496 1185)
24-25 September 1985	Enhanced Biological Phosphorous Removal from Wastewater, Paris, France. (Michel Florentz, Seminaire Phosphore, Anjou Recherche, 52 rue d'Anjou, 75384 Paris Cedex 08, France)
8-10 October 1985	BIOTECHNICA '85, Hannover will concentrate on industrial potential of biotechnology. For further information apply to Deutsche Messe und Ausstellungs-AG, Messegelände, D-3000 Hannover 82, FRG.

21-23 October 1985	BIOTECH 85, USA, Washington Convention Centre, Washington DC, USA. (For further information apply to Online Conferences Inc., Suite 1190, 2 Penn Plaza, New York, NY 10121, USA)
27-29 November 1985	BIOTECH 85, Asia, Hyatt Regency, Singapore. (For further information apply to Online Conferences Ltd., Pinner Green House, Ash Hill Drive, Pinner HA5 2AE, Middlesex, UK).

Advance notice

20-22 February 1986	International Meeting on Interferon and Biotechnology, Havana, Cuba. For further information contact Dr. Manuel Limonta Vidal President Organizing Committee II Seminario sobre Interferon P.O. Box 6072 Havana, Cuba

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