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UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

Genetic Engineering and Biotechnology Monitor

16656

1987/1

Dear Reader,

The progress of work relating to the International Centre for Genetic Engineering and Biotechnology (ICGEB) has reached a stage that research work could begin by September 1987. One building at Trieste (Italy) is ready and the provisional facilities at the National Institute of Immunology in New Delhi (India) will be ready by September. The initial work plan for the Centre has been prepared by the Director, Prof. I. C. Gunsalus, assisted by Profs. A. Falaschi and K. K. Tewari. The following research areas will be addressed: New Delhi Component: (1) Programme on agrobiology (a) control of expression of transferred genes; (b) cytoplasmic male sterility; (c) plant proteins; (d) herbicide resistance; and (e) nitrogen fixation. (2) Programme on human parasitology: (a) malaria; and (b) hepatitis. Trieste Component: (1) Programme on viral diseases: (a) human papilloma viruses; and (b) rotaviruses. (2) Programme on molecular aspects of DNA replication in human cells. (3) Programme on microbiological degradation of lignocellulose.

In addition, training of scientists is envisaged both at the Centre and the affiliated centres, and also in non-ICGEB institutions. Initially attention will be on short-term training. The work plan also envisages co-operation with affiliated centres through (a) advisory services; (b) training for affiliated centre personnel; (c) training organized by affiliated centres; and (d) joint research programmes. A forum of scientists of the Member countries of the ICGEB is expected to be convened in the second quarter of 1988 and to interact with the Panel of Scientific Advisers. Among the workshops under consideration are one on molecular biology of photosynthesis to be held in July/August 1988 at New Delhi, India and a joint workshop with the International Centre for Theoretical Physics to be held at Trieste during the first quarter of 1988.

We hope to start a section in the Monitor on the work of the ICGEB affiliated centres and are inviting these centres to provide us with information on a regular basis on their activities. We are also planning to accept advertisements in the Monitor to a limited extent, and you will find more information on this in a later issue.

Other activities of UNIDO in the field of biotechnology are continuing. Two workshops are foreseen for September 1988, one in Cuba involving Latin American countries and another in Saudi Arabia. Seven senior experts on specific areas of biotechnology visited Kuwait in April 1987 to participate in the development of a detailed biotechnology plan for Kuwait.

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

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You will find extracts of the work plan on research and other activities under the interim programme of the ICGEB in this issue of the Monitor. The work plan is subject to the approval of the Preparatory Committee of the ICGEB which will meet in June 1987.

As of 1987 we will be numbering the quarterly issues of the Monitor, as above. The material contained in this issue also includes items from the last quarter of 1986.

Development and Transfer of Technology Division,
Department for Industrial Promotion,
Consultations and Technology

CONTENTS

A. POLICY, NEWS AND OTHER EVENTS

UNIDO News

Positions available at the International Centre for Genetic Engineering and Biotechnology

Applications are now being processed by the International Centre for Genetic Engineering and Biotechnology (ICGEB). Appointments are open to recent Ph.D. graduates in chemical and biological sciences, including chemistry, biochemistry, molecular biology or biology. Research interest are molecular virology, plant molecular biology, parasitology, bacterial physiology and genetics. At Trieste research centres on the molecular aspects of DNA replication in human cells, the molecular, immunological and pharmacological aspects of human papillomas and rotavirus infection. At New Delhi, the research is focused on molecular aspects of hepatitis virus, plant molecular biology, and parasitology with special emphasis on protozoa infections.

Preference will be given to candidates with publications in peer reviewed journals with strong training in chemistry and biology.

Work plan of research and other activities under the interim programme of the ICGEB

This workplan is drawn up within the framework of the interim programme of the ICGEB, but it should be emphasized that the programme will need to be periodically reviewed and focused in the light of the experience gained, keeping in mind the flexibility required for implementation which will critically depend on the quality and type of scientists recruited and the quality and amount of available laboratory space commensurate with the progress of activities. The workplan is envisaged under four headings:

(1) Research;
(2) Training;
(3) Affiliated Centres; and
(4) Other activities.

Research activities

The New Delhi Component will focus on agriculture and human and animal health and the Trieste Component on industrial applications of biotechnology.

It has however, been necessary to limit the number of research areas for several reasons, keeping in mind the importance of achieving a critical mass of effort with the amount of resources available. In choosing particular research areas (within which topics will have to be more specifically identified as senior scientists are recruited), regard has been paid in particular to the following criteria: adequacy of requirements in terms of equipment and other facilities for research; high scientific content of the problem involved, which is an important point for attracting the most talented and motivated scientists; and the possibilities of obtaining within a reasonable time useful and significant results, considered in context with research in other established laboratories.

Based on the foregoing, it is proposed that the following research areas will be addressed:

New Delhi Component:

(1) Programme on agrobiology:

(a) Control of expression of transferred genes;
(b) Cytoplasmic male sterility;
(c) Plant proteins;
(d) Herbicide resistance; and
(e) Nitrogen fixation.

(2) Programme on human parasitology:

(a) Malaria; and
(b) Hepatitis

Trieste Component:

(1) Programme on viral diseases:

(a) Human papilloma viruses;
(b) Rotaviruses.

(2) Programme on molecular aspects of DNA replication in human cells.

(3) Programme on microbiological degradation of lignocellulose.

Taken together the initial programmes of the two components will focus on important research areas in the field of agriculture and human health, with the possible addition of lignocellulosic degradation. It is considered that scale for industrial application of the research results in the field of human health will be taken up by the Trieste component as they emerge. From the research one might expect the production of diagnostics which are very useful products with high added value and quite adapted to small- and medium-scale industries in developing countries. In the same light, vaccines could be developed, traditional or new, as well as new drugs and applications; these could be obtained either by classical means or by genetic engineering approaches. The pursuit of these possibilities must depend on the achievement of sufficient progress in research.

The programme in agrobiology aims at qualitative and quantitative improvements in agriculture. Work on the control of expression of transferred genes is considered to be fundamental so as to ensure effective results from genetic engineering in terms of actual agricultural output. Attention is also given to the subject of cytoplasmic male sterility so as to enhance the possibilities of obtaining high yield varieties. Focus in this respect will be on pearl millet male sterility, which is an important crop that thrives in arid regions. The work on plant protein quality will concentrate on Amaranthus, again a crop of importance to developing countries. The topics of pesticide resistance and nitrogen fixation will receive attention. Although work on these and other areas is carried out in a variety of laboratories, because of their overall importance it is considered that a "centre of excellence" like the ICGEB should also consider those aspects with defined "niches" in the developing countries and work at the cutting edge of science. Thus the work on nitrogen fixation will concentrate on slow growing Rhizobium which associates with legumes which grow in developing countries.

In regard to the programme in human parasitology, though work is carried out elsewhere in regard to malaria and hepatitis, the point of departure is the development of malaria vaccines suitable to diverse developing-country conditions since the malaria parasite has many stages in its life cycle and each stage is antigenically different and could potentially be interrupted by different vaccines. Likewise, the research programme in hepatitis viruses will emphasize viruses in developing countries, since no such screening has been carried out so far in the work done elsewhere. It is thus possible to tune the research work more closely to the considerations and requirements of developing-country environments.

For the research programme of the Trieste component, recent epidemiological data show that the human papilloma virus represents a particularly important health problem for the developing world, aggravated by inadequate hygiene facilities and

conditions of life. In some regions of Africa papilloma-based genital cancer is the main cause of death by cancer in women. It is considered that there is ample room for novel and significant contributions in this field in a relatively short span of time. Likewise, rotaviruses represent a family of RNA-based viruses of great importance to the developing countries since they are the main cause of infant mortality in most areas of the tropical world, due to their causing particularly severe forms of diarrhoea in infants. The programme on molecular aspects of DNA replication in human cells is expected to have a strict correlation in particular with the study of the molecular and cellular aspects of human papilloma viruses since they grow by using the DNA replication apparatus of the host cell.

The rationale of a programme on microbial degradation of lignocellulose is particularly cogent to the developing countries wherein excess feedstocks are suboptimally used and both pure cellulose and lignin byproducts can have enhanced use and economic value. Work in this field is of interest and importance and deserves additional efforts which may be sources of funds under grants from joint programmes.

The research programme as suggested above, is expected to have relevance to the work contemplated in several affiliated centres. In the light of a careful identification of possible joint programmes, complementary research efforts can be developed with the affiliated centres as additional and new areas of research are promoted. For example, regarding the New Delhi component, Algeria is also interested in nitrogen fixation, Argentina in trypanosomes, China in agricultural plants and hepatitis B vaccine. Cuba is involved in genetic transformation of Gramineae, Egypt is working on plant cell culture and propagation, and Nigeria on hepatitis B vaccine, plant pathogens and malaria chemotherapy. Venezuela has a large programme in Chagas disease, malaria, schistosomiasis, leishmaniasis, and nitrogen fixation. In relation to the Trieste component, Algeria, Argentina, Bulgaria, Cuba, Greece and Nigeria are interested in enzyme engineering. The same countries plus Senegal and Venezuela are also interested in vaccines and diagnostics. Monoclonal antibodies are of particular interest to Algeria, Argentina, Bulgaria, Greece, Nigeria, Venezuela and Yugoslavia. The use of cellulose waste is of interest to Argentina, Chile and Cuba.

Training

One of the central aims of the ICGEB is to provide training, particularly through a two-year training programme. The full scale organization in the Trieste and New Delhi components will require some time as scientists join the Centre and develop work in laboratories to interact most fruitfully with young scientists from member countries. Hence a combination of training approaches is envisaged for the interim programme:

(a) Regular training in the ICGEB under a two-year training programme. Four trainees can be accepted in 1987 and six in 1988 in each component.

(b) Short-term and/or regular training in non-ICGEB institutions is under consideration and could be useful also to screen prospective research scientists for ICGEB.

(c) Short-term training courses of 3 to 8 weeks are planned in the two components or affiliated centres. It is hoped to organize 8 such training courses in all involving at least 80 participants during the interim programme. There will be two or more courses in 1987 and three are in the planning stage for 1988. As an example of the courses proposed, there is a proposal for a training workshop at the ICGEB New Delhi in the field of molecular biology of photosynthesis. Another one, scheduled for 21-25 March 1988, will be organized in Trieste jointly by ICGEB and ICTP on Protein Structure and Protein Modification with workshops and speakers from both major research centres and developing countries. Furthermore, the affiliated centre in Crete has offered a course on molecular genetics. The Centre in Belgrade has offered one on cloning; the centre in Beijing has proposed a course organized by David Hopwood on the molecular genetics of streptomycetes; the Centre in Buenos Aires is proposing a course on general microbiology of soil organisms and nitrogen fixation. Other initial contacts and proposals from member countries have resulted in the mailing of a first volume on "Extra- chromosomal Elements in Eukaryotes" to the libraries of the affiliated centres. A second volume on "Plasmids in Bacteria" is available for the same distribution.

A systematic flow of information to and from member countries, including site visits, must be assured and operating so that ICGEB may be aware of the research and training requirements of those countries; this will help in the planning of training courses and workshops. This mutual awareness of needs and opportunities may be helped greatly by the preparation and distribution by ICGEB to member countries of appropriate brochures and questionnaires.

Affiliated centres

Bearing in mind the interim programme, co-operation with affiliated centres would include:

(a) Advisory services;
(b) Training for affiliated-centre personnel;
(c) Training organized by affiliated centres; and
(d) Joint research programmes.

The activities relating to training have already been indicated. To start other activities, including advisory services and joint research programmes, it is proposed that all countries whose institutions have been granted affiliated status will be visited by a scientific mission of one or more scientist(s), organized by the Director. The Director, the two heads of components and members of the Panel of Scientific Advisers (PSA) will participate in such missions. Through this process the scope for joint research programmes and the possibilities of interactions for mutual enhancement for the affiliated centres is an anticipated objective.

Other activities

(a) Advisory services will be provided to member countries concerning institutional, policy or scientific aspects of research and application of biotechnology. The Director will draw upon the expertise available worldwide and arrange for such advisory services in consultation with the governments and their scientists.

(b) Visiting research scientists with eminent established records will be invited to participate in and advise on research of each component once scientific work has started. Several such visits including those permitted by the Workshop with ICTP on Proteins and the one on Synthesis in Plant Organelles are envisaged for 1988.

(c) Expert group meetings with specific topics of critical importance to each component and member countries' research programmes are foreseen for 1988-1989 with topics to be identified.

(d) PSA meetings are anticipated to be convened once a year as projected in the Statutes with more frequent consultation on selected topics including personnel section, research conferences and an aid for training programmes.

(e) A Forum of Scientists from member countries is to be considered by the PSA at its May 1987 meeting. The Forum will be organized with the aim of assuring the meeting and interaction of the ICGEB Director, Heads of components and PSA with scientists of the affiliated centres and of other member countries.

Appointment of the Heads of Components

Prof. A. Falaschi, on appointment as Head of Trieste Component, assumed his duties on a part-time basis on 1 November 1986, and from 1 April 1987, has established on a full-time basis his office at Trieste to commence his work programme as Head of the Component.

Following the Preparatory Committee's endorsement of the proposal of the Panel of Scientific Advisers, the panel of candidates for the New Delhi component was enlarged to include Prof. K. K. Tewari. The Director of the ICGEB, after careful consideration of the candidates' merits and availability, selected Prof. K. K. Tewari as Head of New Delhi component.

Appointment of administrative and scientific personnel at the New Delhi and Trieste components

As of 13 April 1987, Prof. A. Falaschi has appointed the first supporting staff for the component. As regards the recruitment of scientific personnel for the ICGEB, the Director, assisted by both the Head of Trieste and New Delhi components, prepared terms of reference for senior and junior scientists. A general announcement was subsequently published in leading scientific periodicals. Simultaneously, UNIDO brought the advertisement to the attention of the ICGEB member countries by letter and the UNIDO Project Personnel Recruitment Branch made a similar announcement through the national recruitment services of European countries.

As of 11 May 1987 more than 100 applications for scientific appointments have been reviewed and are under consideration. The screening procedure and final selection is subject to scientific merits, field of expertise, availability of post in the component of choice as well as the time schedule and the research projects to be pursued initially. The advice of the Panel of Scientific Advisers will be obtained in the screening of candidates.

ICGEB - List of affiliated centres

Argentina:

"Fundación Campomar" Instituto de Investigaciones Bioquímicas
Patricias Argentinas 435
1405 Buenos Aires, Argentina
Tel.: 88-4016/4019, Telex: 18694 ibuba ar

Responsible person: Dr. Luis F. Leloir, President

Algeria:

Ministère de l'Enseignement Supérieur
Route de Dely Ibrahim
Beni-Messous-Algerie
Tel.: 79 01 02 or 79 02 49 or 79 19 08

Responsible person: Chekib-Arslane, Conseiller (Adviser: Biotechnology Programme)

Bulgaria

Research Centre for Biotechnology
125 Lenin Blvd., bl. 2
1113 Sofia, Bulgaria
Tel.: 70-55-26/70-41-49
Telex: 22348 teh p.o bg

Responsible person: Dr. Kostadin Ganchev, Executive Director

The Research Centre for Biotechnology (Institution)
Bulgarian Academy of Sciences
Academician Georgi Bonchev Str.
26 block
Sofia

China:

China National Center for Biotechnology Development
54 San Li-he Rd.
Beijing
China
Tel.: 89 42 33
Telex: 22349 Answer back code: SSTCC CN

Responsible person: Dr. Yonghui Liu, Deputy Director

Cuba:

Centro de Investigaciones Biologicas
Ave. 134 entre 23 - 25
Cubanacan, Playa
Habana
Tel.: 20-0071 to 78
Telex: 511072 cubacib

Responsible person: Dr. Pedro Lopez S. [illegible], Director

Egypt:

The Egyptian Affiliated Centre for Genetic Engineering and Biotechnology
ASRT, 101 Kasr El-Eini Street
Cairo, Egypt
Tel.: 55-10-47/54-65-32
Telex: 93069 Answer back code: ASRT UN
Cable: ACASCTI

Responsible person: Dr. Mohamed Abdel Hadji, Director

Greece:

Institute for Molecular Biology and Biotechnology
The Research Centre of Crete
P.O. Box 1527
Heraklion, Crete
Greece
Tel.: 30/81/235967

Responsible person: Dr. F. C. Kafatos, Director

Nigeria:

Federal Ministry of Science and Technology
Medical and Natural Sciences
9, Kofo Abayomi Street
P.M.B. 12793
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Lagos
Tel.: (01)-614622

Responsible person: Dr. O. Ogunye, Director

National Institute for Medical Research
Edmond Crescent
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Yaba
Lagos

Cable: MEDRESCOM, LAGOS

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Genetic Engineering Center
Vojvode Stepe 283
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Belgrade
Yugoslavia
Tel.: 491-198 Office, 491-395 Laboratory
Telex: 11847 VEMONT YU

Responsible person: Prof. Vladimir Glišin, Director

Status of Signature/Ratification of the Statutes of the ICGEB (as of April 1987)

State	Statutes	Protocol	Ratification or Acceptance
Afghanistan	13 Sept. 1983 1/ 28 Mar. 1984 2/	15 Aug. 1984	
Algeria	13 Sept. 1983	4 Nov. 1985	
Argentina	13 Sept. 1983	4 Apr. 1984	
Bhutan	31 May 1984	31 May 1984	7 May 1985
Bolivia	13 Sept. 1983		
Brazil	5 May 1986	5 May 1986	
Bulgaria	13 Sept. 1983 1/	4 Apr. 1984	23 June 1986 3/
Chile	13 Sept. 1983	4 Apr. 1984	
China	13 Sept. 1983		
Colombia	21 Nov. 1986		
Congo	13 Sept. 1983		
Cuba	13 Sept. 1983	4 Apr. 1984	30 June 1986
Ecuador	13 Sept. 1983		
Egypt	13 Sept. 1983	2 Jan. 1986	13 Jan. 1987
Greece	13 Sept. 1983	4 Apr. 1984	
Hungary	13 Jan. 1987		13 Jan. 1987
India	13 Sept. 1983	4 Apr. 1984	9 July 1985
Indonesia	13 Sept. 1983		
Iraq	28 Feb. 1984	23 Oct. 1984	19 Feb. 1985
Italy	13 Sept. 1983	4 Apr. 1984	
Kuwait	13 Sept. 1983		21 Oct.1986 3/
Mauritania	13 Sept. 1983		
Mauritius	19 Sept. 1984	19 Sept. 1984	
Mexico	13 Sept. 1983 1/ 21 May 1984 2/	25 Oct. 1984 1/	
Morocco	19 Oct. 1984	19 Oct. 1984	
Nigeria	13 Sept. 1983	2 May 1985	
Pakistan	4 Nov. 1983		
Panama	11 Dec. 1984	11 Dec. 1984	12 Aug. 1986
Peru	22 Mar. 1984	4 Apr. 1984	
Senegal	29 June 1984	29 June 1984	4 May 1985
Spain	13 Sept. 1983		
Sudan	13 Sept. 1983		
Thailand	13 Sept. 1983		
Trinidad and Tobago	13 Sept. 1983	8 Feb. 1985	
Tunisia	27 Oct. 1983		
Venezuela	13 Sept. 1983	4 Apr. 1984	15 Oct. 1985
Viet Nam	17 Sept. 1984	17 Sept. 1984	
Yugoslavia	13 Sept. 1983	4 Apr. 1984	18 March 1987
Zaire	13 Sept. 1983		

1/ Signature ad referendum
2/ Confirmation of signature ad referendum
3/ Ratified with a declaration

UN and other organizations' news

FAO - Towards free access to plant genetic resources

Further steps were taken recently to increase co-operation in conserving and freely exchanging the world's plant genetic resources (germplasm). A working group of the Commission on Plant Genetic Resources at the United Nations Food and Agriculture Organization (FAO) met for the first time in June 1986 to examine important legal issues concerning germplasm collections, as well as a feasibility study on the establishment of an international fund for germplasm and other technical matters.

The Commission was set up in 1983 and charged with an "undertaking" to ensure the development, strengthening and monitoring of a global system for germplasm. A working group was set up to monitor progress and make recommendations.

Most of the germplasm needed for plant breeding, seed protection and seed improvement is located in gene banks in the industrialized countries, although much of the basic plant material for these collections originally came from gene-rich developing countries, which are often denied access to such resources on the grounds of protecting plant breeders' rights. These resources are widely regarded as vital to the food security of the Third World.

One of the main tasks of the working group was to analyse the legal aspects of the reservations expressed by some industrialized countries about moves to offer greater access to germplasm for Third World countries. It must also find ways to attract the widest possible acceptance of such an arrangement. According to the FAO, some of the reservations are limited to specific problems or to certain types of seed, which in themselves do not present a major obstacle. On the other hand, broader questions of plant breeders' rights and of the demand for unrestricted access to genetic resources, which have been expressed by some 20 countries, are formidable barriers to an international agreement.

Another important issue reviewed by the working group was the relationship between FAO and the International Bank for Plant Genetic Resources (IBPGR), which is staffed by and housed in the FAO headquarters in Rome. The IBPGR, which aims at collecting, preserving and ensuring free access to plant genetic resources, has been severely criticized by some non-government organizations for its alleged collecting of material in developing countries in the name of the FAO and storing it in the industrialised countries, particularly the US.

The working group expressed concern over the financial constraints and lack of infrastructure and of trained personnel in the Third World countries - the frequent causes of bottlenecks in research operations. Consequently, "research and development of valuable germplasm is often transferred to industrial countries outside the natural range of species concerned, thus decisively influencing the research priorities and de facto control over this resource", the working group concluded.

As a result of the group's recommendations, the FAO is appealing to potential donor governments, organisations and industries to give financial support to an International Fund for Plant Genetic Resources, to help Third World farmers. (Source: Asia-Pacific Tech Monitor, September - October 1986).

Social issues

Call for stricter legislation

Tighter legislative and regulatory restrictions, and greatly increased public awareness of

biotechnology research and development activities were on the agenda for action developed at the Committee for Responsible Genetics' conference in November on Creating an Agenda for Biotechnology: Food, Health and the Environment. One recommendation which emerged from the conference was that a research moratorium should be imposed until a new, tighter regulatory framework could be put in place. There was a clear consensus among those attending the conference that current regulations and laws were inadequate to oversee continued safe and socially responsible development in this critical area of scientific research. Part of the problem was felt to lie in the fact that, unlike issues such as nuclear power and toxic waste, there has until now been limited public awareness of these complex issues and little public participation in the decision-making process. The Committee for Responsible Genetics, located at 186A South Street, Boston, MA 02111, USA, plan to move forward actively in the coming months to begin implementing many of the conference recommendations. (Source: Biotechnology Bulletin, Vol. 5, No. 11, December 1986.)

Ethical and social issues of genetic testing

New genetic tests are raising a host of legal, social and ethical issues. Some tests will be able to tell whether a person has an untreatable disease that will strike much later in life, like Huntington's disease. The ability to screen large numbers of people for various disorders raises the questions of who should be screened, who should pay for it, and who should have access to the results. In utero tests inevitably lead to questions affecting abortion and in utero treatments. Legal issues involved in screening are numerous. Employers might dismiss a person found to have a disease that will shorten the employee's working life. By 1991 tests will be available for any human gene. There are already about 1,000 restriction fragment length polymorphisms that detect a site on the genome where a variation in the DNA sequence occurs.

Using the genetic markers for diseases may eventually allow the causative genes themselves to be found, and perhaps this information can help produce effective treatment. However some tests will indicate diseases for which no treatment is known. APKD, for example, can be detected, but it is an adult-onset, incurable disease. Also at issue is whether a screening programme for a given disease should be mandatory or voluntary. Prenatal diagnoses will raise questions of what rights the foetus has to treatment, especially if the treatment puts the mother at risk. No review or licensing process currently exists for genetic screens. (Extracted from Medical World, 22 September 1986)

Regulatory issues

EEC plans draft biotechnology directives

Officials in Brussels are determined to introduce draft regulations for biotechnology in the EEC by next summer. Already the European Commission has set the wheels in motion by arranging expert meetings for January and February to discuss possible drafts. Informal discussions with the US have also started and the Commission is planning a workshop to find points of commonality and determine, possibly, a joint rationale.

The Commission's strategy is likely to be two pronged. A new directive will probably be formulated to regulate planned release of genetically manipulated organisms into the environment. In addition, a Seveso-like directive may be formulated to regulate the waste management and accident controls for biotechnology. It is possible, however, that Brussels will amend the existing Seveso directive on major industrial hazards.

Apart from these plans by DGII, the environment arm of the Commission, two other directorate generals are seeking biotechnology controls. DGIII and DGV are preparing draft regulations on containment, safety and classification of micro-organisms. The proposal is likely to cover other biological agents used in industry.

By developing a Community framework, the Commission believes it will be able to provide a clear, rational and evolving basis for biotechnology and ensure adequate protection of animal and environmental health. As the market for biotechnology products is global the Commission plans to harmonize regulations with the practices of Europe's trading partners.

The OECD is currently developing its own ideas for biotechnology regulations. The organization of developed nations has been drawing up biotechnology guidelines on an ad hoc basis under the auspices of the environment group. It is expected to announce which part of the OECD will take care of the regulations. Most probable choice will be the chemicals group. But once a home has been found, that particular body may find itself with the unenviable task of securing more money. (Source: European Chemical News, 15 December 1986.)

Field testing being carried out in other countries

Scientists from the US National Science Foundation participated in field testing a genetically-engineered rabies vaccine in Argentina last summer without seeking approval from the Argentine or US Governments.

The Argentine Government learned about the test in September and barred any further experimentation.

US officials and scientists said the test, in which 20 cows were innoculated in July with a gene-altered viral vaccine at the agricultural station in Azul, raised questions about the effectiveness of the USA's programme to regulate the products of biotechnology research.

Regulations signed by President Reagan in June do not prohibit US companies or research laboratories from testing genetically altered products in other countries.

The vaccine, developed at the Wistar Institute in Philadelphia, has been undergoing research since 1983.

It was also disclosed that researchers at Oregon State University have conducted field trials on a gene-altered viral vaccine in New Zealand without permission from the US Government. The tests were financed by the Department of Agriculture and approved by two agencies of the New Zealand Government.

A spokesman for the Industrial Biotechnology Association said the revelations reflect a belief by many scientists that US biotechnology regulations are a barrier rather than a safeguard for the emerging industry.

Environmentalists responded by filing a lawsuit which asks the US District Court in Washington to invalidate the White House biotechnology guidelines. The Foundation on Economic Trends said Environmental Protection Agency and the Agriculture Department ignored the advice of their own scientists to permit certain organisms to be released into the environment without review. The suit contends documents show that 22 of the 23 scientists who reviewed the regulations warned against the exemptions. (Extracted from Chemical Marketing Reporter, 17 November 1986.)

RAC eases guidelines for recombinant-DNA releases

At its September meeting the US Recombinant-DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) adopted a major change in its guidelines governing recombinant-DNA deliberate-release experiments. If approved by the NIH's director, this new RAC guideline will be more in line with the proposed government-wide definition of biotechnology, which excludes as "new" for purposes of regulation any organism from which a gene has been deleted or whose genes have been rearranged. In another action, the RAC turned down a request by the Committee for Responsible Genetics, that it ban outright any attempts at germ-line - as distinct from somatic - gene therapy. It opposed the proposal primarily as being premature in the present stage of genetic research. (Extracted from McGraw-Hill's Biotechnology Newswatch, 6 October 1986)

A call for order in biotechnology regulation

The Industrial Biotechnology Association (IBA) of the USA is issuing a call for clear jurisdiction over genetic-engineering experiments to avoid what it calls "agency shopping" by experimenters among the various governmental units that regulate biotechnology. A report released at the association's annual meeting in San Francisco in October calls for organisms to be more clearly defined. (Extracted from Chemical Week, 29 October 1986.)

Panel reports on pig pseudorabies testing

The US Recombinant DNA Advisory Committee has completed its review of allegations that researchers at Baylor University and Texas A&M University may have violated National Institute of Health guidelines by testing a genetically engineered pseudorabies vaccine for pigs without prior review by the universities or NIH. The RAC panel concludes that the primary researcher violated at least the intent of the NIH guidelines, if not the letter. There is some ambiguity, apparently, over whether the vaccine as developed by the primary researcher, Saul Kit of Baylor and associates falls under the definition of having a "recombinant DNA molecule", because the final product is not directly genetically altered and no foreign DNA is introduced. Different advisory panels disagree on this point, but most would say notification procedures should be followed. Another sticky point is whether the vaccine was "introduced into the environment". Again, definitions differ. USDA, for instance, does not consider normal laboratory uses or husbandry uses of biological products to be released into the environment. Still, RAC concluded some violation had occurred and has ordered that Kit's research on animals be monitored and reviewed carefully for the next three years. It also emphasizes that whenever there is a question on procedure in any genetic engineering experiment, it is best to get approval first. (Reprinted with permission from Chemical and Engineering News, 27 October 1986, p. 20. Copyright 1986, American Chemical Society)

ACS suggests changes to biotechnology guidelines

Responding to recently announced guidelines covering the US Federal Government's regulation of products developed through genetic engineering and other new biotechnologies, the American Chemical Society has suggested making some changes in the way these guidelines mesh with the Toxic Substances Control Act. ACS believes a permitting structure for genetically engineered organisms should be established under TSCA to make that law consistent with others regulating such organisms. Specifically, ACS sees the need for an institutional permit granted to a research institution as a whole for many environmental release experiments, so individual investigators will not have to deal with EPA separately. To get a permit, the institution would have to provide many details to EPA on its research and would have to set up an internal environmental review committee to approve release experiments.

ACS also maintains that the definition of a new organism under TSCA should not include those made by introducing DNA from other micro-organisms of the same genus. The society recommends an exemption for organisms that are solely used as intermediates in contained manufacturing processes, maintaining that these organisms' use in fermentation and bioreactor systems will not present an unreasonable risk. ACS also supports an exemption for research and development work on genetically engineered organisms when the work is properly contained. There should be provisions, however, for review by EPA of field tests conducted for non-commercial purposes at academic or other institutions. (Abstracted with permission from Chemical and Engineering News, 27 October 1986, p. 63. Copyright 1986, American Chemical Society)

General

Biotechnology, ecological approaches could increase Third World harvests

Some 230 million rural households in Africa, Asia and Latin America never shared in the green revolution that brought increased harvests to many developing countries, concludes a new study from the Worldwatch Institute, a Washington-based research organization. According to Edward C. Wolf, author of Beyond the Green Revolution: New Approaches for Third World Agriculture, "This group of nearly 1.4 billion people in the Third World holds the key to future increases in world food production."

"The world's population is projected to grow from today's 5 billion to 6.2 billion over the next 13 years, though little new land will be brought under cultivation by then", Wolf said. "Just to maintain food consumption levels will require a 26 per cent increase over the 1985 average grain yield. And by 2020, feeding the projected population of 7.8 billion will require grain yields 56 per cent higher than 1985 levels."

High-yielding varieties of wheat and rice, first widely introduced to developing countries 20 years ago, quickly increased food production. New seeds, fertilizers, and pesticides boosted crop yields of Asian and Latin American farmers who had access to irrigation systems and markets for their crops.

"But these conditions prevail on less than a third of the 423 million hectares planted to cereal grains in the Third World", Wolf observed. "And costly farm chemicals are beyond the means of most subsistence farmers. On a large share of the 300 million hectares that remain, productivity has not measurably improved."

Biological approaches that regenerate natural soil fertility can help Third World farmers raise productivity on marginal land. In addition, biotechnology, which allows researchers to manipulate the genetic material of plants, could be used to improve Third World staples including millet, cassava and tropical legumes that have received little research attention. By joining biotechnologies with the insights of traditional farming practices, it may be possible to raise yields and reduce the chance of crop failure due to erratic rainfall and infertile soils.

"But progress could be slowed by a shift in the control of agricultural research to the private sector", Wolf cautioned. "Private firms have no incentive to produce the low-cost, locally adapted crop varieties needed by the vast majority of Third World farmers".

Researchers supported by governments and international agencies are now turning to a new challenge: developing crops and technologies for farmers who do not irrigate and cannot afford fertilizers and pesticides.

Farm-grown nutrient sources, for example, can substitute for purchased fertilizers. Research in the Philippines shows that farmers who grow a nitrogen-fixing fern called Azolla in rice paddies are able to cut nitrogen fertilizer use by half without sacrificing yields.

"Chemical fertilizers can often be applied most cost-effectively if they are combined with organic materials", Wolf noted. Research in Burkina Faso has shown that compost, straw and manure can enhance the contribution of nitrogen fertilizer by 20 to 30 per cent even under semi-arid conditions.

Other biological approaches are gaining credibility as researchers reappraise traditional farming practices. "Though traditional methods have limitations, they are not archaic practices to be swept aside", Wolf said. "Traditional farming constitutes a foundation on which science can build".

"Until recently, a kind of myopia has kept the research community from recognizing the opportunities for agricultural innovations that lie in traditional practices", Wolf said. In West Africa, 70 to 80 per cent of the farmland is sown to more than one crop at once. But only about 20 per cent of the research effort in sub-Saharan Africa focuses on intercropping.

To make traditional agricultural practices more productive, farmers need new crop varieties. "It took decades of work to produce high-yielding wheats and rices by conventional breeding", Wolf observed. "Biotechnology offers cheaper and quicker ways to improve other Third World staples".

Efforts to use biotechnology to improve subsistence food crops, underway at the 13 international agricultural research centres sponsored by the Consultative Group for International Agricultural Research, can offset the tendency of private corporations to apply new techniques exclusively to crops that are widely traded on the world market. Funding for the centres reached $170 million by the mid-eighties. But funding sufficient to underwrite more complex research tasks and changing technologies at the international centres is by no means assured.

"The degree to which the private sector will set the research agenda could jeopardize improvements Third World farmers need", Wolf said. "An expanded commitment to public research, at both the national and international levels, is needed to ensure that Third World priorities command attention". (Source: News Release, 1 November 1986.)

Biotechnology forecast

By 1991, biotechnology products could comprise a US$5 billion market, according to International Resource Development (Norwalk, CT). Drugs for humans could account for $3 billion; drugs for animals, $1.5 billion; and miscellaneous other products like testing kits and imaging devices, $500 million. The biotechnology market could expand much more rapidly than traditional pharmaceuticals for several reasons. Clinical testing of genetically altered products is faster because they are made of natural, rather than synthetic, molecules. Thus many future products could earn approval after only two years. Another factor favourable to biotechnology products is that several different US federal agencies will oversee the industry, thus speeding approval and reducing confusion. According to an analyst at Arthur D. Little, Genentech and Cetus are expected to be the most successful of biotechnology firms, eventually evolving into independent drug companies with their own manufacturing and marketing arms.

Biotechnology companies are beginning to be viewed as commercial ventures and will become major contributors to the US economy in 10 years, according to a study by Arthur Young High Technology Group. However, some observers expect that the industry will not endure on its own and will gradually merge with pharmaceutical and chemical companies. Only large companies with average pretax earnings of US$2.3 million/year did not show losses in 1985, while small firms earning US$1.3 million/year lost an average US$2.9 million. Public equity offerings are becoming more important as firms expand, and account for 27 per cent of financing for small firms, 42 per cent for mid-size firms and 61 per cent for large companies. (Extracted from Industrial Week, 10 November 1986 and Chemical Week, 3 December 1986)

African Regional Network on Microbiology

(i) Historical background

In 1977, at the Fifth International Conference on Global Impacts of Applied Microbiology (GIAM V) in Bangkok, Thailand, African participants made a resolution to establish an African Regional Network on Microbiology. It was agreed that Nigeria should serve as a temporary headquarters of the Network, and the Nigerian Society for Microbiology (NSM) was mandated to convene the inaugural meeting at which Regional Network Officers would be elected. Therefore since February 1978, the Nigerian Society for Microbiology undertook the secretarial duties of the proposed network and letters were sent out to all known microbiologists and microbiological organizations (including all faculties of science, medicine, veterinary medicine and agriculture) in various institutions in Africa informing them of the Bangkok resolution on the formation of a regional network on microbiology in Africa. NSM encouraged them to form such national organizations.

During the Sixth International Conference on Global Impacts of Applied Microbiology in 1979 in Lagos, Nigeria, 60 participants from the African region at the Conference met in a round table discussion and inaugurated the African Regional Network on Microbiology. Nigeria was made the temporary headquarters and the Executive Committee of the Nigerian Society for Microbiology was to constitute the Management Board until such a time when a Regional Board can be elected.

(ii) The objectives of the African Regional Network on Microbiology

The primary objectives of the network are to strengthen national faculties and institutions of microbiology in basic research, through regional programmes and activities and also to spread the benefit of network activities to individual interested scientists in participating countries. Another important objective is the need for co-operation and collaboration among microbiological centres within the African region so that international scientific bodies, such as the ICRO/UNEP/UNESCO panel on Microbiology could effectively make their resources available and participate in the various microbiological programmes going on in different parts of Africa. The resources of these international bodies are currently being effectively tapped and utilized by the American Regional Network and the South East Asian Network to solve some of their specific regional microbiological problems.

(iii) Organizational Structure of the African Network

(a) The Regional Network will consist of microbiologists in all centres in Africa, including universities, research institutions, industries and other private sectors.

(b) A regional network is designed to include one point contact, with normally an institution or society, in each participating country. However, in the absence of any established national society, each individual could identify himself as a "proten national point-of-contact" pending the formation of a national society. In each case, this national point-of-contact shall provide the channel of communication from the regional network to other institutions or groups which are working in the field of interest of the network in the country.

(c) One of the national points-of-contact which is well staffed and with adequate equipment in the area of a defined specialization of the network will be selected to serve as the Regional Network Headquarters, and an official of this centre wil serve as Executive Secretary.

(d) There shall be a regional co-ordinating board which shall be made up of representatives of the various national points-of-contact.

(iv) Activities of the Regional Network

All the activities of the network shall take place within the region and shall involve a high level of co-operation between participating institutions. One of the most important long-range results of network activities is the personalities and linkages developed among scientists in the region.

(a) Exchange of personnel: there would be an exchange of scientists between participating institutions for periods of one to three months, mainly in connection with development of co-operative research programmes of development of new teaching programmes.

(b) In-service training courses: there would be courses on specific high-level topics to upgrade the level of teaching and research in network member countries and institutions.

(c) Seminars, workshops, symposia and scientific meetings: these would encourage exchange and dissemination of knowledge among the scientists in the regional network.

(d) Visiting lecturers and professors: provision would be made to arrange for visits of eminent scientists from one institution or country to another within the regional network and other international networks.

(e) Provision of equipment: expensive scientific equipment for training and/or research could be purchased and maintained on a regional basis.

(f) Regional collaboration in postgraduate training in microbiology: with the establishment of an African Regional Network on Microbiology, it should be possible henceforth for many African countries to pull their manpower and material resources together for training postgraduate students in general and applied microbiology. Hitherto, many African students still have to go to Europe and America to obtain postgraduate training and qualifications. These overseas training programmes have recently become too expensive for many African countries, including Nigeria. In addition, the overseas training programmes are often irrelevant to the immediate needs of these African countries.

(g) Dissemination of information: newsletters, journals and regular review articles on the activities of the African Network on Microbiology shall provide information about the major developments and research that is going on in various participating countries. These will guide international microbiological organizations in planning collaborative scientific programmes with the African Regional Network.

The coming together of African microbiologists should be the beginning of co-operative efforts to wipe out microbiological agricultural, veterinary and medical problems in Africa.

Further information may be obtained from: Professor M.A. Emejuaiwe, IMO State University, P.M.B. 2000, Etiti, Nigeria.

AIDS: Africa faces a gloomy future

The number of Africans who will die of AIDS will escalate long before scientists in the West know more about how to fight the virus that causes the disease. According to a report AIDS and the Third World, recently published, up to a quarter of young, educated people in parts of central Africa are already infected with the virus. The report, by the Panos Institute, which monitors the Third World and the Norwegian Red Cross, says that AIDS could kill half the population in some African countries.

Panos's numbers are based on the prediction that everyone who is infected with the virus, known as the human immunodeficiency virus, will eventually develop AIDS and die. The US's National Academy of Sciences does not agree, however. The academy recently estimated that between 25 and 50 per cent of those who are infected with the virus will develop AIDS. There is little dispute that almost all who do develop AIDS eventually die.

Africa is suffering the worst effects of the disease. The spread of AIDS on the continent does not follow the pattern in the West. Unlike the West, AIDS does not spread primarily as a result of homosexual contact or by sharing hypodermic needles. Few countries screen blood supplies for the virus, although several are preparing to do so.

In central and east Africa, epidemiologists found that 0.75 per cent of the population is being infected every year. In central Africa, this means that each year there are between 550 to 1,000 new cases of AIDS per million adults.

In Africa, AIDS is often characterized by "slim disease", where people suffer from chronic diarrhoea, and by infection such as tuberculosis or cryptococcosis, a fungus that invades the central nervous system. Symptoms appear more often in the gastrointestinal system or the skin, while in the West the first symptoms usually occur in the lymphatic system or the lungs. A form of pneumonia known as pneumocystis carinii affects 63 per cent of European AIDS patients. But only 14 per cent of Africans with AIDS living in Europe have contracted pneumocystis.

Men and women in Africa are infected in equal numbers. In Europe and the US, there are 16 times more men infected than women. Further analysis shows, however that those Africans who contract the disease between the ages of 20 to 29 are predominantly female. (Extracted from New Scientist, 27 November 1986)

B. COUNTRY NEWS

Austria

Chemie Linz signs biotechnology accord with MIT

Chemie Linz has entered into a licensing agreement with the Massachusetts Institute of Technology (MIT) in the US to synthesize organic intermediates using lipase enzymes. The technology, developed by Alexander Klibanov and his colleagues at MIT, allows for the stereoselective synthesis of important pharmaceutical and agrochemical intermediates.

Some of the important products that Chemie Linz may synthesize include the active isomers of 2-bromopropionic and 2-chloropropionic acids. These are key intermediates in the synthesis of various phenoxypropionic acids, an important family of herbicides.

Although details of the Chemie Linz and MIT deal have not been revealed, the Austrian company plans to scale up the laboratory scale process and start pilot production by 1989. Production capacity will range from 50-1,000 ton/year, according to demand. (Extracted from European Chemical News, 8 December 1986)

Belgium

Belgian licences

BIOPLANT, the Belgian plant tissue culture firm, is moving further into biotechnology and looking for potential licensees for its conventional technology. The firm has recently established Bioplant Research which will investigate gene splicing techniques with other researchers.

In addition, the firm has established an Italian subsidiary and plans to form an FRG subsidiary to boost exports. The company exports more than 95 per cent of the 4 million vegetable and ornamental plants grown annually. Biggest markets for the firm are the Netherlands, UK, FRG, France and Italy. (Source: European Chemical News, 1 December 1986)

Canada

New facility to develop veterinary products

The wholly-owned company of the University of Alberta, Canada, Chembiomed, plans to develop veterinary and agricultural products at a new Can$16 million Edmonton facility. State and federal funds are contributing towards the construction of the unit which is expected to start in June 1987. The company plans to develop products that allow early detection of microbial infections in livestock. Moreover, the firm also wants to market diagnostic kits for fungal diseases in plants. (Source: European Chemical News, 17 November 1986)

Recent publications

The following biotechnology publications are available from the Biotechnology Unit, Ministry of State for Science and Technology, 8th Floor West, 240 Sparks Street, Ottawa, Ontario, K1A 1A1. Telex No: 053-4123 Facsimile: 613-996-7887.

1986 Canadian Biotechnology Sourcebook: Commercial Organizations Involved in Biotechnology Research, Development or Manufacturing
National Biotechnology Advisory Committee Annual Report 1985-86
Federal Expenditures for Biotechnology 1981-1986
Provincial Governments' Biotechnology Expenditures and Activities 1985-86.

China

Biotechnology exhibition opens

China is planning to join the world's leading biotechnology researchers over the next five years.

To promote academic and technical exchanges in the field, an international exhibition on biotechnology and life sciences took place in Beijing's Military Museum of People's Revolution.

Some 37 companies and corporations from around the world attended the exhibition, which was sponsored by the China International Trust and Investment Corporation, the China Hua Yang Technology Trade Corporation and the China Convention Service Limited.

A symposium on biotechnology in China was held in Beijing before the exhibition. (Extracted from China Daily, 16 October 1986)

French university's links with Chinese institute

France's Compiègne University of technology has joined up with the Shanghai Institute of Industrial Microbiology to develop industrial processes using biotechnology. Although the arrangement will eventually involve many industries where biotechnology can be applied the first projects will focus on the production of ethanol, enzymes and organic acids. (Source: European Chemical News, 15 December 1986)

Cuba

Research programme

An ambitious scientific research programme has been implemented, with an increasing focus on biotechnology R & D. Those now underway include animal vaccines, interferon, biomass conversion and high-protein food additives. Researchers have cloned the toxic gene of the micro organism that causes red water fever in cattle. The Center for Biological Research has supplied Cuban doctors with interferon for testing against cancer and viral diseases. Currently, Cuba is the world's second largest producer of human-derived interferon. The State-owned pharmaceutical firm MediCuba will market several forms of interferon worldwide and will also include genetically engineered interferon in its product line. Meanwhile, at the National Center for Scientific Research, geneticists are working on new methods for improving sugarcane. One method, somaclonal variation, is a process by which cells from a single plant can be induced through hormone manipulation to develop into variants that exhibit new genetic properties. (Source: High Technology, November 1986)

EEC

EEC grants ten years of product protection for biotechnology drugs

Trade ministers from the European Economic Community (EEC) have agreed to protect biotechnology pharmaceuticals from competition by generic products for ten years from the time they are first marketed by the inventor. They set the marketing license term for conventional drugs at six years. The decision to "harmonise" licensing for the 12 EEC member-states was made earlier at the International Market Council meeting. The ruling goes into effect from 1 July 1987.

The legislation was introduced to protect the rights of innovators of high-technology products. At present, patent laws protect the basic discovery but

not the process between discovery and marketing which involves testing and which can take as long as ten years. The new measures bring the EEC into line with the USA and generally follow the US Patent Term Restoration Act of 1984.

European countries currently grant marketing licenses for generic drugs on presentation of full documentation, or an abridged application. The systems vary from country to country, but in general the southern-tier states - Greece, Spain, and Portugal - grant generic licenses to second applicants on abridged documentation at any time.

In general, it takes three years from first marketing for a product to reach its optimum sales in the country of origin, perhaps four to six years throughout the whole of Europe. Drugs thus copied benefit from the original's success, while avoiding lengthy animal toxicity testing and human clinical trials required of the first producer.

Under the new ruling, no abridged applications - which demand only pharmaceutical information as proof of ability to produce the product - will be accepted. Copiers must now undertake all of the trials and testing that the originator had to carry out. Whether the new protection lasts six or ten years depends on the product's "high-tech" status. National legislatures are free to extend conventional drug protection to ten years as well. This is expected to be the case in France and the German Federal Republic.

Deciding in which category a product belongs is the responsibility of the Commission's proprietary medicine and veterinary committees. (Source: McGraw-Hill's Biotechnology Newswatch, 15 December 1986)

Finland

Bio-control

Streptomycetes are finding new applications as biological control agents. This further utility came to light during studies at the Agricultural Research Centre at Jokioinen into Sphagnum fuscum peat. Freshly dug, this light-coloured material is the most common substrate for greenhouse cultivation in Finland. It has the marked advantage over soil of being entirely free of plant pests and pathogens. Several years ago, Risto Tahvonen and his colleagues began investigating whether this was a chemical or microbiological phenomenon, and found that the peat's natural microbial flora strongly inhibited the growth of seed- and soil-borne fungal pathogens. Steam sterilization completely abolished this inhibitory effect, which reappeared when they added fresh, non-disinfected peat. Trichoderma viride was one potent agonist, but another major contributor came from species of Streptomyces, which now have proved particularly convenient for the control of greenhouse pests.

On a practical scale, the outstanding success so far has been with cucumbers. Yields have increased by 10 per cent, and it has been possible to maintain productive stands until the end of the growing season without the need to replant. Wilt disease in carnations has also been checked so effectively that the area of plants that has had to be destroyed in two year cultivations has been under 10 per cent, compared with 30-40 per cent for untreated plants. (Source: Biotechnology, vol. 4, December 1986)

Japan

New technique to produce animal protein

A new technique will lead to the mass production of animal protein from plants, according to University of Tokyo researchers. It involves the creation of a powerful vector of RNA from tobacco mosaic viruses which infect tomatoes and other plants. The RNA vector is 10 times more effective in the rate of gene reproduction versus DNA vectors. Because of the strong infectivity of tobacco mosaic viruses, the RNA vector penetrates plant cells easily. The University of Tokyo researchers took an enzyme gene from a colon bacillus, incorporated it into the RNA vectors and fixed them onto the surface of the tobacco leaves. The RNA vector was found to reproduce the enzyme gene chloramphenicol acetyltransferase in large quantities. (Extracted from Japan Economic Journal, 4 October 1986)

Cell-fused algae feed fish

Nisshin Oil Mills Ltd., Tokyo, has begun selling cell-fused Chlorella, a green alga, as feed for flounders, hardtails and prawns. Researchers combined the cells of a marine species with high fatty-acid content with a fast-growing freshwater species. The hybrid, trade-named Marine Omega A, is priced at ¥28,000 ($185) for 20 litres.

Replicating animal vector cloned

University of Tokyo researcher Hiroyoshi Ariga announces "the first DNA fragment that autonomously replicates in mammalian cells," ('autonomously replicating sequence', ARS). Ariga originally isolated this mammalian-cell vector from mouse-liver DNA as a segment whose replication depended on the T antigen of SV40. The 100 kilo-base sequence produces up to 10,000 copies per cell, and has remained stable in host cells for at least two months. "I expect to find the origin of replication of chromosomal DNA in this fragment," Ariga declares. (Source: McGraw Hill's Biotechnology Newswatch, 15 December 1986)

Biodegradable polymer

Mitsui Toatsu Chemicals has developed Japan's first biodegradable polymer for surgical sutures or drug delivery systems. The polymer, made from polyglycolic acid and polylactic acid, degrades inside the body with the glycolic acid disappearing after three months and lactate in a year. (Source: European Chemical News, 15 December 1986)

Hungary

Hungarians scaling up production and export of restriction-enzymes

Hungary, the sole exporter of restriction enzymes to the COMECON countries, is scaling up output of endonucleases and expanding its markets. The Reanal Laboratory-Chemical Factory in Budapest, which holds the licence to deal in endonucleases, exports them through the state foreign-trade monopoly, Medimpex, to COMECON, the FRG and the UK.

Reanal recently signed a partnership agreement with Vepex Contractor Ltd. to increase production. Vepex is a state-owned firm that provides venture capital to commercialise Hungarian inventions and developments in genetic engineering, monoclonal antibodies, immunology and diagnostics. The scale-up will raise enzyme output from its present four million units a year to 10 million units. If demand warrants, its capacity can be increased to 80 million units a year.

Under the agreement, Vepex is responsible for development, production and analytical testing of the enzymes, Reanal for packaging, transportation (at -20°C) and marketing.

The Biochemical Institute of Szaged, an arm of Hungary's Academy of Sciences, develops and produces endonucleases for Vepex under a research contract with Reanal. Its Biological Center now operates a small plant that produces 30 kinds of enzymes for

genetic-engineering uses. The four million units to be synthesized and purified in 1986 will enable the Center to curtail imports from Western suppliers, and expand export.

The new pilot plant, covering 2,000 square metres on three levels, is being built next to the Center at a cost of 193 million forints ($4.5 million) and is expected to go on line in mid-1988. The project is jointly funded by Vepex, 90 million forints, and the Government, 103 million. (Extracted from McGraw Hill's Biotechnology Newswatch, 3 November 1986)

Netherlands

Dutch firms in biotechnology push

Dutch companies are increasing investment in biotechnology. Both Hogen International and Zaadunie are establishing new research laboratories to support their efforts in the agricultural sector.

Hogen, the joint venture of the US concern Molecular Genetics and the Dutch government's industrial products firm NIP, is spending $6.4 million on facilities at Leiden. Researchers will develop products for the agricultural and tillage industries including new plants based on gene manipulation and vaccines.

At Enkhuizen, Zaadunie is building a laboratory for crop improvement for start up next spring. The company is already investing several million guilders annually in biotechnology research. In addition, Rabobank is collaborating with Covecs and the co-operative ETH on a feasibility study for a commercial project on new breeding methods.

Biotechnology research in agriculture is currently financed by the Dutch Government. The state provided funds of Dfl. 50 million last year with at least a further Dfl. 50 million this year. (Source: European Chemical News, 1 December 1986)

Gist-brocades buys drug plant

In a bid to increase penetration of the US generic antibiotics markets, Gist-brocades, the Dutch biotechnology concern, is to acquire SmithKline Beckman's facility at Freeport in the Bahamas. The Dutch company expects to spend about $30 million buying and converting the plant to make 7 amino-deacetoxy cephalosporinic acid (7-ACDA), a key intermediate in the production of oral cephalosporins. Start up is expected for the last quarter of 1987. (Source: European Chemical News, 8 December 1986)

Portugal

Portugal seeks funds for agricultural biotechnology centre

In order to establish a national biotechnology centre, Portugal is seeking funds from the World Bank and the European Economic Community. In addition, seven local institutes and universities have already agreed to support the new Instituto de Biologia Experimental e Technologica (IBET). The centre, which has the official backing of the Ministries of Education and Agriculture, has already been allotted building space on the campus of the National Agrarian Research Institute just outside Lisbon.

The idea behind IBET is to co-ordinate Portugal's biotechnology efforts under one roof. Some 20 scientists are expected to occupy the centre within the next few years. Research will initially concentrate on agriculture and nutrition and the resulting technology will be transferred via the Institute de Participacoes de Estado. This State Participation Institute manages the government shareholdings in mixed-capital companies. (Source: McGraw-Hill's Biotechnology Newswatch, 3 November 1986).

Spain

Spain markets monoclonal diagnostics in the absence of bio-regulations

With the in vitro diagnostics field so underdeveloped, it will take years before regulatory authority is demanded by Spain, according to Jose Pellon, biotechnology director of Invesgen SA, a biotechnology firm located in Madrid. In the past three years, with the backing of the Induyco Investment Group, Invesgen has grown from a one-person operation to a team of 55. Their primary activity, since its formal founding in March 1985, has been the marketing of AIDS and hepatitis B tests for Pasteur Diagnostics, Paris.

By mid-1987, the company plans full-scale sales of its own low-cost monoclonal diagnostics for rheumatic diseases, including rheumatoid factor and sero-active protein markers. Invesgen has submitted these tests for regulatory approval to other European countries. (Extracted from McGraw-Hill's Biotechnology Newswatch, 3 November 1986)

Sweden

Swedish company to establish US biotechnology research unit

Pharmacia, the Swedish biotechnology and drugs group, will build a US genetic engineering arm rather than through acquisition. To be based at La Jolla in California, the new company, Pharmacia Genetic Engineering Inc. will focus on production of diagnostics and pharmaceuticals. Recruitment of scientists has begun and operations are scheduled to begin next January.

A number of projects are already planned although details have not been made public. An early target will be the production of diagnostic components using genetic engineering.

The first diagnostic products from the new venture will probably reach the market by 1989-90. Commercialization will be speeded up by the use of Pharmacia's existing development, clinical testing and marketing infrastructure. (Extracted from European Chemical News, 6 October 1986)

United Kingdom

Delays freeze production of factor VIII

A plan to make Britain self-sufficient in the supply of a vital product for clotting the blood of haemophiliacs has run into further delays. New equipment for freeze-drying blood plasma is now installed in a new factory at the Department of Health and Social Security's Blood Products Laboratory in Hertfordshire, but delays in building the factory mean it is unlikely that the equipment will be ready to meet all of Britain's needs before the end of the decade.

The health department wants to be self-sufficient because it is costly to import factor VIII from the US, which currently supplies over half of the country's needs. The delay in completion is not the only difficulty affecting the ability of the Blood Products Laboratory to make enough factor VIII: many blood transfusion centres cannot supply enough plasma to the laboratory in the first

place. Not as many people are giving blood, as they unwarrantedly fear catching AIDS.

There are 2,500 haemophiliacs in Britain, and about 40 per cent are infected with the AIDS virus. Of these, 19 have developed AIDS, and all but one has died.

The equipment of the Blood Products Laboratory consists of 10 freeze-dryers, which can produce about 100 million units of factor VIII a year from 450,000 litres of blood plasma. This should be enough to supply all of Britain's haemophiliacs.

The plasma is frozen in a vacuum and the frozen water in the plasma turns to vapour without first turning to liquid. Proteins in the blood, including factor VIII, are left behind and can then be purified. Air-drying would destroy the complex molecules of these proteins. The new date for completion is "early 1987" and commercial production of factor VIII will begin in 1988. (Extracted from New Scientist, 6 November 1986)

Gene engineers probe antibiotics

British scientists and drug companies are seeking to maintain Britain's lead in the genetic manipulation of organisms that produce antibiotics. The programme, costing £1.4 million over the next three years, is financed by the Science and Engineering Research Council (SERC) and the Department of Trade and Industry as well as companies such as Beecham, Glaxo and ICI.

Commercial antibiotics are made by soil-living bacteria known as streptomycetes (strepo) and by moulds. But the genetic switches which determine whether these moulds and strepo make simple biomass or antibiotics are not properly understood. The carriers that transfer new or additional genes into moulds or strepo are primitive compared to those used for transfers to Escherie coli, the bacteria widely used in genetic engineering. The new programme aims to increase knowledge of the organisms that produce antibiotics, and so improve production of antibiotics. (Source: New Scientist, 13 November 1986)

Centre for dev-loping new varieties of plants to be sold

The British Government is to sell the Plant Breeding Institute in Cambridge. The PBI creates many of the new varieties of crops grown on British farms. A central issue behind the sale of the PBI is whether a private company will do the research needed to ensure that crops retain the genes that help plants to resist attack by pests and fungi - plant pathogens. The fear is not that a private business will be unable to undertake such research, but whether it will be motivated to do so. Investment in the health of crops, particularly in their genetic resistance to disease, is a long-term activity, too long perhaps for many companies to show a serious interest in it.

If farmers can sow varieties of crops that can resist attack by plant pathogens, they can abandon expensive chemicals. The companies also know that clever plant breeding can produce crops that can respond to particular herbicides or insecticides. Thus companies can patent both chemicals and varieties of crops. Monsanto, an American chemicals company, has, for instance, produced a variety of cereal crop that can survive a particular brand of herbicide. Farmers can spray a field with weedkiller without fear of destroying that particular crop.

The Plant Breeding Institute carries out research into all aspects of plant breeding. Building on its research into plant genetics, particularly the way genes help plants to resist diseases, the institute has supplied new varieties of crops to farmers. Before new varieties reach the farmer, however, they have to be approved by the government's seed-testing station at the National Institute of Agricultural Botany in Cambridge. The station tests each new variety rigorously, which can take several years, before seed companies can sell it to farmers. Approved varieties appear on the institute's National List. When the variety appears on the National List, it is protected by plant-breeders' rights. The statutory body responsible for conferring this is the Plant Variety Rights Office, part of the Ministry of Agriculture, Fisheries and Food.

To win a position on the National List, the new variety has to be quite distinct from other varieties; it has to be uniform in that members of the variety cannot be too different from one another. And, finally, the variety has to be stable - it has to remain true to its description after repeated reproduction or propagation. The variety must also be worth growing - someone, somewhere must want to buy it.

Part of the testing of a new variety includes the assessment of its yield, the quality of the crop and its resistance to disease. The National Institute of Agricultural Botany tests a few of the most promising new varieties even more rigorously. If a new variety passes these tests then it appears on the institute's Recommended Lists. This is an even more exalted position than a place on the National List. The government's seed-testing station advises farmers that varieties on the Recommended Lists should be grown in preference to others.

The government has decided that it will sell the plant-breeding departments at the PBI together with the National Seed Development Organisation (NSDO), the establishment that receives the rights to breed all new varieties that come from public institutions. These rights are the plant breeders' equivalent of patents. Seeds companies look upon these rights to protect their investment in the research and development of new varieties. This has led to criticism that such rights are not in the public interest. The NSDO can license the varieties developed by the PBI to anyone who wants to sell them, and takes a royalty in return. What is left of the PBI, the basic research into plant breeding, will move out of the PBI's building at Cambridge into a new Institute of Plant Science Research. This new institute is a collection of existing laboratories with a new identity. The new institute, which will not be under one roof, will include the research carried out at such places as the National Vegetable Research Station, the John Innes Institute, which researches into plant genetics, and even some research at the Rothamsted Experimental Station, which works in the wider field of plant sciences. (Extracted from New Scientist, 27 November 1986)

Venture capital backs new biotechnology firm

Senior researchers from G.D. Searle's UK operation have established a new biotechnology company with the support of leading venture capital firms. The new company, British Biotechnology, plans to develop new chemical and biological drugs, both independently and via collaboration with established companies. It aims to generate short-term income with sales of research products, such as designer genes and carbohydrates. Biotechnology will not be

the only string to its bow. A major thrust is to be devoted to synthetic organic chemistry, backed up by computerized molecular design technology.

Research efforts in this area will focus primarily on active site-directed competitive inhibitors of key regulator enzymes for the treatment of rheumatoid arthritis, asthma, cardiovascular disease and viral infections. The company plans to focus particular efforts on developing a therapeutic strategy against the AIDS virus and has set up an advisory group staffed by leading international experts.

In the molecular biology area, British Bio-technology has a number of first-, second- and third-generation recombinant DNA products in its sights. The company hopes to produce novel proteins for the treatment of thrombosis, bone disorders such as osteoporosis, wound healing and various cancers and viral diseases.

Specific targets are epidermal growth factor (for wound healing applications) and novel, second-generation tissue plasminogen activator-type compounds (for thrombosis). The company is currently negotiating collaborative arrangements with a number of established pharmaceutical and biotechnology concerns, mostly in the US. (Extracted from European Chemical News, 8 December 1986)

Molecular recognition programme

A major molecular recognition research programme is being launched by the UK Science and Engineering Research Council (SERC), with a budget of more than £7 million over the next three years. The programme will seek to gain a fundamental understanding of the way biological molecules recognize and interact, both with each other and with other chemicals. The SERC programme will examine both relatively simple problems, such as how an enzyme recognizes its own particular substrate from a mixture of chemicals, to far more complex interactions of larger molecules: the interaction of DNA with enzymes during cell division and protein synthesis, for example, is fundamental to our understanding of disease.

Centres for molecular recognition research are being set up and these will not only conduct high quality research of their own, but will also act as a focus for the SERC programme. Smaller, 'satellite' groups throughout the UK will be able to use the sophisticated instrumentation and special expertise available at the centres. (Extracted from Biotechnology Bulletin, vol. 5, No.11, December 1986)

Deliberate release of genetically engineered virus

What is thought to have been the world's first deliberate release of a genetically marked baculovirus insecticide, Autographa californica (AcMPV), has taken place in a British 'cabbage patch' ecosystem. Scientists at the Natural Environment Research Council Institute of Virology (IOV) are trying to improve the efficiency, particularly the speed of action, of the insecticide.

The parent virus has been the subject of extensive safety testing in the USA and elsewhere. For more than a decade it has been used to control caterpillar pests in various parts of the world. Like other baculoviruses, AcMPV does not infect or harm vertebrates, plants or invertebrates - other than a limited number of moth caterpillars that are recognized pests. Experiments at the IOV have shown that AcMPV does not have a deleterious effect on beneficial or non-target insect species. Nor, unlike chemical pesticides, does the virus leave chemical residues in the environment.

Before the first release, the marked AcMPV was extensively tested in the laboratory, with considerable attention paid to its genetic stability and biological phenotype. The laboratory analysis included replication studies involving more than 50 generations in insect tissue culture (sequential plaque assays) and successive passaging through caterpillars. No genetic instability of either the virus or the marker was detected. The IOV concluded that both the cloned marked and unmarked viruses have a highly restricted host range among UK moth species.

The actual release was undertaken in a field facility, consisting of a netted compound that prevented dispersal of the host or its interaction with other insects or predators. (Extracted from Biotechnology Bulletin, vol. 5, No. 9, October 1986)

USA

Panel attempts to clarify biotechnology regulations

In its first major report on biotechnology in nearly two years, the USA's House Science & Technology Subcommittee on Investigations & Oversight has tried to sort through the happenings of the past year and determine what has been accomplished. It has been a significant period, during which several events have occurred that will shape the future for biotechnology in the US. Among them are the creation of a co-ordinated biotechnology regulatory framework within the Government and the highly contentious "release" of two biotechnology products into the environment.

Central to the issue has been the Administration's attempt at regulation. This is embodied in the framework for biotechnology regulations, which tries to use current laws to regulate the different uses of biotechnology. First proposed in December 1984, and revised in June 1986, this framework draws together the sundry responsibilities of the Environmental Protection Agency, Food & Drug Administration, Department of Agriculture, and National Institutes of Health to regulate research and commercialization of biotechnology. By applying different laws to the diverse expected products of genetic engineering and other recombinant DNA methods, the Administration believes it can cover most, if not all, situations.

But clarity in the system is coming slowly. Two incidents in the past year caused some anguish as researchers butted heads with the regulators over what can and cannot be done. In the first incident, Advanced Genetic Sciences Inc., a California biotechnology company trying to commercialize bacteria that would slow frost formation on certain plants, ran afoul of EPA regulations by testing the plant pathogenecity of the genetically engineered bacteria by injection into trees.

The second incident also involved the question of what constitutes a release. In this instance, a Baylor college of medicine researcher developed a vaccine for swine pseudorabies using recombinant DNA techniques and tested it on an experimental animal farm.

In the meantime, of course, other legitimate proposals for doing recombinant DNA field experiments have been delayed as each of these "releases" are examined in detail. EPA has not approved a field test of a pesticide-like bacteria even though its special scientific review panel said that it was probably safe under the proposed conditions.

The upshot of these incidents is that Congress, in particular, has become suspicious of the regulatory agencies' ability to adequately monitor

the growing use of genetic engineering. From testimony presented at several hearings, the subcommittee has distilled some of the recurring problems and has made recommendations that might help bring some order to the confusion. One major obstacle in the Government's oversight, it finds, is the lack of ways to assess accurately potential risks of altered organisms in the environment. The subcommittee would like to see the Biotechnology Science Co-ordinating Committee (BSCC) - the oversight group formed under the co-ordinated framework - set up research priorities to fill in the information gaps in this area.

At the individual agencies, the subcommittee sees the need for consistency and clarity. It recommends that USDA better co-ordinate the activities of the science and education division and its marketing and inspection division so that products such as the pseudorabies vaccine do not slip through the cracks. This could be accomplished by working through the department's Agricultural Recombinant DNA Research Committee, or some other future central committee within USDA. EPA has stepped forward with its regulations under TSCA and the pesticide laws, but the subcommittee recommends that EPA promulgate new regulations defining significant new uses for organisms, removing the pre-manufacture notification exemption for research and development activities, imposing reporting requirements for certain field experiments, and redefining "small business".

The report does not recommend new legislation from Congress to control biotechnology research and application. If new problems arise, such as happened with recent releases of recombinant DNA organisms in Argentina and New Zealand, Congress' interest may solidify. But, barring a serious problem from a release in the US, either approved or unapproved, it seems that the current government regulations are going to be used to regulate these new products for some time to come. (Abstracted with permission from Chemical and Engineering News, 1 December 1986, pp. 19-20. Copyright 1986, American Chemical Society)

Ice-minus test stopped

The first field test of bacteria that have been genetically engineered to protect plants against frost damage will not, after all, take place this year. The University of California, which is proposing the test, agreed with opponents that it would re-examine safety issues before going ahead. Because the test cannot be performed during the winter months, it is now unlikely to take place before next spring.

The test was first proposed by Steven Lindow of the University's Berkeley campus in 1982. Lindow plans to spray potato plants with a genetically altered strain of Pseudomonas syringae that has had removed the gene responsible for producing an ice-nucleating protein. Because the protein in naturally occurring P. syringae acts as a focus for ice crystal formation on host plants, Lindow hopes that the engineered form will reduce frost damage.

The out-of-court agreement now reached obliges the university to review all the safety evidence once again and to decide within 30 days if a local impact report is indeed needed. But the plaintiffs have also agreed to provide any new evidence they want taken into account, and if they disagree with the university's assessment have only a further 30 days in which to sue. Numerous and expensive preparations for the experiment had to be abandoned when the temporary restraining order was issued on 4 August, just two days before the test was due to start. (Extracted from Nature, vol. 323, 4 September 1986)

Anti-cancer agents sought in remote flora

The US National Cancer Institute is launching a search for anti-cancer agents in plants from remote areas of the world and has awarded five-year contracts to three institutions: to the New York Botanical Garden (for collecting plants in South America); to the Missouri Botanical Garden (for Africa); and to the University of Illinois, Chicago (for Southeast Asia). The New York Botanical Garden's Institute of Economic Botany, for example, will gather 1,500 plant specimens annually from tropical rain forests, focusing especially on plants with medicinal properties used by Indian tribes. The NCI will test aqueous and organic solvent extracts for anti-tumour activity, using a new in vitro screening procedure. During the past 23 years, the NCI has developed a number of drugs from plants in easily accessible world areas, but the increasing destruction of tropical rain forests lends urgency to the collection of unique flora from remote areas, before many of these plants become extinct. (Reprinted with permission from Chemical and Engineering News, 24 November 1986, p. 12. Copyright 1986, American Chemical Society)

Option agreement for merger of Hunt Research Corporation into new subsidiary, Quest Blood Substitute, Inc.

Quest Biotechnology, Inc. has signed an agreement with the control stockholder of Hunt Research Corporation to vote for a merger with a new Quest subsidiary, Quest Blood Substitute, Inc.

Hunt Research Corporation, whose principal investigator is Dr. C. Anthony Hunt, Associate Professor of the Department of Pharmaceutic Chemistry at the University of California, San Francisco Medical Center, holds the rights to several patents in the area of modified hemoglobin. Dr. Hunt has been conducting research to develop a blood substitute product. Such a product could offer advantages over conventional blood transfusions including the elimination of disease transmission and the need for blood typing and cross matching.

Quest is currently identifying and reviewing additional blood substitute technologies for potential acquisition and development. A new subsidiary, Quest Blood Substitute, Inc., will focus on this research activity and related emerging technologies. (Source: Company News Release, 9 September 1986)

Patient-centred cancer research company announces results

Biotherapeutics Incorporated, a patient-centred cancer research company, announced their financial results for the second quarter of 1987 and the six months ending 31 October 1986.

Total revenues for the second quarter increased to $838,823 as patient referrals from an expanding base of physicians throughout the United States continue to grow. Patient-funded research accounted for $553,323 of those revenues, up over 300 per cent from the same period one year ago and over 500 per cent year-to-date.

Some of the company's notable accomplishments during the period include:

A growing body of scientific data continues to unfold supporting Biotherapeutics' individualised approach to cancer research and the establishment of biotherapy as the fourth modality of cancer treatment (along with chemotherapy, surgery and radiation therapy). These data further validate the company's

plan to establish cancer research laboratories in conjunction with existing clinical oncology programmes and physicians throughout the United States and in selected areas outside the United States.

Biotherapeutics has entered into two important corporate relationships. In September the company entered into a collaborative agreement with International Genetic Engineering Incorporated (INGENE). Biotherapeutics will evaluate INGENE's proprietary human tumour antigen associated with tumour regression. Upon successful completion of required pre-clinical testing and development activities and subject to authorization by regulatory authorities, the company will conduct studies to evaluate the safety and clinical efficacy of the new therapeutic. The company has also established a collaboration with Syncor International Corporation, the nation's largest radiopharmacy company. This collaboration is aimed at developing distribution channels for custom-tailored cancer therapeutics incorporating radioisotopes.

Biotherapeutics Incorporated, with corporate offices in Franklin, Tennessee, contracts with clinically suitable cancer patients to perform laboratory research services designed to develop custom-tailored therapeutic options employing biologicals and biological response modifiers. Biotherapeutics, which currently employs over 100 professionals, intends to establish a network of cancer research laboratories in conjunction with major hospitals and oncology groups throughout the United States and in other developed countries. (Source: Company News Release, 2 December 1986)

New biotechnology centre

The Center for Advanced Research in Biotechnology in Rockville - established by the University of Maryland, the Department of Commerce's National Bureau of Standards and Montgomery County, Md. - will be located at the county's Shady Grove Life Sciences Center. Biotechnology companies are expected to join in CARB's research.

First announced in 1984, CARB is now putting together multidisciplinary teams of scientists and engineers with state-of-the-art facilities. The organization has been housed at NBS, where researchers from the bureau and the University of Maryland have undertaken several research projects taking advantage of specialised NBS laboratories.

When the new CARB building is ready in December 1987, it is expected to accommodate 100 researchers. Between 65 and 90 scientists from NBS and the University of Maryland will work at the new site. The remainder of the 100 researchers working at the centre will be guest scientists and engineers from industry, other universities, and government agencies. Up to one third of CARB's research staff will be visiting industrial fellows. Both co-operative and proprietary research will be possible at CARB. (Extracted from Chemical Marketing Reporter, 17 November 1986)

Dairy farming

University Genetics has opened a $4.9 million genetic conversion centre for cows to improve the economics of dairying. The Farm Services centre in Fresno, CA., will apply the latest genetic management and manipulation methods on a herd of 1,500 Holsteins. Embryo manipulation and transfer, rapid pregnancies, new diagnostics and statistical breeding will be tested. (Source: Chemical Week, 19 November 1986)

USSR

Bacteria which eat methane

Coal mines can be made safe from gas explosion by using bacteria to absorb the methane found in many mines, according to scientists at the Soviet Union's Institute of Microbiology who have grown strains of bacteria normally found on the beds of rivers, lakes and seas, in microbiological factories, and mixed them with a saline solution to mimic their natural habitat. They have then pumped this solution through bore-holes into a coal bed some six months before mining begins. The methane is destroyed in situ. The mixture is also sprayed on to the coal face and on to coal as it is cut. This has reduced methane production by 50 per cent.

The institute is currently testing the methods on an industrial scale in four mines in the Donetsk coal fields.

Previously, miners cutting and loading the coal had to stop periodically while the coal face was properly ventilated to prevent dangerous build-ups of methane. The problem increases as mines become deeper and production methods more efficient.

The new technique is expected to substantially reduce the time machines stand idle. (Source: New Scientist, 30 October 1986)

Nitrogen fixation

Bacterial fertilizers are being developed by researchers at the Institute of Biochemistry & Plant Physiology. Bacteria found in the roots of wheat apparently form a symbiotic relationship and stimulate growth of the plant. Processing seeds with such bacteria could improve the performance of other crops without the need for chemical fertilizers. The nitrogen-fixing bacteria can also be produced on a large scale and mixed in with a carrier such as peat. Meanwhile, other researchers are developing crop-protecting vaccines. A weak strain of blight can produce immunity against a wide range of blights. The technique has been used on potatoes, tomatoes and sugar beet. Vaccines might also be produced for cereal crops. (Extracted from New Scientist, 27 November 1986)

C. RESEARCH

Research on human genes

DNA amplification technique simplified

A heat-stable DNA polymerase isolated from the thermophilic bacteria species Thermus aquaticus, which grows in hot springs, has allowed scientists at Cetus Corp., Emeryville, California, to simplify a DNA amplification technique for determining genetic information. The technique, called the polymerase chain reaction procedure, uses DNA polymerase to make as many as one million copies of a specific target DNA sequence. The procedure consists of a series of repetitive cycles, one step of which involves high temperatures. This inactivates the DNA polymerase originally used in the reaction, thus requiring the addition of enzymes at each cycle. The heat-stable polymerase catalyzes the reaction when added only once. According to the company the improvement may allow the development of new diagnostic tests for infectious and genetic diseases based on specific DNA probes. It will also be incorporated into research instrumentation being produced by Perkin-Elmer/Cetus Instruments. (Reprinted with permission from Chemical and Engineering News, 6 October 1986, p. 20. Copyright 1986, American Chemical Society)

Slow molecular switch cloned

The techniques of the genetic engineer have recently been pressed into service by those trying to understand the signalling systems of the brain. A team of scientists in Kyoto, Japan, led by Shosaku Numa has been spectacularly successful in cloning the molecules that determine how a cell responds to electrical information. The latest molecule to be cloned, sequenced and reproduced in a functional form is the second of two kinds of receptor for the neurotransmitter acetylcholine - the so-called muscarinic receptor.

Acetylcholine is the transmitter that motor nerves release on to muscles to stimulate them to contract and also communicates between nerve cells in various parts of the nervous system, including the brain.

Scientists have known since the First World War that there are two kinds of receptor for acetylcholine: the nicotinic receptor, which is activated by nicotine and blocked by the poison curare, and the muscarinic receptor, activated by muscarine and blocked by atropine. The nicotinic receptor has been much easier to study, because the junctions between nerves and muscles are more accessible than other junctions (synapses) between nerve cells. It also turns up in vast numbers in various species of electric fish and eel.

The muscarinic receptor belongs to a different family altogether, and the sequence for it seems to include seven regions that span the membrane. Crystallographic studies of rhodopsin from bacteria suggest that the conformation of this family of molecules does not include a water-filled channel like that of the nicotinic receptor. The muscarinic receptor is expected to be very similar.

All these molecules with apparently very different functions exert their effects by activating an enzyme within the cell called a G protein. There are at least three different kinds of G protein, all with different effects, but they all bring about relatively slow changes in the cell's biochemistry that will influence its responsiveness to incoming signals.

The response to acetylcholine of the muscarinic receptor seems to be to adjust the general state of readiness of the cell. The nicotinic receptor, in contrast, reacts to acetylcholine by rapidly opening its pore and allowing ions (charged atoms) to pass through. This brings about a short-term switch in the electrical potential of the cell membrane; if the area over which the change takes place is large enough, the cell will fire an impulse.

Numa and his group found that when they inserted their cloned muscarinic receptors into the membrane of a frog's egg cell, the response to acetylcholine was just as expected. After a delay of several seconds, current began to flow into the cell. This was quite unlike the first response of cloned nicotinic receptors in the same environment.

The purpose of work like that of Numa and his colleagues is to understand these processes at the level of the individual molecules. (Extracted from New Scientist, 9 October 1986)

Viroids and introns

It can be satisfying when two conundrums fit together - they may just form one big puzzle, but at least some loose ends have been tied together.

Viroids are the smallest infectious particles known, consisting solely of naked RNA. So far as scientists have been able to tell after years of study, the RNA does not code for a single protein - yet somehow this "silent" genetic material can cause disease in the plant hosts. Introns are silent, too - bits of genetic material that can be seen in most DNA, only to be snipped out of the complementary RNA before it is translated into protein. Now comes evidence for an idea first proposed in 1979: that viroids are "escaped" introns.

According to Gail Dinter-Gottlieb, (now at Drexel University in Philadelphia, who did the work at the University of Colorado in Boulder) there is a striking similarity in the nucleic acid sequences, and possibly in the structures, of viroids and a certain class of introns. These "group 1" introns can be found in both plants and animals, and in all three cellular organelles (in chloroplast, nuclear and mitochondrial RNA), as a group, they are defined by a shared, 16-nucleotide consensus sequence.

The evidence is strong for a close relationship between viroids and introns, though it remains unclear whether viroids evolved from introns, or merely share a common ancestor molecule. However, at least one group 1 intron shares yet other viroid sequences, stretches of RNA responsible for modulating the severity of infection. The similarity leads to the question of whether introns might be pathogenic. Perhaps some renegade intron escaped the normal regulatory processes of the cell, and took up an infectious "life"-style. (Extracted from Science News, Vol. 130, 11 October 1986)

Tumor necrosis factor may have wider role

Another function seems to have been found for tumor necrosis factor (TNF), a polypeptide produced by the immune system in response to bacterial infections and that also seems able to selectively kill tumor cells. According to Ken Takeda, Kunio Konno, and colleagues at Showa University, Tokyo, and Green Cross Corp., Osaka, TNF is identical with another factor found in the immune system called differentiation inducing factor. The Japanese researchers reached this conclusion, because both factors have the same molecular weight, have identical amino acid sequences for the first 20 residues starting at the N-terminal end, and are neutralized by the same mouse monoclonal antibody. Thus, one of the natural functions of TNF appears to be to stimulate non-differentiated immune system cells to develop into macrophages. Last year, researchers at Rockerfeller University showed by similar methods that TNF is also identical to a factor called cachectin, which causes cells to stop absorbing fatty acids and can lead to cell death through shock. The Japanese researchers suggest that all of these functions may be interrelated in a complex feedback system that controls the maturation of immune system cells.

Like interferon before it, tumor necrosis factor (TNF) appears to have antiviral as well as anticancer activity. Findings in the FRG and US show that TNF has pronounced and broad-ranging antiviral activity.

Both interferon and TNF are soluble messenger proteins produced by cells of the immune system to elicit responses in other cells. Both are produced naturally in mammals in response to bacterial infections. Interferon was discovered as a natural antiviral agent and has since been shown to be able to kill certain types of cancer cells selectively. TNF, on the other hand, was first identified in 1975 because of its tumor-cell-killing ability.

The current work was conducted at the German Cancer Research Center in Heidelberg, at the University of Ulm, and at BASF in Ludwigshafen; and by Genentech Inc. in South San Francisco. Both groups were trying to determine whether TNF's anticancer effect might be an indirect one caused by that substance's inducing the production of interferon. Instead they find that the factor acts mainly on its own, not only in killing cancer cells but against viruses.

The mechanism of action of TNF against viruses is not known. It appears to have two effects: it imparts protection against viral infection to certain cell lines, presumably by interfering with an early step in viral infection, and it selectively kills cells that have been infected with virus. (Abstracted with permission from Chemical and Engineering News, 13 October 1986 p. 19 and 3 November 1986 p. 6. Copyright 1986, American Chemical Society)

Ironing out the flaws in cancer therapy

Tumour cells can be inherently resistant to drugs. In these cases, the neoplasm retains the capability of the normal parent tissue to avoid being killed by toxins. Epithelial tissue, which acts as a natural detoxifier, produces particularly stubborn tumours such as those of the colon, kidney and liver. Cancers with inherent resistance can also acquire more resistance through repeated exposure to drugs.

Anticancer drugs work by inducing damage to the DNA of the tumour cells. Almost all accepted anticancer drugs are either products of plants with alkaloid bases, such as periwinkle, or antibiotics and work by causing fragmentation of DNA. Many drugs target the same spot on DNA: an enzyme called topoisomerase. This enzyme knots a circular piece of DNA and then unknots it. It works by breaking a segment of DNA, which translocates, and then resealing the strands. Topoisomerase is essential to the replication of DNA, as it governs elongation of the strands, separation of daughter molecules, and termination of synthesis by reforming the DNA into a circle.

Anticancer drugs "catch" the enzyme after it has broken a segment of DNA and then "freeze" it so that it cannot finish its job. As scientists have observed experimentally in E. coli treated with quinine derivative, the extensive degradation of DNA caused by the capture of topoisomerase sends a biochemical signal that induces the cell to self-destruct. DNA topoisomerase is present in high amounts only in proliferating cells, which fits neatly with the observation that slow-growing tumours show greater resistance to drugs than do skin or lymphatic cancers.

Normal cells are damaged also in the process, Robert Schimke, a molecular biologist from Stanford University, sees several ways in which DNA damage can lead to multidrug resistance in the targetted cells. By causing its strands to break, the drugs inhibit the replication of DNA. However, when the drug is withdrawn and DNA synthesis starts up again in mid-cycle, several oddities result: sister chromatid exchange becomes unequal; extra DNA from killed cells becomes available for transcription, and so-called minute chromosomes, formed during the breakage, cause further over-replication. All these, Schimke says, contribute to gene amplification - extra copies of genes and over-expression of their protein products.

In evolutionary terms, amplification means variety. The more genes initiated, the more proteins are transcribed, and the greater the chances for mutations, some of which will confer drug resistance. As there will always be some DNA available for replication, the drugs will not be able to outrun the mutant resistant cells.

Schimke offers another possible explanation of chemotheraphy's tragic flaw. Instead of killing the cells directly, anticancer drugs may cause chromosomal aberrations that eventually result in the cell's death. This idea has been confirmed in cytogenetic studies of mdr cell lines from Chinese hamsters and humans.

The question remains of how exactly a mutation confers resistance. One route is a change in a protein in the cell membrane that prevents the drug from being transferred into the cell. This is precisely what Victor Ling of the Ontario Cancer Institute found two years ago in ovarian cells of the Chinese hamster. Using monoclonal antibodies in an mdr cell line, Ling detected an over-expressed membrane protein of high molecular weight. In hamster, mouse and human cell lines, increased expression of this protein corresponded to increased resistance, and low expression corresponded to sensitivity to anticancer drugs.

The structure and function of this membrane protein, called P-170, can easily account for the decreased accumulation of drugs so often seen in mdr cells. P-170 looks like conjoined twins, and its cytoplasmic domain resembles the structure in the bacterium E. coli that transports energy. The rest of the protein moves in and out of the cell membrane, creating pores. From this structure, says Ling, one can speculate that P-170 acts as an efflux pump, moving substances - including drugs - out of the cell. Alternatively, P-170 may pump out an unknown molecule to which the drugs bind.

Although P-170 is the current favourite among molecular biologists, there are other reasons for the failure of cancer chemotherapy that have little or nothing to do with this protein. Inherent resistance; size, location and blood supply of the tumour; and the patient's prior treatment all influence the effectiveness of drug therapy. Furthermore, there are other key proteins that are over-expressed in mdr cells. Protein kinase-C is involved in many physiological responses, such as the secretion of insulin and histamine and the release of prolactin from the pituitary. The common characteristic is outflow, and given that the kinase is present in high amounts in mdr lines, it may be controlling the expulsion of drugs from the cell. Another over-expressed protein, glutathione, protects cells by destroying free oxygen radicals and other toxins, including, perhaps, anticancer drugs. Changes in the morphology of cells can create a resistant phenotype as well. Here there may be no over-expression of proteins, but structural anomalies such as vacuoles cause the cell to accumulate the drugs in the cytoplasm, where they do nothing, rather than in the nucleus.

The picture is brighter for the development of new drugs. Now, instead of relying on empirical results, scientists can target drugs that interact with P-170, protein kinase-C and glutathione, or that inhibit protein synthesis. Of course, the problem remains of how normal cells would handle such disruptions. Further down the line is the use drugs riding piggyback on a monoclonal antibody. The drug can be immobilised so that it does not penetrate the cell membrane but does create sensitivity to the antibody, which can then move in for the kill. Most elegant but, for the present, least feasible of all is the transfer of genes, either to enhance the toxicity of a drug or to protect normal cells against chemotherapy. (Extracted from New Scientist, 30 October 1986)

Biotechnology team in DNA advance

Scientists at Genetics Institute, Inc., have produced a human protein which may be used to treat cancer and infectious diseases. The protein, called macrophage colony stimulating factor (M-CSF or CSF-1) was produced by recombinant DNA technology. It stimulates blood cells involved in the body's natural defenses.

M-CSF promotes the production and stimulates the activity of macrophages, which play an important role in the body's defense against disease. It is believed that augmenting macrophages with M-CSF will be useful in the treatment of certain infectious diseases, such as those affecting the lungs.

In addition, M-CSF therapy, either alone or in combination with antitumor monoclonal antibodies, may strengthen the body's ability to fight cancers.

Genetics Institute has commenced pre-clinical testing of M-CSF and plans to begin human clinical testing in 1987.

Previously, natural M-CSF had been isolated in small quantities from human urine. Through a collaboration with Japanese scientists at Morinaga Milk Industry Company Ltd., Jichi Medical School, and Tokyo University, Genetics Institute has shown that its genetically engineered M-CSF is structurally identical to the natural protein.

Also at Genetics Institute, Inc., scientists have discovered a new human gene that helps red blood cells reproduce themselves. The gene is for the GM-CSF protein, which stimulates red blood cells and two types of white blood cells, granulocytes and monocytes. Tests on monkeys showed that GM-CSF increased white cell recovery seven times in one monkey, and caused a rapid recovery of another monkey's white-cell level after his immune system had been nearly eliminated by a virus. However, GM-CSF does not stimulate T and B cells, the most important white blood cells. After years of believing that such a protein, interleukin-3, exists (it is found in mice) but not being able to locate it in humans, scientists at Genetics Institute believe they have located the protein. While they don't yet know what it can do to help cure diseases, let alone what its side-effects are, researchers believe that the discovery of interleukin-3 may be as important as that of penicillin. It might be used to boost the immune systems in AIDS patients, as well as to revitalize cancer patients' immune systems that have been broken down by chemotherapy. (Extracted from The Economist, 11 October 1986 and Chemical Marketing Reporter, 15 December 1986)

Effects of TIL

Tumor-infiltrating lymphocytes (TIL) are 50-100 times more effective at killing tumor cells than lymphokine-activated killer cells, according to S. Rosenberg of the US National Cancer Institute. The TIL lymphocytes were isolated from tumors in mice that had been infected with two types of sarcoma. The cells were incubated with interleukin-2 and were then injected into mice with lung and liver cancer. A few million pure TIL cells eliminated 96 per cent of small metastasized cancers. TIL cells also worked well on large tumors when the immune system was first shut down with cyclophosphamide or radiation. Large tumors are immune to attack from LAK cells. TIL cells need very small amounts of interleukin-2. TIL cells can also be isolated from human tumors including melanoma and kidney tumors and some adenocarcinomas. Human TIL cells kill the same type of melanoma cell in vitro. The US Food and Drug Administration approval for further trials is expected shortly. (Extracted from New Scientist, 25 September 1986)

Hereditary eye-tumor DNA reveals first silent oncogene

An oncogene that isn't there supplies the latest clue to the cause of cancer. Unlike the 30 or so genetically dominant oncogenes now known to be involved in making cells malignant, this new gene is recessive, which means its loss or absence triggers tumors; its presence prevents them.

This at any rate is the picture proposed by the two-centre team of scientists that has just announced isolating the recessive oncogene by not finding it in the genomes of retinoblastoma and osteosarcoma tumor cells. Led by ophthalmologist Thadeus P. Dryja of the Massachusetts Eye and Ear Infirmary, Boston, Mass., and oncologist Stephen H. Friend of the Whitehead Institute for Biomedical Research in Cambridge, Mass., the researchers reported their feat of molecular detection in October 1986.

The task force is beginning efforts to clone and express the product of the gene, to determine whether some malignant properties of retinoblastoma and osteosarcoma cells can be reverted on introduction of cloned sequences thought to represent the Rb gene.

A pair of recessive oncogenes, one from each parent, are thought to be present in every human, serving to curb the dominant oncogenes' tumorogenic activity. If both recessives are lost or inactivated, either by inheritance or acquired mutation, predisposition to the two childhood cancers could be greatly heightened by the absence of these "stop-signals" governing unbridled cell growth.

The team constructed a 4.7-kb cDNA hybridization probe that surveyed a 70-kb region on human chromosome 13, thought to contain the retinoblastoma-oncogenic locus. It detected matching RNA transcripts in healthy human cells but not in retinoblastomas, osteosarcomas and other tumor types, including kidney and lung cancers.

Children who inherit a mutated recessive gene, says Dryja, not only have a greater incidence of the eye-tumor, but half of those who also develop osteosarcoma probably owe this second cancer to the same mutation. (Source: McGraw-Hill's Biotechnology Newswatch, 3 November 1986)

Scientists pinpoint dystrophy gene

After a long search, researchers think they have found the gene for Duchenne muscular dystrophy. The gene that is defective seems to be enormous, and probably codes for one of the similarly large proteins recently discovered in muscles, but an effective treatment is still many years distant. The new discovery is reported by Louis Kunkel of the Children's Hospital in Boston, and his colleagues there and at Harvard University. It is the latest finding in a series of advances over the past few years by collaborating researchers in London, Oxford, Toronto and Boston.

The first clues to the location of the gene came from patients with Duchenne muscular dystrophy (DMD) who were missing bits of their X chromosome. The biologists reasoned that the DMD gene must lie somewhere along the deleted sequences. By looking for differences between DNA from healthy people and boys with DMD, they found a variety of such sequences, one of which was dubbed pERT87. Kunkel and his colleagues then supposed that if pERT87 is really part of a gene for an important protein (which the DMD defect must be), it will turn up in other species. He looked for, and found, pERT87 in horses, frogs, chickens, gorillas, mice and hamsters. He then began to search muscle tissues for a protein that in part matched the genetic sequence of pERT87.

Kunkel took samples of fetal muscle and extracted its messenger RNA. He used pERT87 as a probe to fish for its equivalent in messenger RNA (mRNA). The result was the latest breakthrough. Kunkel found a mRNA with a short sequence that matched pERT87. This mRNA must be linked to a gene, at work in fetal muscle, that now becomes a strong contender for the gene at fault in DMD.

We still do not know whether DMD is caused by lack of an essential protein, or by various defective forms of it. Both may be true. To further complicate matters, biologists are not even sure that only one defective protein is at the root of the disease. Some people with DMD also suffer from mental retardation, which could spring from another defective gene.

A third of all cases of DMD arise from new mutations, which suggests that the area of the X chromosome that houses the crucial gene is far from stable. The pattern of deletions in people suffering from DMD is also complicated. These findings suggest that there is no easy answer to DMD. Therapy, or even a simple biochemical test to detect carriers of the defective gene, are still a long way off, but the new genetic insights should, in the end, help in understanding the biological origins of this particularly horrific human affliction. (Source: New Scientist, 30 October 1986)

'Revolutionary' antibody design

Genex Corp. of Gaithersburg, Md., has filed patent applications relating to the design of novel, single-chain antibodies, developed using the company's protein engineering technology. Conventional antibodies, including monoclonals, consist of four cross-linked protein chains - two identical long chains, called "heavy" chains, and two identical short or "light" chains. Both the heavy and light chains contain a constant region, which is the same for all antibodies of a given class, and a variable region that binds a specific antigen and is therefore different for each antibody.

Genex's single-chain antibodies are hybrid molecules, constructed by connecting specific sections of the light chain variable region and specific sections of the heavy chain variable region with short peptide linkers. Using computer analysis, the company's scientists designed the length and composition of the peptide linkers as well as their site of attachment to the variable regions. Unlike conventional antibodies, single-chain antibodies are expected to be manufactured in genetically engineered micro-organisms. Their primary advantages are anticipated to be smaller size, greater stability and significantly lower cost. (Source: Biotechnology Bulletin, Vol. 5, No. 9, October 1986)

Stanford scientists scrutinize lymphoma oncogene product

By cloning the oncogene thought to be responsible for follicular lymphoma - the most prevalent adult cancer of the blood's B cells after Hodgkin's disease - pathologist Michael Cleary of the Stanford University School of Medicine is now analysing the structure of that gene's protein product in the hopes of blocking its activity. One surprise discovery: the substance is related to protein produced by the Epstein-Barr virus, which is known to affect B-cell growth.

Oncogenes are the tumorogenic form of proto-oncogenes, which are benign useful DNA sequences - until transformed by some environmental stress. In the case of the B-lymphocyte oncogene, he suggests, this molecular insult occurs when maturing B cells - manufacturers of the body's antibodies - rearrange the antibody genes on their chromosomes. Sometimes, this DNA-shuffling goes wrong: the gene and the future proto-oncogene both break in half, and the latter, if translocated to another chromosome, turns malignant, and sets off the follicular lymphoma. (Source: McGraw-Hill's Biotechnology Newswatch, 3 November 1986)

Enzyme research advances protein engineering

A series of modifications of the enzymes subtilisin produce subtle, often predictable shifts in various properties of the protein, according to research at Genencor and Genentech. Subtilisin is an important commercial enzyme - it is a protease used in detergent formulations - and it is an excellent model for serine hydrolase enzymes, which operate by a similar mechanism. Serine hydrolases include proteases and lipases. The researchers aim to put the machinery for protein engineering into place for work on other enzymes. Work on subtilisin suggests that lipases can be modified to improve transesterification reactions for conversion of inexpensive oils into higher value triglycerides. Research focuses on turnover number, substrate binding, substrate specificity or catalytic efficiency, the pH profile of reaction kinetics, enzyme stability and type of reaction catalyzed.

Subtilisin hydrolyzes peptides bonds, cleaving bonds adjacent to certain amino acid residue more efficiently than others. Researchers tried to alter the pH profile of subtilisin's catalytic activity, but the change in the enzyme produced results nearly the opposite of what the scientists had predicted. (Abstracted with permission from Chemical and Engineering News, 13 October 1986, pp. 23-25. Copyright 1986, American Chemical Society)

New addition to herpes family

Researchers from the National Cancer Institute and five other institutions have isolated a novel herpes virus from six patients who had unusually high levels of a type of white blood cell known as a B lymphocyte.

Electron microscopy of the patients' blood revealed large, short-lived cells containing a virus that by size and shape belongs to the herpes family. Unlike its relatives, the virus *in vitro* infects only fresh B cells. Antibodies against the other herpes viruses didn't attach to the new one.

The discoverers isolated the virus from people who had also been infected with the AIDS virus and four people who had not. They also report finding no evidence of the new virus in 12 other AIDS patients, indicating it is not a necessary factor in AIDS.

Just what sort of problems the virus causes remains to be seen. The four non-AIDS patients in the study had lymph node abnormalities or white-cell cancers. But the virus can also infect with no outward signs - the researchers found it in four of 220 healthy people tested.

As the first new herpes virus in more than 20 years, the virus is likely to receive a lot of attention. It may be responsible for one or more of the many apparently infectious illnesses whose agents have not yet been identified, and it may shed light on other members of the herpes family. (Extracted from Science News, Vol. 130, 8 November 1986)

Hepatitis virus resembles plant viroids

The molecular architecture of the hepatitis delta virus (HDV) has been unravelled by two research teams, one in the US and one in the Netherlands. HDV

is responsible for many of the more serious cases of hepatitis among those infected with the hepatitis B virus. The researchers found that the delta virus contains a single-stranded circular loop of RNA consisting of about 1,700 nucleotides. "This is the first animal virus identified with a circular RNA genome," the Dutch group notes. In this and other respects, HDV shows an unexpected resemblance to plant viroids, which cause a number of plant diseases. These similarities fuel speculation about HDV's possible plant origin. The complete RNA structure of the virus is expected to aid scientists in developing methods to prevent and treat infections. The US research effort was led by scientists at Chiron Corp., Emeryville, Calif., the Dutch effort by scientists at the Primate Center of the Netherlands Organization for Applied Scientific Research (TNO) in Rijswijk. (Reprinted with permission from Chemical and Engineering News, 13 October 1986. Copyright 1986, American Chemical Society)

Hepatitis agents defined

A mysterious particle that piggybacks onto the hepatitis B virus has been characterized, and the hepatitis B virus itself has now been grown in the laboratory. These two advances promise to accelerate the speed of hepatitis research.

The discoveries relate to the blood-borne hepatitis B virus. While some people, though infectious, carry the virus with no ill effects to themselves, others are chronically ill and may also develop liver cancer. Hepatitis B infection, for which there is no treatment, can be complicated by the delta agent - a "defective" virus that exists only in conjunction with the hepatitis B virus. Delta infection, believed to be on the rise worldwide, can make chronic hepatitis B infection lethal.

Myron Essex and his colleagues at the Harvard School of Public Health have grown the hepatitis B virus in the test tube. They inserted hepatitis B genetic material into cells from human liver cancer and were able to isolate cells that produced particles immunologically and structurally identical to the hepatitis B virus.

With the virus in hand researchers will be able to screen a wide variety of drugs against the virus in an in vitro setup. The same group previously had inserted the virus's genetic material into bone marrow cells, but the production of virus particles was transient. The newly reported cell line has been producing viruses for a year.

The ability to culture hepatitis B virus is also expected to speed research on the delta agent. Knowledge of the "satellite" virus, as researchers call it, was boosted when two laboratories described its structure, sequence and function. Delta's genetic material was described as a single-stranded circle of RNA similar in size and shape to certain agents that infect plants. In addition, the US group determined the agent's genetic sequence and discovered antibodies to a protein encoded by the RNA in the blood of patients with delta infections.

These new findings will someday enable researchers to develop a blood test for diagnosing delta infection - which currently must be diagnosed through liver biopsy - and will allow researchers to conduct experimental vaccine research. (Extracted from Science News, Vol. 130, 11 October 1986)

One-cell origin for atherosclerosis?

Atherosclerotic plaque cells contain genes that cause uncontrolled growth, and these genetic elements, when transferred into other cells, cause them to become cancer-like, New York University researchers have found.

Despite the high prevalence of atherosclerosis, the cause of the condition is one of the great mysteries of cardiology. Two major theories have been developed by different researchers at the University of Washington in Seattle. One is the response-to-injury hypothesis, which holds that atherosclerotic plaques appear where the blood vessel has been injured. The other is the monoclonal hypothesis, in which plaques are essentially benign tumors that arise from single smooth-muscle cells.

The NYU report supplies a mechanism for the monoclonal hypothesis. Arthur Penn, Bruce Hindich and their colleagues looked at the proliferating smooth-muscle cells of atherosclerosis by applying techniques developed for the study of genes that are believed to make single cells grow into cancer.

If the monoclonal hypothesis is borne out, the next step is to discover what activates or mutates the responsible gene. Among the possible initiating events are viruses or chemical carcinogens. As for the role of high serum cholestrol in plaque development, while it is unquestionably a factor, its role in these particular events is unknown. (Extracted from Science News, Vol. 130, 15 November 1986)

Genes governing slow-onset brain degeneration discovered

Pursuing the newly discovered "clock gene," neurologist Stanley B. Prusiner of the University of California School of Medicine, suggests that control of this genetic time-setting mechanism in the body may some day make it possible to postpone the onset of Alzheimer's disease from the seventh or eighth decade of life to age 150.

Prusiner points out that "elucidating the molecular basis of these timing mechanisms may provide important new insights into the biological processes responsible for the degenerative neurological diseases of later life." Besides Alzheimer's, the molecular clock in all late-onset diseases may be re-set.

If this ever becomes possible, people would be spared contracting multiple sclerosis and Creutzfeldt-Jakob disease in their 20s or 30s, Huntington's in their 30s or 40s, amyotrophic lateral sclerosis, (Lou Gehrig's disease) and Parkinsonism in their 50s and 60s, Alzheimer's in their 70s and 80s.

Because these human dementias develop so slowly over a lifetime, their molecular basis cannot be researched directly. The closest animal model is a slow fatal infection of the nervous system in sheep and goats called scrapie, because the itch-frenzied animals scrape their skins off against trees, walls and fenceposts. Scrapie can be readily transferred to rats, mice and hamsters, and in these Prusiner and his co-workers have identified the gene that controls the timing of the disease.

This clock gene determines that one breed of mouse inoculated with the scrapie infective agent will die between 200 and 385 days later - ripe old ages for a rodent. Another murine species, with a different variant of the clock gene, succumbs in 110 to 116 days; a cross between the two dies in a mid-way time span, proportionate to the genetic mix.

This latency-calibrating sequence, which controls incubation time before open onset of the disease, and determines susceptibility to scrapie, is linked on mouse chromosome 2 to the gene for a scrapie-causing protein that Prusiner named the 'prion'. The two genes are so close together on the

chromosome that they may be one and the same, he suggests. But curiously, the DNA sequence is the same in healthy and infected animals, which means that whatever it is that causes scrapie must develop in the gene product after that protein is expressed.

According to one theory, the clock-prion gene complex occurs in all mammals, but only infected ones alter the protein's structure so that the body's enzymes can no longer degrade it, and it accumulates as the filamentous plaques found in the brains of mice, sheep and humans with dementia. (Source: McGraw Hill's Biotechnology Newswatch, 3 November 1986)

Drug shows promise for Alzheimer's disease

An experimental drug that blocks the destruction of acetylcholine in the brain significantly improved the memories of 16 to 17 elderly people with Alzheimer's disease in a clinical trial at two Pasadena, Calif., hospitals. The drug called 1,2,3,4-tetrahydro-9-aminoacridine, or THA, overcomes the effects of the disease on patients in intermediate stages of the disease, similar to L-dopa treatment for patients with Parkinson's disease.

The evidence comes from a study in which oral doses of THA led to an improvement in Alzheimer's patients with moderate to severe dementia, and restored some of them to a previous level of competence. For now, the drug is only available to researchers. The side-effects of the drug have been minor.

Dr. William Summers, a psychiatrist who led the study team, has no illusions that THA will work indefinitely. The drug can be expected to create only a temporary plateau for sufferers from Alzheimer's disease and the eventual decline will be rapid. The time between diagnosis and death remains the same, with or without treatment: six-eight years.

Meanwhile, physicians need a reliable test that can detect Alzheimer's disease while the patient is still alive. A good test for the living is getting closer, thanks to the recent discovery of a chemical called A-68 by Dr. Peter Davies and his graduate student, Mr. Benjamin Wolozin, both at New York City's Albert Einstein College of Medicine.

A-68 is a protein that (so far) seems to be unique as a marker for Alzheimer's disease. Its advantage is that it is found not only in the brains of living people who are believed to have the illness, but also in their spinal fluid. Several drug companies would like to use the chemical for a test that could be done by taking some spinal fluid from the patient - not a trivial procedure, but at least a feasible one.

If it works, the test could be at least as helpful to the large number of people who are mistakenly thought to have Alzheimer's disease as to those who really do have it. Confusing Alzheimer's with other disorders - such as depression, anxiety, alcoholism and malnutrition - is all too common and deprives its victims of appropriate and already available therapies.

Also, Alzheimer's disease has a slow and insidious start. This means that if - as Dr. Davies believes - A-68 appears in the very early stages of the illness, detection may make it possible to find a way to reverse it or at least prevent it from getting worse. There is a further possibility that A-68 plays some role in causing or activating the disease by altering the behaviour of one or more genes in the cells of the brain. Whether such a gene, or collection of genes, exists is unknown. But if it does, a plausible suspicion is that it will be found on chromosome 21.

Dr. Carleton Gajdusek and his colleagues at America's National Institutes of Health (NIH) have made what may be a crucial finding, and it points to chromosome 21. The discovery concerns amyloid, a starch-like material with a protein component that is found both in normal aging brains and in those of people with any one of several brain disorders, including Alzheimer's disease. Dr. Gajdusek and the NIH team have identified a collection of genes on chromosome 21 which are the blueprint for a substance used by the body to make the protein portion of amyloid.

With that information, it should now be possible to learn whether the amyloid in a normal aging brain differs from Alzheimer's amyloid and whether the latter, in turn, differs from the amyloid found in other brain disorders, such as Parkinsonism. That the genes should be on chromosome 21 also fits with what is known about Down's syndrome - the most common kind of congenital mental retardation. People with the syndrome have three copies of chromosome 21 instead of the normal two. Examining their brains after death shows that virtually all Down's patients who live into their thirties or forties get Alzheimer's disease.

Although people without Down's syndrome who get Alzheimer's usually get it later, there is strong evidence that the disease has a marked genetic component. In fact, many carriers of the putative Alzheimer's gene (or genes) may be spared the dementia only because it tends to come on so late in life that something else kills them first. (Abstracted with permission from Chemical and Engineering News, 17 November 1986, p. 32. Copyright 1986, American Chemical Society, and The Economist, 22 November 1986)

First human MAbs produced

Human monoclonal antibodies have been produced for the first time by researchers at US National Institutes of Health. Conventional MAbs are made from rodent spleen cells and 'immortal' cancer cells, but these may stimulate an immune response in humans. The new production technique starts with white blood cells donated by healthy volunteers. The cells are exposed to fluorescently tagged proteins. These proteins attached to cells making antibodies against the protein, and a cell sorter picked out these protein/blood cell complexes. The cells were then immortalised with Epstein-Barr virus. Only two proteins have been tested with this approach, and it remains to be seen if the technique can work for other proteins. (Extracted from Science News, 1 November 1986)

Mass production of blood protein

In laboratories throughout the world scientists are chipping away at the technological barriers to marketable biotechnology products. A step in that direction is the possibility of manufacturing blood proteins with medical potential. The breakthrough has been brought about by two genetic engineers of the Stanford Research Institute of California. They have developed an "expression vector" process. Using bacterial rather than human cells, they have engineered synthetic genes that can reproduce, or "express" blood proteins. They have also developed the scale-up vector process that produces those desired biological products.

The system has been applied to three proteins. These proteins have demonstrated significant efficacy in laboratory tests on animals, and in limited human experiments. Two of the proteins - one with the potential to accelerate wound healing, the other to combat cancer - are found in human blood. The third, hirudin, is derived from the salivary glands of leeches, is effective in preventing blood coagulation.

Genetic engineers have found a cost-effective way around the problem by using expression vectors, which allow a given protein to be introduced into a foreign host, usually bacteria. The vector then triggers the cell to produce the protein in quantity.

Unique to the expression vector system is the chemical "switch" that tells the cells when to produce the protein at maximum capacity. The switch needs to stay off at first because the protein is capable of killing the bacterial cells before they have a chance to grow. Once the cells reach their peak population, the "switch" is turned on and the protein is produced. The more cells, the more protein.

It took more than four years of research, but now the expression and isolation process can be completed in a few days, and is refined enough for use on an industrial scale to mass produce proteins for potential use as drugs. (Source: Asia-Pacific Tech Monitor, September/October, 1986)

Activin investigated as treatment for infertility

A hormone with a structure similar to inhibin's has the opposite biological effect. It might make an effective treatment for infertility, according to scientists at the Salk Institute. Activin is composed of two of inhibin's subunits. Both hormones are found in the egg in the ovary and both work by influencing follicle-stimulating hormone (FSH), which causes the egg to grow. While inhibin inhibits the pituitary gland's secretion of FSH, activin stimulates it. Inhibin enhances the activity in the ovary of aromatease, an enzyme that makes the A ring of progesterone aromatic, transforming it into estrogen. The increase in estrogen at the early follicular stage causes the pituitary gland to release more FSH, enhancing fertility. Since low FSH levels are a major cause of infertility in women, the new hormone has been tagged as a potential treatment. The protein is too large to be chemically synthesized, so scientists at Genentech expect to have better results expressing it via recombinant techniques. (Extracted from Industrial Chemical News, September 1986)

Mosquitoes could maybe control malaria

Malaria is killing millions of people each year despite large and expensive programmes both to destroy the mosquitoes that carry the malarial parasites and to develop drugs to combat infection. Many strains of Plasmodium falciparum, the most important human malaria parasite, are now resistant to most drugs and vaccines against the disease are still at an early stage of development.

A group of researchers in the United States is now trying another line of attack. They have found a strain of the mosquito Anopheles gambiae, the main vector of malaria in Africa, that halts the life cycle of some malarial parasites and prevents them from developing as far as the infective stage. Frank Collins and his colleagues at the National Institutes of Health at Bethesda, Maryland, and the Center for Disease Control, Atlanta, initially bred a strain of Anopheles gambiae (called G3) that puts the simian malarial parasite, P. cynomolgi, out of action just after it crosses the gut wall. Collins and his team found that these mosquitoes rarely had oocysts in them. And if there were no oocysts, there can be no sporosoites and no subsequent infection. What they did find in these insects were lots of small dark structures on the outside of the gut wall. When they examined the structures in the electron microscope, they turned out to be ookinetes that had been encapsulated with a substance like melanin. Once inside the capsules, the parasites died. This type of reaction occurs in some other insects in response to infections.

Once the researchers recognized this trait, they selectively bred two lines of mosquitoes - one that kills the parasite and the other susceptible to it. The traits continued through more than 40 generations, which suggest that a simple genetic mechanism is involved. Furthermore, the resistant form was not only resistant to the simian parasite but also showed varying degrees of resistance to other species, including P. falciparum.

Collins and his team suggest that the introduction of this trait into natural mosquito populations might be a possible strategy for control of the disease, but there are 65 species of mosquito that transmit malaria - 20 of them in Africa - and 4 species of parasite, so eradication would be extremely difficult. There is an opening for a new technique.

Meanwhile, trials on humans began in November in the US of a possible vaccine against malaria. It is the first synthetic malaria vaccine to be tested, developed by Ruth Nussenzweig's team at New York University. It is aimed against the stage of the malaria parasite that is injected by mosquitoes into humans, the sporosoite.

Unlike later stages of the malaria parasite, sporozoites are wrapped in a simple protein coat. Plasmodium falciparum, the most dangerous malaria parasite in humans, has a coat made up of a sequence of only four amino acids, repeated many times. The sequence is easy to synthesize chemically. The one other anti-sporosoite vaccine now under trial is produced by genetically engineered bacteria and is expected to be more expensive.

Nussenzweig says the prospect of a vaccine should not divert money from conventional malaria control programmes. (Extracted from New Scientist, 6 November 1986)

Huntington's disease: Clues to the culprit

Huntington's disease starts with a genetic defect on the short arm of chromosome 4, and leads to a withering of the brain. Beginning and end are known, but the agent of the disease inside the body has been a mystery. Researchers at Stanford University report evidence that the cause of the disease may be one of a group of compounds called excitotoxins. According to Dennis Choi, who led the study, the work further suggests that research should focus on one of the three types of neuronal receptors for excitotoxins. He speculates that the degeneration of nerve cells in the brain seen in the disorder is triggered by the improper activation of this receptor, called the NMDA receptor. If borne out, the work may someday provide a basis for therapeutic intervention in Huntington's.

The work, is the latest development in research between Choi's group and one led by Joseph Martin of Harvard Medical School. A year ago, Martin showed that the destruction of nerve cells in Huntington's does not proceed wholesale in certain areas of the brain, as had been thought, but instead shows a distinctive pattern: one group of neurons, containing the enzyme NADPH-d, is to some extent spared.

Both groups have investigated the excitotoxins. These compounds have paradoxical actions: they can excite a neuron to fire or they can kill it, probably depending on length of exposure, according to Choi. But though they are potentially dangerous some excitotoxins are present in considerable amounts in the brain. That has made them a suspect in many neurological disorders. With a simple failure of the mechanisms that normally compartmentalize or clean up excitotoxins, there is the potential for widespread neuronal destruction. (Extracted from Science News, Vol. 130, 11 October 1986)

Bombesin

Bombesin is a peptide that stimulates growth and division of mesenchymal and epithelial cells (page 1117). Upon binding to the surface of a sensitive cell, it activates a biochemical pathway that enhances DNA synthesis and the activity of the proto- oncogene c-myc. It has now been shown as a result of research at the University of California, that G proteins, a class of proteins that respond to various neuro-transmitters and peptide hormones, play a part in this pathway. Scientists at the university found that stimulation of cells by bombesin could be inhibited by pertussis toxin, a potent inhibitor of G-protein activities. A second growth factor, platelet-derived growth factor, which stimulates the same cells as bombesin, retained its activity in the presence of pertussis toxin, suggesting that this factor uses different intracellular signals for producing its effects. Besides being found in normal endocrine cells, bombesin is also associated with some human tumor cells (such as those of small cell carcinomas of the lung), where it may be involved in stimulating characteristic unchecked growth of such tumors. (Source: Science, Vol. 234, p. 1051)

Vaccines possible from T-cells

Conventional vaccines promote resistance to disease by engaging the body's immune system. They imitate the disease itself - indeed, they usually are real germs, "attenuated" by infection into other animals to reduce their virulence. They work by inducing the immune system's B cells to produce antibodies, which swamp the germ when it infects again. But in some germs, such as influenza, the proteins recognized by antibodies keep changing, thereby enabling the virus to evade immune attack. Some scientists say research has focused too closely on the B cells. They think vaccines can work against influenza by priming the other branch of the immune system as well: the T cells.

It is already evident that antibodies are not the only weapons that combat viral disease. A team led by Dr. Ita Askonas at the National Institute for Medical Research (NIMR) at Mill Hill in London demonstrated in the laboratory the existence of "killer T cells" that work against a broader range of influenza viruses than antibodies do. Then a team led by Dr. Andrew McMichael of the John Radcliffe Hospital in Oxford showed that this was true in the body as well as the laboratory.

Killer T cells are known to break up the cells they attack and also to produce gamma interferon. Science has long recognized their crucial role in combating diseases like cancer but the suggestion that they formed a second line of defence against viruses is new. It implies that a completely new type of vaccine might eventually be developed to prompt killer T cells to attack those cells infected by viruses. Researchers must first learn how the virus triggers the T cell response.

Scientists at the John Radcliffe Hospital and NIMR have been trying to discover how killer T cells - and the "helper" T cells that stimulate them - are activated by influenza viruses. They chose 'flu because it can evade the body's antibodies by changing its outer coat and so making itself unrecognisable. It seems that, just as B cells are triggered to produce lots of antibodies by a specific piece of protein on the infectious agent, so T cells are activated by a "marker" that identifies the infectious agent. In 'flu, one marker is a viral protein called the nucleoprotein, which is found in the viral core and is therefore hard for the immune system to spot. A clue to how to recognise nucleo-protein came from studies of helper T cells. The cells could not identify many proteins until they were fragmented. (Extracted from The Economist, 11 October 1986)

Protein T may thwart AIDS virus

Scientists in the US may have discovered a way to upset the mechanism by which the AIDS virus locks onto host cells. Recent experiments at government laboratories show that an apparently harmless synthetic protein mimics a section of the virus and can take its place on a cell's membrane. The protein, a sequence of eight amino acids, is called "peptide T". It blocks the receptor site on a cell where the AIDS virus would normally bind itself.

The AIDS virus has found suitable receptors on white blood cells of the human immune system and on brain cells. But, according to Candace Pert who discovered peptide T, if you treat a victim with a drug based on peptide T, the receptor sites could all become "booked up". With nowhere to lock in, the virus would eventually be washed out of the body.

Pert, a pharmacologist at the National Institute of Mental Health, has pioneered work in neurochemicals, recognizing a similarity between the AIDS virus's favourite target on human cells, known as the T4 antigen, and receptors that process information for the brain and immune system.

The AIDS virus often attacks the brain, causing dementia and other neurological disorders. Pert's team decided to employ a computer to compare the amino acid sequences on the envelope of the AIDS virus with those of all known proteins in order to find matching sequences.

The computer came up with an octapeptide, a sequence of eight amino acids of which five were threonine, leading to the moniker peptide T. It matched a sequence on another virus, Epstein-Barr. Intrigued by this improbable coincidence, Pert's team synthesised the octapeptide for further study.

They found that when brain and immune cells with T4 antigens were first exposed to even low concentrations of peptide T or any of three synthetic relatives, the cells strongly resisted subsequent invasion by the AIDS virus. The peptide may prove able to raise antibodies in people at risk of infection and thus act as a vaccine. (Source: New Scientist, 18 December 1986)

Body's own immune system could combat AIDS

Scientists in San Francisco claimed that for the first time they had evidence that the body's immune system could ward off the AIDS virus.

The discovery may explain why about 70 per cent of those infected with the AIDS virus do not come down with the disease, or demonstrate only mild symptoms.

It also suggests that harnessing the body's own immune system may be a more effective treatment for the disease than using drugs, which are usually highly toxic.

The work, carried out by Jay Levy of the University of California at San Francisco, is based on cells cultured from the blood of three healthy homosexual men. The men had antibodies to AIDS but had not developed the disease. Levy's group believes it now knows why these three men remain healthy.

The three men had no detectable virus in their blood, but the virus appeared in cultured samples of their blood after the removal of suppressor T cells that were marked with the surface protein CD8. Removal of the suppressor T cell meant that the remaining cultured blood cells were primarily helper T cells, another form of white blood cells that produce antibodies. Helper T cells are the principal target of the AIDS virus.

In a subsequent experiment on the cultured cells from one of the men, replication of the AIDS virus was again suppressed when the CD8 T cells were returned to the culture after an absence of three weeks.

The researchers believe that T cells bearing the CD8 protein produce some as yet unidentified substance - perhaps interleukin-2 or interferon - that interferes with replication of the virus in infected T cells. The virus is not killed, but it is kept in check. (Source: New Scientist, 18 December 1986)

Insects may be implicated in AIDS transmission

A physician studying the incidence of Acquired Immune Deficiency Syndrome (AIDS) in Belle Glade, Florida, says that environmental factors, rather than sexual contact or intravenous drug abuse, may be responsible for the majority of AIDS cases there. Writing in the November/December 1986 issue of Genetic Engineering News, Mark E. Whiteside, M.D., co-director of the Institute of Tropical Medicine in Miami, Florida, claims that Belle Glade represents a tropical pattern of AIDS transmission where insect-borne viruses, known as arboviruses, act as cofactors in the development of AIDS.

"Repeated exposures to certain insect-borne viruses are one of the things that lead to a weakening of the body's defenses over time. When the cellular immune apparatus is broken beyond repair, certain opportunistic infections and cancers come along which are collectively called AIDS", Dr. Whiteside said.

Dr. Whiteside, who has been involved in clinical work and research on AIDS since 1981, believes AIDS results from the interaction of more than one viral agent. He says that previous research studies have shown that arboviruses can activate retroviruses in animals. A retrovirus, human immunodeficiency virus (HIV), is thought to cause AIDS in man.

Based on AIDS patterns in Africa, the Caribbean and South Florida, and having ruled out AIDS patients in the high-risk categories, Dr. Whiteside says AIDS in the tropics primarily afflicts poor people in economically depressed surroundings. According to Dr. Whiteside, studies implicating the heterosexual transmission of AIDS in the tropics are seriously flawed by inadequate controls, bias, and lack of data.

"Until better studies are carried out and more is known", writes Dr. Whiteside, "the conviction that AIDS is due to sexual habits among poor people in the tropics or in South Florida seems to me a narrow and quite prejudiced attitude."

Dr. Whiteside also cites studies demonstrating that animal retroviruses - such as bovine leukemia and equine infectious anemia - are transmitted "mechanically" to other animals by insects in conditions of crowding and in areas with an abundance of insects. Referring to the survival of the AIDS virus (HIV) in the common bedbug, Dr. Whiteside says that scientists must explore the possible role of insects in the spread of HIV.

"Although you don't hear much about it," he writes, "a number of researchers from around the world are just beginning to examine the role of insect transmission of the human retrovirus, HIV."

While warning against unsafe sex practices and intravenous drug use, Dr. Whiteside also calls on public health authorities and educators to take steps to reduce environmental hazards implicated in the tropical pattern of AIDS transmission. Adequate housing, sanitation, protective field clothing, and the control of insect and rat populations are important public health measures that need to be implemented. (Source: News Release, 18 December 1986)

Human DNA intact after 8,000 years

For nearly three years, scientists working at a central Florida peat bog have been dredging up 8,000-year-old human skeletons with skulls that contain shriveled, remarkably preserved brains. They now report that four of the brains have yielded the oldest-known examples of human DNA and cellular structure.

Molecular biologists are now attempting to clone genes or gene fragments from the prehistoric pieces of DNA so that they can be compared to corresponding modern genes.

Preservation of soft tissue in the soggy bog demonstrates that intact DNA can survive in other than extremely arid conditions, which greatly widens the sites where ancient genetic material may be found.

Previous DNA recoveries from archaeological remains have involved dried tissue. One researcher detected human like fragments of DNA in 3 of 23 Egyptian mummies and cloned some of the 2,400-year-old DNA segments in bacteria. Bits of DNA from a quagga, an extinct horselike animal, have also been cloned.

The yield of DNA from the Florida specimens was about one per cent of the amount normally obtained from fresh tissue. DNA analysis is being conducted by Philip J. Lupis and William W. Hauswirth of the University of Florida College of Medicine in Gainesville.

In addition to the DNA findings, microscopic examination of samples taken from the cerebral hemispheres, cerebellum and brain stem revealed, according to the researchers, "limited but definite" remains of cell structure and patterning similar to that found in modern brains. (Extracted from Science News, Vol. 130, 8 November 1986)

Research on animal genes

Germ-line gene therapy cures thalassemia in mice

After correcting the severe anemia of beta-thalassemia in laboratory mice by gene transfer, a research team at Columbia University, New York City, is now working on a mouse model for sickle-cell anemia. Molecular geneticist Frank Costantini, at the University's College of Physicians and Surgeons, and his associates are seeking to convert their thalassemic mice into a murine model of sickle-cell anemia, for which no animal counterpart exists today. Costantini points out that a sickle-cell mouse model will be useful in testing drugs aimed at therapy.

Three years ago a research laboratory in Triangle Park, North Carolina, discovered a spontaneously mutated DBA/J mouse with all the symptoms of human beta-thalassemia - notably, hemolytic anemia, insufficient beta-globin synthesis, misshapen red blood cells, early death.

Costantini bred the mutant with mice he had induced to express human hemoglobin in quantity, by microinjecting fertilized eggs of normal mice with cloned human beta-globin genes, a 7.7-kilo-base DNA sequence. Two of the injected eggs grew into mice producing human hemoglobin. When these mated with the mutant, five of their offspring had healthy

haemoglobin and red blood cells. (Extracted from McGraw-Hill's Biotechnology Newswatch, 6 October 1986)

French claim 'first' in DNA-sexing of bovine embryos

A task-force of 30 French scientists from four research institutes announced last September a system that determines the sex of week-old calf embryos. Their process is based on DNA hybridization of the male-only Y chromosome. When developed as a detection kit, the method is expected to permit large economies in cattle breeding via frozen transplanted embryos.

The project cost some 10 million francs ($1.5 million), one-third of it provided as a subsidy from ANVAR - French National Agency for Commercialization of Research.

The system's advantages for industrialized and developing countries are that the shipping of frozen embryos of known sex across international borders will overcome the myriad of international sanitary regulations that regulate the movement of cattle; the production and sale of livestock will be simpler and cheaper; herd managers will know in advance the numbers of bulls and cows they are stocking; the fact of being able to inoculate two definitely male embryos into a single cow will be an economic leap forward. At present when two embryos of unknown gender are implanted, and turn out to be one male, one female, the latter is often born a sterile freemartin, owing to mixing of blood and chromosomes in utero; and endangered breeds and species may be more readily conserved.

One salient example cited is India, whose 182 million cows and bulls - 15 per cent of the world's bovine population - may not be slaughtered for religious reasons, and where milk is in crucially short supply. Implanting a preponderance of female embryos would ease this dairy shortage greatly.

ANVAR expects to place its DNA-probe sexing kit on the market in one or two years, for sale to embryo-cloning and stock-raising enterprises.

The entire test takes "one or two days at most," say its developers, compared with much longer times for chromosome karyotyping, or immune assay that detects the Y antigen - two other methods now under development elsewhere. No false positives are possible using the DNA probe, according to the French, though false negatives may result from faulty biopsy technique. The base-pair length of their probes is proprietary information, as is the micro-excision method.

To help it work out the various procedures France's National Agricultural Research Institute, INRA, enlisted the Pasteur Institute, French Atomic Energy Commission and National Institute of Medical Science and Research.

In the USA, a pioneer cloner of calf embryos is Rio Vista Genetics, San Antonio, Texas. It holds two patents on freezing and thawing of embryos, and this year will ship some 5,000 to customers worldwide. (Extracted from McGraw Hill's Biotechnology Newswatch, 6 October 1986)

New hormone will transform dairying

Trials have begun on British farms of a new genetically engineered growth hormone for cattle that will increase milk yields by more than 20 per cent. The hormone is known as bovine somatotrophin (BST) and could be in commercial use within four years.

Gary Schwemmlein, the European director of the animal science division of Monsanto, one of six pharmaceutical giants involved in a race to develop the hormone, says the firms are between them spending $10 million on research and development around the world.

BST is a polypeptide secreted by the pituitary gland. It stimulates cell division, bone growth and protein synthesis. Of more interest to farmers is its role in encouraging milk production. It appears to do this by mobilizing body fat and diverting glucose and fatty acids away from the formation of tissue.

In 1981, Dale Bauman of Cornell University's Department of Animal Science in the US first demonstrated that recombinant BST produced increases in milk yield at least equal to natural BST. Daily injections with the recombinant compound produced increases ranging from 23 per cent to 41 per cent, depending on the dose.

Companies now developing BST for the commercial market have identified milk production as the biggest potential agricultural market for the products of genetic engineering.

The key to unlocking this vast market is the development of a suitable delivery system for the hormone. Daily injections are not practical for most farms. The ideal system would deliver the hormone at a constant rate over, say, thirty days before being replaced.

The difficulties in devising an injectable, slow-release formulation for a complex polypeptide - it has a molecular weight of 22,000 - are formidable, far greater than the development of implants for the relatively simple carbon-ring structures of steroid hormones.

The hormone will continue to be administered by daily injections in the large-scale trials now under way in the US and Europe. At least one company has set up trials on British dairy herds. The aim of the trials is to study the long-term effects of BST on dairy cows. The investigators want to find out about the nutritional needs of treated animals, and how to return them to the correct energy balance at the end of lactation. They will also be watching for possible toxic effects and for any sign of an upper limit to doses beyond which the cows produce no extra milk.

Along with data on safety, the results will be a key part of the evidence presented to licensing authorities. The manufacturers claim that they expect no serious opposition to registration of somatotrophin, at least over fears about human health. (Extracted from New Scientist, 2 October 1986)

Bovine growth hormone

A US government-sponsored study may finally answer the question of whether bovine growth hormone, which promises to increase milk yields significantly if it is approved by the US Food and Drug Administration (FDA), will hurt the dairy industry by flooding the market with lower-priced milk. The US Department of Agriculture intends to analyze the hormone's potential economic effects and to quantify its potential impact on the federal milk price support programme. On 29 September the FDA denied a petition by a number of groups that it prepare an environmental impact statement (EIS) before approving bovine growth hormone. FDA said an EIS isn't appropriate at the investigational stage. It left

open the possibility, however, that it would file an EIS later. (Source: Chemical Week, 5 November 1986)

Research on plant genes

Sparking off nitrogen fixation

Nitrogen fixation - the process of forcing nitrogen from the atmosphere to react directly with hydrogen to form ammonia - is accomplished with ease by some bacteria and blue-green algae. Chemists, on the other hand, have to go to great expense to mimic these lowly organisms. The problem is that inactive nitrogen molecules will not react to make ammonia without a large input of energy. Japanese scientists have now found that by passing a large electric current through nitrogen, they can provide sufficient energy for the nitrogen to pick up hydrogen from water and produce ammonia.

Professor Kaoru Harada and chemists at the University of Tsukuba made ammonia from nitrogen gas, water and acid using a technique called "glow discharge". Glow discharge involves passing an electric current through a gas, in this case nitrogen, onto the surface of water. The effect is similar to a bolt of lightning passing through the atmosphere down to Earth. This excites the nitrogen sufficiently to force it to react with water, probably by breaking the bonds in the nitrogen and water molecules to give free nitrogen and hydrogen atoms. These atoms then combine to form NH and NH_2 radicals on the way to NH_3 (ammonia). Nitrate ions NO^- are also present in the solution. If the potential across the gas is sustained, then ammonia forms at an ever-increasing rate.

Unfortunately, such large amounts of energy are required to produce the glow discharge that the Haber Process, the method used industrially to combine nitrogen and hydrogen, probably remains more economical. But the researchers also found that if they added organic acids, such as acetic acid or proprionic acid, to the solution, glow discharge led to the production of the amino acids glycine and alanine. (Source: New Scientist, 2 October 1986)

Canola

For canola farmers, the revolutionary benefits of biotechnology are almost at hand. A Canadian biotechnology company, Allelix Inc., of Toronto, has developed a genetically superior strain of canola that promises two important advantages over current strains on sale to farmers: higher yields, and more effective weed control. Scientists at Allelix and the University of Guelph accomplished this by protoplast fusion, which involves the mixing of the cellular contents of two body or somatic cells that make up plant tissues. The canola line they developed took almost two years of research, in which two thirds of the project's direct costs were funded by the National Research Council's Technology Transfer Group, with the balance and most overheads picked up by Allelix.

Until recently, farmers wanting to plant canola had been unable to do so if their fields were contaminated with weeds like wild mustard or stinkweed, because herbicides used to control them also killed canola. In 1984 a "TTC" variety of canola, tolerant to triazine herbicides, was released, allowing farmers to control weeds with triazines without damaging canola crops. However, the TTC variety came with a high price tag - a yield level 10-20 per cent below the best non-resistant canola varieties along with attendant problems of oil quality.

Scientists at Allelix and the University of Guelph theorized that, if the triazine resistant variety could be hybridized with another strain of canola, perhaps the 'kick' or increase in vigor normally associated with hybridization would compensate for the low yield that seemed to go along with the herbicide resistance. Their idea was to develop a canola strain with two critical traits: resistance to triazine; and male sterility. The latter trait is important if the vigor that attends hybridization is to be maintained from one generation to the next, since canola can self-pollenate. With such a plant in hand, it would always be necessary to pollenate it with some other canola variety, which could be chosen for its oil content and quality characteristics as well as high yield. Unlike seeds from canola varieties, which can be harvested by farmers for use the following year, hybrid seeds must be continually recreated in the production fields of seed companies.

The Allelix-Guelph group had the advantage of knowing where in the plant cells the two traits were found - not in the nucleus as one might expect, but in organelles of the cytoplasm which contain their own DNA, the mitochondria and the chloroplasts; the trait for male sterility is found in the mitochondria, while triazine resistance resides in the chloroplasts.

Using techniques developed by Allelix, the team of scientists isolated individual somatic cells from a male sterile strain as well as from a triazine-resistant strain of canola. In the fusion technique, the cell walls are first removed using enzymes, creating what are called protoplasts, or "naked" plant cells with their outer membranes intact. These cells are then coaxed into fusing together in a medium that contains polyethylene glycol, a chemical relative of automobile antifreeze. (Unlike the result of a sexual cross, the fused cells contain a mixture of the cytoplasmic contents of both strains.) These cells can be derived from various parts of the plants, but leaf cells from one line fused with shoot cells from another offered the best combination of fusion efficiency and regeneration.

An interesting aspect noted by the researchers was that the initial fusion product usually contained a mixed population of mitochondria and chloroplasts, but that this situation changed as the new cell divided and began to multiply. (Extracted from Science Dimension, 1 October 1986)

Gene transfer in corn

Recent genetic engineering experiments with maize by researchers at Friedrich Miescher Institute in Basel, Switzerland, and John Innes Institute in Norwich, England, mark the first time a member of the grass family has been infected by a virus carried by the bacterium Agrobacterium. The procedure, called agroinfection, is the increasingly common laboratory technique used to transfer selected DNA into plants by adding that DNA to the DNA of Agrobacterium then allowing the bacterium to "colonize" plants - which it does by transferring part of its DNA (including the foreign, "third party" DNA) into the host plant's own genetic material.

The success with viral DNA demonstrates for the first time that agroinfection is an efficient way to induce foreign DNA expression in corn cells. Moreover, the results extend the possibilities of using beneficial DNA - such as those that code for resistance to viruses - to genetically improve a plant family that includes all the cereal grains, sugarcane and many sources of animal feed. (Source: Science News, Vol. 131, 17 January 1987)

Gene transfer in maize

Alloplasmic plants with a cell nucleus from one parent but cytoplasm from another can greatly speed trait selection. Conventional plant breeding techniques take years to produce improved varieties. Male sterile alloplasmic plants are unable to produce pollen, yet can bear fruit. D. Lonsdale of the Plant Breeding Institute (Cambridge) has identified a gene which might be responsible for male sterility in maize. If this gene can be introduced into normal fertile plants, male sterile plants can be produced for selective breeding. Other researchers are trying to combine mutant plants resistant to the herbicide atrazine with male sterile plants. (Extracted from New Scientist, 6 November 1986)

Gene-altered cotton plants express new trait

A research team at Agracetus (Middleton, Wis.) has placed a foreign gene into cotton and attained expression of the new trait in whole plants.

The accomplishment is significant because the gene splicing was achieved using a commercial strain of a major US field crop. This clears the path for scientists to develop commercial cotton lines with improved genetic traits such as increased insect resistance. Agracetus says its gene expression system gives reproducible results in cotton; the firm has filed a patent application.

The foreign gene added to cotton was a bacterial gene that codes for resistance to the antibiotic kanamycin. Kanamycin resistance is not a commercially important trait, but it is a trait that, for research purposes, is easily monitored. The gene enables scientists to separate cells that have incorporated new genes from those that have not during early stages of cell growth.

In work designed to reduce cotton farmers' reliance on pesticides, the Agracetus scientists now are trying to engineer cotton plants that will secrete their own, natural insect-killing toxin. (Abstracted with permission from Chemical and Engineering News, 22 December 1986, pp. 5-6. Copyright 1986, American Chemical Society)

Natural photosynthesis inhibitor identified

A natural substance that shuts down a plant's photosynthetic pathway at night has been isolated and characterized by a team of British and American researchers. S. Gutteridge and colleagues at Rothamsted Experimental Station, Harpenden, UK, along with collaborators at the UK National Institute for Medical Research, the University of Dayton, and Du Pont, have identified 2-carboxy-D-arabinitol-1-phosphate as the natural substance that inhibits the enzyme ribulose-1,5-bisphosphate carboxylase (RuBPCase) in potato plants in the dark. This enzyme plays a key role in converting atmospheric carbon dioxide into carbohydrate during photosynthesis. The researchers used a combination of proton NMR, gas chromatography, and mass spectrometry to characterize the inhibitor. It is structurally very similar to the six-carbon intermediate of a plant's carbohydrate-forming reaction, suggesting that the inhibitor binds to the same site as the intermediate on the activated enzyme. Light decomposes the inhibitor, leaving the enzyme in its activated form, ready to spring into action. (Reprinted with permission from Chemical and Engineering News, 24 November 1986, p. 12. Copyright 1986, American Chemical Society)

Fireflies light up world of gene engineers

A six-member team from the biology and chemistry departments at the University of California at San Diego announced that it had successfully placed into tobacco plants the gene that lights up fireflies. The plants glow in the dark with a greenish-yellow colour.

The entire plant - root, stem, leaves and branches - can be seen with the naked eye after about ten minutes glowing. Or it can be photographed using time exposures of about 15 minutes.

The significance of the work is that it promises to provide an invaluable research tool for learning how and when different genetic instructions switch on and off in higher organisms. The luciferase gene that generates light in the firefly, will be used as an easily detectable marker to tell scientists what happens during genetic engineering experiments.

The gene has also been expressed in the cells of monkeys and mice, but the scientists will not discuss the research until it has been published in the scientific literature. It means, however, that the technique will be useful for tracking experiments involving both plant and mammalian cells, including human cells.

In plants, for example, scientists could tag various genes with firefly luminescence and see how each responds to environmental changes such as varying light, stress, and temperature. One application would be experiments involving drought resistance.

The scientists from the University of California at San Diego isolated and cloned the luciferase gene from the firefly. The enzyme from the gene acts as a catalyst in the reaction that produces light. Using Agrobacterium tumefaciens, a bacterium that causes tumours in tobacco plants, the scientists succeeded in transferring the luciferase gene into growing tobacco plants.

Twenty-four hours after infecting the plants with Agrobacterium, the researchers detected light by watering the plants with a compound called luciferin. Light is generated when luciferin reacts with the enzyme luciferase and the chemical adenosine triphosphate (ATP). (Source: New Scientist, 13 November 1986)

Research on yeast and fungus genes

Ability of white rot fungi to degrade straw investigated

There is continuing public concern about the burning of straw in the summer. The Agricultural and Food Research Council (AFRC) is funding a number of projects in this area, including a study at Dundee University on the monitoring of straw-burning using satellite data. On the biotechnology front, the AFRC is funding work at the University of Manchester's Institute of Science and Technology (UMIST), jointly funded by British Petroleum's Venture Research Unit and focusing on the ways in which lignin is degraded in nature. The work has centred on Phanerochaete chrysosporium, the lignin degrading white rot fungi.

The UMIST group, under Prof. P. H. A. Broda, has been working on the fungus for five years and is unravelling the poorly understood molecular genetics of these fungi by isolating mutants deficient in certain functioning genes or enzymes and by creating genes and their products. Clones have been isolated which carry genes expressed specifically in the ligninolytic or lignin breakdown phase of fungal function. A generalised method for mapping these clones using restriction fragment length polymorphism analysis has been developed.

It has been found that lignin is also attacked by some actinomycete bacteria. Whereas the fungi only degrade lignin when they are in a starved condition, and the end product is carbon dioxide, the bacteria carry out the process during normal growth - and yield soluble products. This has great biotechnological potential and rapid progress is being made in the characterization of the extracellular proteins involved. (Source: Biotechnology Bulletin, Vol. 5, No. 11, December 1986)

Research on viral genes

How nature can make a lethal virus

Viruses are not always the harmful agents of disease they are believed to be. Many, perhaps most of them, are harmless. Many produce brief and unnoticed infections which are soon beaten off by the immune system. Others may cause more persistent infections which nevertheless do not harm. Three American biologists have now shown how "harmless" viruses still pose dangers. They found that the genetic material of two relatively harmless ("avirulent") viruses can combine within infected cells to generate new and lethal forms of the virus.

Ben Javier, Farhad Sadarati and Jack Stevens of the University of California, Los Angeles, observed the creation of lethal viruses from avirulent viruses in mice. They administered two types of avirulent herpes viruses to the footpads of mice so that the mice were infected with both types of virus at the same time. About two-thirds of the mice died. Mice that received similar doses, or doses up to 100 times larger, of either virus alone all survived.

To establish the cause of these dramatic effects of "co-infection" Javier and his colleagues isolated and examined the viruses in the brains of mice that died and found that the brains contained many new "recombinant" viruses, which must have been generated by the exchange of DNA between the genomes of the two harmless forms. If they injected any one of the new forms of virus into the footpads of mice, they were lethal.

Genetic recombination between viral genomes is not a new discovery. Some virologists are exploiting the mechanism to try to generate harmless forms of harmful viruses for use as vaccines. But Javier and his colleagues claim that their experiments are the first to show that recombination between avirulent viruses in co-infected animals can generate harmful new types of virus. This demonstration of two avirulent viruses giving rise to lethal new hybrids is of broad significance to virology as a whole. It reminds us that we should treat all viruses with great caution, including any we administer as vaccines. (Source: New Scientist, 27 November 1986)

Research instrumentation

Probes and proteins

Scientists at McGill University in Montreal are opening a new door on the secrets of the cell, using ribonucleic acid (RNA). RNA is almost universal to life. "Messenger" RNA, one of ribonucleic acid's three main forms in normal cells, carries the instructions locked in DNA or deoxyribonucleic acid, the molecules that carry a cell's genetic information. Using information copied from DNA, the messenger RNA acts as a template for assembling other molecules called proteins, which form or control the construction of all living systems.

Dr. Kelvin Ogilvie, who heads a synthetic RNA research programme at McGill, has modified a "gene machine" of his own invention to make RNA as well as DNA. Ogilvie's team now synthesizes RNA in sizes that are "chemically large, though small so far as cellular RNA is concerned." These bits or "sequences" of RNA have several research applications, including cell-free protein synthesis (i.e. protein manufacture outside the cell) and as probes of cell systems.

Normally cells assemble protein inside themselves. Protein synthesis outside the cell, says Ogilvie, "is like taking the guts out of a cell. You call only the cell parts, including RNA, that are necessary to make the proteins you want. Using such a 'non-living cell' eliminates any possibility of creating a dangerous bacterium." Although various teams around the world have demonstrated cell-free protein synthesis experimentally, Ogilvie estimates that it will be "at least five years" before the technique is perfected.

RNA cell probes are tools that pry into the inner workings of a cell. Composed of RNA molecules foreign to the test cell, the probes "trick the cell into a stress response by exposing it to RNA sequences it's not used to seeing," Ogilvie says. "The cell then give up a lot of secrets when you perturb it in this way."

RNA cell probes are particularly applicable to the study of viruses. Ogilvie hopes the new probe methods will help his team and other researchers unravel some of the mystery of how a virus takes control of a living cell and order it to make copies of the virus. Synthetic RNA is also crucial to the study of viroids, tiny infectious pieces of RNA that can cause extensive damage to crops.

The McGill team has already synthesized a class of compounds called glycerocides, which seem to inactivate viruses in rabbits and mice. Ogilvie says that glycerocides are effective against viruses responsible for influenza, herpes I and II, and cytomegalovirus (CMV), another highly-contagious member of the herpes family. Although clinical trials of these compounds are being delayed because of a patent challenge in a US court, Ogilvie is optimistic that the case will be cleared up soon, paving the way for pharmaceutical applications.

Two other McGill University researchers have developed a computer programme that allows them to watch how white blood cells move in a variety of chemical environments, as well as in the presence of cancerous tumor cells. The technique is important because white blood cells are the backbone of the immune system, attacking and disposing of foreign invaders in the body. Accurately plotting the movement of white blood cells could give medical researchers valuable clues to the body's response to a host of diseases.

Until now, it has not been possible to do this. Manually, it simply takes too long to look over hundreds of photographs and accurately plot the movement of even a single white blood cell.

Martin Levine, an electrical engineer at McGill along with Peter Noble, a physiologist at McGill's Faculty of Dentistry, has just finished writing a book describing the system. (It's called Computer Assisted Analyses of Cell Locomotion and Chemotaxis, published by CRC Press, Boca Raton, Florida, 1986.) In developing their programme Levine and Noble specifically wanted to be able to see and plot the development of a white blood cell's pseudopod in specific chemical environments.

The goal is to observe how white blood cells are affected by toxic substances by computing their motility. The first step in the process involves converting magnified optical images of a single white blood cell into electrical signals which are then stored in a computer.

However, programming a computer to distinguish a developing pseudopod from a bulge in a white blood cell's wall proved to be a difficult task. One problem is the shape of such cells which are always changing. When writing a computer programme great care must be given to definitions. Accoding to Levine, what he and Noble have really done is define in a quantifiable way what a pseudopod actually is.

The algorithms that define the cell as a "medial axis transform" - a skeleton-like representation of the cell - are written in the computer software language, Fortran. End-points of the skeleton correspond to potential pseudopod sites. On the computer screen the white blood cell is seen as a wiry, skeletal form that moves about the field of view.

A second language, OPS-5, an artificial intelligence language developed at Carnegie-Mellon University, decides which protrusion is in fact a pseudopod by applying a series of "if-then" rules.

Noble observed white blood cells actually moving away from tumor cells that are in a late stage of development, says Levine. They weren't attacking the cancer cells, as one might expect.

The next step in the research, according to Martin Levine, is to look at cell movement in three dimensions. They will accomplish this by focusing the microscope on different planes of the samples containing the white blood cells. Where a single sample now consists of only one video frame, the 3-D sample will comprise 10 to 20 frames. (Source: Science Dimension 1/1986 October 1986)

New reagents for enzyme immunoassay

Laboratoire des Stallergenes has introduced its new range of reagents for the enzyme immunoassay of eicosanoids, Ace-Eicosanoids. The reagents are used with the Ace System that is time-effective due to automated stages of distribution, washing and reading. A second antibody fixed to a solid phase eliminates the need for a centrifugal step. The enzymatic tracer gets rid of all the inconvenience associated with the use of radioisotopes and enables a very sensitive detection that is equal to or better than that obtained with radioactive tracers. (Extracted from Clinica, 12 September 1986)

Computer-aided DNA sequence

A computer-aided DNA sequencer has been developed to rapidly read the order of bases in a DNA strand, without the large amount of tedious but highly skilled labour involved in current sequencing methods, according to L. Smith of California Institute of Technology. Determining the order of bases in DNA helps scientists decipher the DNA behind many diseases and basic biological processes. Some scientists have recently suggested that a major effort be made to map the entire human genome, which would require sequencing over 3 billion bases. Unlike manual techniques, the DNA sequencer does not require expensive and potentially hazardous radioisotopes. Applied Biosystems will distribute its version of the DNA sequencer on a limited basis in late 1986 and commercialise it in early 1987. It worked closely with the Caltech group, but its instrument is significantly different from the Caltech prototype. Applied Biosystem's device does 16 seperate sequences per day with each sequence identifying 250-350 bases. Each machine will cost nearly US$90,000. (Extracted from Industrial Chemical News, September 1986)

BAEKON4000 series pulforeiser pulsed electrophoresis control system

BAEKON4000 series pulforeiser is an electronic control system which, together with an auxilliary power supply, permits single-dimension pulsed electrophoresis (i.e., Field Inversion Gel Electrophoresis) to resolve macromolecules (DNA, RNA, and protein) of large molecular weight. Pulsed electrophoresis can be accomplished by alternating the electric field. BAEKON4000 series pulforeiser, using solid-state computer technology, allows the presetting and calibration of the forward and reverse migration time, as well as the bi- and uni-polar modes of electrophoresis. The system has front-panel-mounted sockets for a pair of banana plugs from the auxiliary power supply and for a pair of banana plugs to the electrophoresis apparatus. There are two models of BAEKON4000: BAEKON4001 and BAEKON4002. BAEKON4002 Advanced Model has more control features: greater range of migration time, mono- and multiple-run-time ratio control, and employs user friendly software through keyboard control. BAEKON4000 Pulforeiser is 42 cm wide, 8.5 cm high, 22 cm deep, and weighs 2 kg. Available in 120 V 60Hz and 230V 50Hz. (Source: Company News Release, 21 November 1986)

Endocrinology research - hormone secretion and response studies - facilitated by Extracellular Matrix

Extracellular matrix (ECM)-coated tissue culture plastic ware, produced by International Biotechnologies (IBT) Ltd., is now available for the culturing of cells from endocrine organs, facilitating the study of hormones, enzymes, growth factors and other cellular products. ECM closely resembles the basal lamina of the body within which cells naturally differentiate, attach and migrate in vivo, and in combination with serum-free media provides a much improved surface for the culturing of epithelial and endothelial cells.

1. Hormone secretion

The following unique properties of the ECM/serum-free combination renders it a favourable substratum for the culture of hormone secreting cells, thus facilitating the secretion of cellular products:

- ECM induces differentiation, as it provides the basement membrane which is critical for secretory cells to express their differentiated functions;
- Serum-free media suppress the growth of fibroblasts, resulting in almost pure epithelial cell cultures;
- As ECM allows the growth of cells in serum-free media, the absence of serum proteins facilities easier purification of secreted material;
- ECM stimulates the proliferation of cultured cells and increases the amount of secreted materials, resulting in increased yields

ECM has been successfully used in culturing hormone and protein secreting cells such as pituitary cells, pancreatic B-islet cells, granulosa cells and hepatocytes.

2. Hormone responsiveness

ECM promotes hormone response research as the ECM modified cellular physiology to make it more

responsive to hormones and other naturally occuring factors. In contrast, cells plated on artificial substrate or isolated matrix components do not respond to these factors. Furthermore, by growing hormone responsive cells in a serum-free environment, it is possible to eliminate the effects of other hormones and growth factors present in the serum, and to study the isolated effects of a specific growth factor or hormone.

3. Industrial and biotechnological applications

In the future production of cellular materials, the ECM/serum-free combination is expected to:

- Increase the yield of production and secretion of hormones, enzymes and growth factors in tissue culture;
- Result in easier purification of cellular products due to the absence of serum proteins;
- Foster large scale growth using bulk culture vessels or microcarriers coated with ECM;
- Provide a variety of products.

(Source: Company News Release, November 1986)

D. APPLICATIONS

Pharmaceutical and medical applications

Schering-Plough readies new gene-spliced drugs

Schering-Plough, the US drugs company, is building upon its development and commercialization of alpha interferon with the cloning of two more gene-spliced proteins which could have broad applications in cancer therapy and the treatment of infectious diseases.

The products, interleukin-4 (IL-4) and granulocyte macrophage colony stimulating factor (GM-CSF), come from Schering-Plough's Dnax research institute, which the company acquired in 1982. They are both in animal testing and human trials could start in a year or so.

IL-4 and GM-CSF are both T-cell factors. IL-4 has demonstrated in laboratory animals the ability to stimulate the natural disease-fighting cells. The company believes it will have broad clinical application in the treatment of infectious diseases, cancers and anaemias. It is too early to say what specific human conditions it will be useful against, however.

On the other hand, GM-CSF stimulates the production of white blood cells and could be extremely useful in counteracting the adverse side effects of cancer chemotherapy.

Schering-Plough claims to be the only company to have cloned and expressed IL-4 and has filed for broad patent protection. With GM-CSF, however, it is in a race with several other drug and biotechnology concerns, including Immunex. (Extracted from European Chemical News, 6 October 1986)

Porton develops AIDS drug

Porton International, the biotechnology group, is developing an antiviral compound which laboratory tests indicate may be several times more active against the AIDS virus than other drugs currently being evaluated.

Provisionally called human immune virus antiviral (Hiva), the compound is under rapid development at the group's various subsidiaries in collaboration with the Centre for Applied Microbiology and Research (CAMR) at Porton Down in the UK. Porton acquired the rights to the compound from an unnamed Californian scientist earlier this year and has filed patent applications around the world.

Detailed information on Hiva is sketchy. It is described as a naturally occurring product - not a protein - obtained by extraction and is thought at this stage to work by blocking reverse transcriptase. Animal toxicity and chemical structure studies are under way with a view to putting the chemical into clinical trials as soon as possible. Because of the nature of the compound and its source, Porton does not envisage problems in large-scale production, should its efficacy and safety be established.

Porton is considering marketing the product itself in the US and Europe rather than licensing it to established drug company. Marketing efforts can be targeted at the specific AIDS treatment centres therefore a large sales force will not be needed.

As part of a broad R&D programme related to the AIDS area, Porton is also working on a gene-probe diagnostic to detect AIDS viral antigens. The company's scientists have synthesized a gag gene which is common to the two strains of AIDS virus known to date. (Extracted from European Chemical News, 6 October 1986)

Wellcome invests in AZT production

Wellcome, (UK) is to invest $21.3 million on extended research into its potential AIDS treatment drug, AZT. The announcement came shortly after Wellcome embarked on an extended set of phase-two clinical efficacy trials.

Accompanied by the redirection of research resources is a plan to expand both production plants at Dartford, UK and Greenville, North Carolina to cope with increased demand for the drug.

Wellcome is to supply AZT free of charge to AIDS treatment centres in the US and Europe. The drug, however, will only be available to those patients who meet "strictly defined immunological criteria." Wellcome suspects that this may well be as many as 6,000 people in the US and 500 in Europe.

US health officials are moving with unusual speed to set up a new round of clinical tests for the drug. The new tests will include different groups of AIDS patients, as well as persons infected by the AIDS virus but not yet showing symptoms of the disease. Wellcome has received FDA approval to distribute the drug to AIDS patients who have recovered from at least one bout of Pneumocystis carinii. However, a new study suggests that AZT may be most effective when given within hours of infection. The study found that the disease-preventative effect of AZT in mice was strongest soon after viral infection, but when given much later, when death was close, the drug prolonged life but could not prevent death. Prolonged therapy with the drug caused the mice to develop severe anemia, a side effect also seen in human trials. Preliminary research by a different group has uncovered another anti-AIDS drug that appears to be far less toxic than AZT, although it has not yet been tested in humans.

Pilot AZT studies are going ahead in the UK for a few patients, but further studies are needed to

establish for how long patients can tolerate treatment, and how long a positive response can be maintained. Additional clinical trials are also necessary to indicate whether AZT can be used for Kaposi sarcoma sufferers and symptomless virus carriers. (Abstracted with permission from Chemical and Engineering News, 6 October 1986, p. 20. Copyright 1986, American Chemical Society and European Chemical News, 24 November 1986)

Test to detect AIDS virus

Oncor has developed a blood test that can detect the AIDS virus. The test uses a radiolabeled RNA fragment of genetic material that binds to a complementary segment of viral RNA. The patient's white blood cells are mounted on microscope slides and exposed to a solution containing the RNA probe. Radiation from radioactive nuclei from the probe exposes a photographic emulsion allowing researchers to locate virus particles using an ordinary microscope. Oncor claims that its test is more sensitive and specific than current antibody test, which can give negative results for recently infected people whose immune systems have not yet produced antibodies or positive results for those who are not actual carriers. Oncor's test would be able to confirm the presence or absence of the virus in such cases. Oncor is offering limited laboratory services using its AIDS test to physicians and scientists for research applications only. It will soon begin clinical trials on the test and hopes to introduce a test kit for researchers in 1987. Enzo Biochem is evaluating a DNA-based diagnostic test for the AIDS virus. Cetus plans to market its DNA-based test in 1987. (Abstracted with permission from Chemical and Engineering News, 6 October 1986, p. 6. Copyright 1986, American Chemical Society)

Viral protein pieces show promise towards AIDS vaccine

Two research groups working independently have produced synthetic versions of two different amino acid sequences that eventually might lead to the development of a vaccine or treatment for acquired immune deficiency syndrome (AIDS). The two sequences are fragments of a much larger glycoprotein called gp120 that forms the outer coat, or envelope, of human immunodeficiency virus (HIV), which causes AIDS.

One group at Repligen Corp. of Cambridge, Mass., has shown that a genetically engineered version of one sequence, when injected into animals, elicits antibodies that can neutralize HIV in a test tube. This fragment, dubbed PBI, contains 180 amino acids, or 37 per cent of the protein building blocks that make up gp120.

The second group, at the US National Institute of Mental Health (NIMH), synthesized an eight-amino-acid sequence called peptide T that prevents HIV from attaching to - and entering - human cells. The peptide does this by occupying receptors on the cell surface that the virus would use to gain entry.

The PBI finding is significant for several reasons. First, it establishes that only a small segment of gp120 is necessary to trigger the production of neutralising antibodies to HIV. Second, PBI does not carry carbohydrate residues as does the native gp120, and third, Repligen scientists have shown that the common bacterium Escherichia coli can be engineered to produce PBI economically and in large quantities. The process of testing the experimental vaccine in chimpanzees, has begun.

Using genetically-engineered bacteria the researchers believe that the antibody-producing protein section can be mass produced at low cost. The fragment is a segment of a surface coat protein, gp 120, of the virus. By using this fragment, antibodies to the AIDS infection have been produced in animal studies without the danger of the disease transmission which requires the viral nucleic acids.

Repligen's research is similar to vaccine work proceeding at Genentech. Earlier this year, scientists reported that they had induced mammalian cells in culture to produce a slightly larger version of gp120 called gp130. When rabbits and guinea pigs were inoculated with gp130 (which came complete with carbohydrate residues), antibodies were produced that were shown to neutralize the AIDS virus in vitro.

The discovery of peptide T grew out of NIMH research into brain peptides and their receptors. These studies have shown that the brain and immune systems share many of the same peptide messenger chemicals and receptors. The researchers discovered that cells in certain parts of the brain have the same receptor - T4 - that HIV uses to enter cells of the immune system. The "key" portion of viral gp120 that binds to the T4 receptor "lock" of human cells turned out to be an octapeptide (peptide T) that is structurally very similar to a known neuropeptide called vasoactive intestinal peptide (VIP).

Instead of exposing people to relatively large segments of the AIDS viral coat so they might develop antibodies against it, a vaccine based on peptide T would require that the body develop an immunity against only the much smaller, but critical, "connection point."

Peptide T or compounds like it also might be useful clinically in slowing the spread of the AIDS virus in persons who have already been infected. Peptide T and several analogs at concentrations as low as about 0.1 nM were found to prevent HIV from binding to the T4 receptor. The experiments were done using brain membranes from humans, monkeys, and rats. (Abstracted with permission from Chemical and Engineering News, 15 December 1986, pp. 4-5. Copyright 1986, American Chemical Society and European Chemical News, 15 December 1986)

Possible vaccine against spotted mountain fever

Using cloning and recombinant DNA techniques, microbiologists at the National Institute of Allergy and Infectious Diseases' Rocky Mountain Laboratories in Hamilton, Mont., have produced a possible vaccine against Rocky Mountain spotted fever. Caused by the bacterium Rickettsia rickettsii, the tick-borne disease destroys cells of the vascular system, leading to low blood volume and fluid-swollen tissues.

Members of the Hamilton team recently described protection against the disease in mice, using antibodies against two surface antigens of R. rickettsii. Those antigens, however, are difficult to purify, and the bacteria are difficult to grow in culture. To optimize the system, DNA coding for the antigens has been introduced into Escherichia coli to create a recombinant E. coli capable of producing large quantities of the antigens. Preparations of the E. coli successfully protect mice against lethal doses of R. rickettsii, and experiments are being expanded to include guinea pigs. Preliminary results suggest that the cloned vaccine may also be effective in other species. (Source: Science News, Vol. 131, 17 January 1987)

Recycling brewer's yeast to make drugs

Delta Biotechnology Ltd., UK, plans to produce saleable proteins such as human serum albumin (HSA) by exploiting yeast after it has performed its initial task of generating ethanol for the brewing

industry. Elimination of the capital and revenue cost needed to support the production of biomass gives Delta's strategy a considerable edge over more conventional approaches. The company, which maintains close ties with MIT, Oxford, and Cambridge, employs over 30 researchers in Nottingham. Delta arose from a collaboration between Bass plc, which claims to be Europe's leading brewery in terms of R&D, and Cavendish Technology Partnerships Ltd., specialists in recombinant DNA blood products.

The patented Delta process, which will be limited initially to totally inert proteins, has no influence on the basic brewing operations or the quality of the beer. The idea is to modify Saccharomyces cerevisiae genetically so that genes coding for desirable proteins remain silent until they are triggered and expressed in a process separate from brewing. Delta senior scientist Ted Hinchcliffe described the two key elements developed for the biosynthesis of HSA. These are a plasmid containing yeast genes and the HSA gene alongside a promoter gene that is triggered only by galactose. Inserted into S. cerevisiae, the plasmid remains dormant during brewing because wort does not contain this particular sugar. Once the yeast has completed its primary work and has been removed from the brewery, however, addition of galactose activates the HSA gene and the yeast then begins its second useful life.

Delta emphasizes the convenience and safety features of their method, which they say will be applied to a variety of therapeutic proteins and modified animal feed products over the coming years. Brewers have vast experience in cultivating yeast, the genetics of which are well understood. And, in contrast to Escherichia coli, there is little or no evidence of human toxicity. (Extracted from Bio/Technology, Vol. 4, November 1986)

Salmonella screening test

BioControl Systems (Kent, Wash.) is marketing a screening test it calls Salmonella 1-2 that detects Salmonella bacteria in food and dairy products. The company says that its polyclonal antibody kit, which uses a proprietary assay method, can provide results in 24 hours, while culturing methods can take three or four days. The product owes its speed to the ability to encourage the growth of Salmonella, discourage the growth of competing bacteria, and isolate the Salmonella. (Source: Chemical Week, 12 November 1986)

Recombinant erythropoietin success

Amgen (Thousand Oaks, CA) reported success using recombinant human erythropoietin in treating the anemia associated with chronic renal disease in patients undergoing kidney dialysis. Although the results are preliminary, erythropoietin caused significant increases in the percentage of red blood cells in the blood of patients who received the drug in trials at the Northwest Kidney Center (Seattle, WA). In other projects, the Food and Drug Administration (FDA) approved the use of Endotronics' (Coon Rapids, MN) Acusyst-P cell culture instrumentation for interleukin-2 trials against human cancer underway at the University of Minnesota. (Source: Bio/Technology, Vol. 4, October 1986)

Companies vie for growing clot-dissolving drug market

Genentech has filed a European production licence application for its tissue plasminogen activator product - TPA. Yet despite US interest shown in the drug, the European market is likely to be dominated by Beecham's Eminase product, according to Ian Moore, drugs analyst for Morgan Grenfell Securities.

By 1992, Moore predicts, the European market for fibrinolytics, such as TPA, Eminase and the more conventional urokinase and streptokinase drugs will be $186 million. Leading will be the Beecham drug. Beecham's established knowledge of the European market and its head start with the product has secured its position.

By contrast, TPA products will dominate the US, Japanese and rest of the world markets. Nevertheless the battle for the $575 million sales anticipated for TPA is likely to be very intense and competitive. Already Genentech is taking an aggressive stance on patents. The US biotechnology firm threatens to issue writs against other drug companies it sees producing TPA using its own patented techniques.

Clinical studies with both Genentech's TPA and Beecham's product show that both drugs are more effective than the conventional urokinase and streptokinase drugs. Both TPA and Eminase have similar clinical profiles and show significantly improved potency rates, 85 per cent and 92 per cent respectively, over streptokinase with a success rate of returning blood flow to coronary arteries of 55 per cent. Moreover, being a bacterial protein streptokinase can promote unwanted antibody formation. A similar effect with Eminase is likely to restrict its use in Japan as the bacterial-derived product will also be antigenic.

Cost of production of both urokinase and now TPA is likely to be the major stumbling block to growth. Those firms concentrating on the process technologies are therefore most likely to succeed. Other new compounds are now being developed.

TPA is also seen as an aid against lung clots. Scientists at two Boston hospitals say that clinical tests on TPA also works better against lung blood clots than treatments currently in use.

Researchers at Brigham and Women's Hospital and Beth Israel Hospital used tissue plasminogen activator, or TPA, produced by Genentech Inc. of South San Francisco, Calif. in the experiment. A spokeswoman for Brigham and Women's Hospital says that the experimental drug dissolved the lung clots in 37 out of 40 patients tested. "Heparin," the drug usually used, has a success rate of only about 5 per cent. (Extracted from Chemical Marketing Reporter, 10 November 1986 and European Chemical News, 24 November 1986)

Winning the war against malaria

A team of scientists from the USA, Thailand and Brazil has reported the development of a new deoxyribonucleic acid (DNA) probe which offers significant possibilities for the early diagnosis of malaria.

The new DNA probe is labelled with a radioactive isotope which identifies the organism in infected blood by staining it with radioactivity. This is easy to detect because a dark spot appears on X-ray film. By extension, new techniques might be developed which recognize the difference between drug-resistant and drug-sensitive strains of malaria.

Field tests involve pricking a finger to take a sample, analyzing the blood and spotting it on to nitrocellulose paper which allows the DNA probe to combine with the matching DNA in the blood, that is, the specific genetic protein that causes a parasite to be a parasite.

Today malaria threatens about one-third of the world's population. Since the disease's epidemical period from 1970-75, when the malaria-carrying Anopheles mosquito developed resistance to the chemical used, medical researchers have intensified their efforts to eradicate the disease.

This inexpensive and simple method can detect the parasite effectively, thus enabling the evaluation of the control programmes. More than 1,000 samples can be processed under this system. A microscopist, on the other hand, can analyse 40 to 50 samples a day only. (Source: World Water, Vol. 9, No. 4, May 1986)

Trials of 'safer' whooping cough vaccine

The Medical Research Council is about to begin testing a new vaccine against whooping cough on British children. Extensive trials of the vaccine have already taken place in Sweden and it is widely used in Japan.

Most British children are vaccinated with a whole-cell vaccine, prepared by methods which have remained largely unchanged for 40 years. The new preparation, known as acellular vaccine, contains only the active ingredients of the whooping cough bacterium necessary to immunise against the disease.

The Wellcome Foundation is the only company still making the whole-cell vaccine in Britain. Other firms stopped, in the face of growing public anxiety that the vaccine may cause irreparable and massive brain damage in some children.

Acellular vaccine is made by isolating and the combining only the components of the whooping cough bacterium (Bordetella pertussis) that are thought to provide immunity. The other components, which are contained in the whole-cell bacterium, are unnecessary for immunity and may be dangerous.

Three acellular vaccines will be tested: one from France, a Japanese vaccine provided by the Cyanamid Corporation of the US, and one produced by Britains's Centre for Applied Microbiology and Research at Porton Down.

The three vaccines will be give to groups of 50 infants, in combination with diphtheria and tetanus vaccines according to the government's present immunisation programme. The performance of the new vaccines will be compared with that of a control, Wellcome's whole-cell vaccine, known as Trivax Ab. The trials should establish whether the acellular vaccines are safer. (Extracted from New Scientist, 13 November 1986)

Another r-DNA hepatitis B vaccine on the market

Earlier this year, Merck Sharp and Dohme received approval to market its genetically engineered hepatitis B vaccine in the US. Now SmithKline Biologicals (Rixensart, Belgium) has received regulatory approval to market such a vaccine in Belgium. SmithKline expects that within the next year its yeast-derived vaccine, Engerix-B, will be approved and marketed in many countries in Europe, Southeast Asia and Africa. The manufacture of its vaccine is more efficient than that of plasma-derived hepatitis B vaccines, which became available in the early 1980s. The plasma vaccines are made by extracting a hepatitis B surface antigen from infected blood of chronic hepatitis B carriers. The plasma-derived vaccines require about 65 weeks processing and control time, compared with about 10 weeks for the genetically engineered vaccine. Whereas the supply of plasma-derived vaccines depends on the availability of hepatitis B carrier blood, the supply of the genetically engineered vaccine can be scaled up to meet demand. The company currently has a genetically engineered vaccine against malaria in clinical development.

Separately, Du Pont has developed a surface antigen test for hepatitis B that the company says is ca[illegible]le with its HTLV-III antibody test. The two tests will screen donated blood to minimize hepatitis B transmission through transfusions of whole blood or blood products. (Source: Chemical Week, 5 November 1986 and 10 December 1986)

DNA fingerprinting used for forensic tests

Lifecodes (Elmsford, NY) have developed a test that identifies individuals according to genetic information in cells. Since standard forensic tests such as blood typing are often inconclusive or impossible to perform, many criminals cannot be charged because of inconclusive evidence. The test developed by Lifecodes, as well as Imperial Chemical Industries (UK), is based on DNA fingerprinting. Since each person's DNA pattern is different from everyone else's, a sample of blood, semen or skin can positively identify an individual. Such tests can be conducted years after a crime has been committed because DNA is not easily destroyed by the elements. In the tests, laboratory personnel extract DNA from a specimen using DNA probes. These are sequences of DNA tagged with radioactive chemicals so they can be located with laboratory instruments. The probes determine patterns in the DNA, which are then compared to the patterns of samples being studied. Since these tests are lengthy and require fairly large tissue samples, more sensitive tests are being developed.

Cetus (Emeryville, CA) developed a technique that boosts the power of DNA probes so they can be used with tiny samples of DNA. Enzymes are used to make copies of the DNA, thus providing more sites for the probes to look on to. Though tests on DNA still need improvement, criminal experts are beginning to accept the validity of the tests findings.

Humagen (Charlottesville, Va.) has developed a forensic test kit for use in court cases involving sexual assault. The kit is based on MHS-5, a monoclonal antibody that identifies a seminal fluid protein. Humagen says the test is sensitive enough to detect one one-billionth of a gram of seminal protein and can detect the protein in laboratory samples that are up to six months old. A trained technician can run the test in 20 minutes, the company says, and results can be available two hours later. Humagen has begun selling the kit to forensic laboratories and hospital emergency rooms. (Extracted from Chemical Week, 12 November 1986 and Business Week, 1 December 1986)

Technique used against transplant rejection

Bone marrow transplants can avoid graft-versus-host disease if monoclonal antibodies are used to remove T lymphocytes from donated marrow, according to researchers at Cambridge University (UK). Host-versus-graft disease can also be eliminated by the use of monoclonal against two types of lymphocytes in the peripheral blood. The technique has been tested in mice receiving bone marrow transplants. T cell depletion with antibodies could be effective in preventing rejection of many kinds of transplants. (Extracted from New Scientist, 18 September 1986)

Livestock applications

Bovine somatotrophine

Bovine somatotrophin (BST) will increase milk yields by 20 per cent. There are at least six firms racing to bring BST to market, including Monsanto, American Cyanamid and Eli Lilly. BST is a polypeptide secreted by the pituitary gland to stimulate cell division, bone growth and protein synthesis. It also mobilises body fat and diverts glucose and fatty acids away from the formation of tissue. Sales of

the hormone, which is produced recombinant DNA techniques, could total 100,000 kg/yr. The key will be the development of a suitable drug delivery system. Daily injections are deemed impractical. The large molecule (molecular weight 22,000) makes long-term delivery of a constant rate difficult. Tests of the hormone using daily injections are being conducted in the US and Europe.

Little fear has been shown over health effects, because peptide hormones are generally degraded by the stomach and somatotrophins are largely species specific. However, farmers, environmentalists and animal rights activists may protest against the introduction of the drug, largely based on an economic analysis of the product. Some 80-90 per cent of New York's dairy herds would be treated with the product within three years of its introduction, forcing milk prices to fall, offsetting any advantage gained by the farmers. Opponents also claim that within five years of its introduction, 50 per cent of US dairy farms would be eliminated. The number of dairy farms has falled 77 per cent in 20 years anyway. The drug producers say the compound would simply let farmers produce more milk at lower cost, and that small farmers would still be able to compete with large farmers. (Extracted from New Scientist, 2 October 1986)

Agricultural applications

Luciferase gene as genetic tag

The gene for luciferase can be used as a genetic tag, according to researchers at the University of California (San Diego). Luciferase catalyzes a chemical reaction between luciferin and ATP, which causes the luciferin to glow, as in fireflies. The gene is an attractive tool because it is easy to detect the glow in single cells or whole plants. The luciferase gene might be linked to a target gene to reveal which cells are expressing the target gene, and whether that gene can be activated by environmental stimuli. The luciferase assay may also offer a nondestructive test for inherited plant traits. (Extracted from Science News, 15 November 1986)

Better mushroom production

Yields of Britain's most valuable protected crop, the cultivated mushroom Agaricus bisporus, could be boosted considerably as a result of progress in biological control. Jim Lynch and colleagues from the Glasshouse Crops Research Institute (GCRI) at Littlehampton in Sussex said that 5-10 per cent of the UK's production of mushrooms was lost and a further 10 per cent downgraded in market price as a result of infestation with blotching. The disease is caused by Pseudomonas tolaasii, but this bio-type of P. fluorescens is itself antagonized by other fluorescent pseudomonads. Using exclusive zone assays and tests with sections of freshly excised mushroom cap, the Littlehampton researchers identified several such isolates that inhibited P. tolaasii not only in the laboratory but also under commercial cropping conditions. Just one application of certain pseudomonads, applied in aqueous suspension, reduced the incidence of blotch disease by up to 50 per cent. The bacteria were non-phytotoxic and did not lower mushroom yield.

GCRI researchers are also working on another potential method of increasing the production of A. bisporus. D.A. Wood and collaborators are attempting to heighten conversion of the lignocelluloses upon which edible basidiomycetes are cultivated by seeking mutants with increased enzyme activities. The scientists have worked with Coprinus bilanatus, which although not a cultivated mushroom is used as a genetic model for A. bisporus and has a similar breeding system. After UV-irradiating the fungus, they have used appropriate substrates to screen for mutants with altered cellulase, xylanase, and other activities. Those isolated so far have had pleiotropic effects on enzyme production, although some of these changes have been sufficiently large to be of practical value. With the annual world production of edible mushrooms estimated at 1.5 million tonnes (of which about two-thirds is A. bisporus), reducing disease and increasing production could have important economic consequences. (Extracted from Bio/Technology, Vol. 4, December 1986)

Successful test of gene-altered plants

The first authorized outdoor test of genetically engineered plants has been pronounced a success by Agracetus (Middleton, Wis.), an agricultural biotechnology company. Tobacco plants, put into the ground on 30 May were harvested from 11-13 August. Winston Brill, the company's research and development chief, reports that no special insect or disease problems showed up during the trial. Agracetus is using the new field-test data in work with other plants that are commercially more attractive such as corn, cotton and soybeans. The company planted both genetically engineered tobacco and regular tobacco at a site near Agracetus headquarters. The engineered plants were made by using an inactive yeast gene inserted into a gene required for cytokinin biosynthesis. The field test showed there were "no major differences" between the two types of tobacco "with regard to root weight, seed yield and plant vigor." Agracetus managers stress that the trial was designed to test only those factors because in earlier greenhouse studies, disease resistance was successfully passed through plant seeds from one generation to the next. (Source: Chemical Week, 22 October 1986)

Method to reduce bitterness in citrus found

A major problem for the citrus industry worldwide is formation of bitterness in citrus juice and products within hours after extraction from the fruit, making them unsuitable for processing. Affected are certain varieties of oranges, grapefruits, lemons, and mandarins, plus minor citrus fruits such as Natsudaidai, Iyokan, and Ponkan. The problem is estimated to cause losses for California's citrus industry alone of $6 million to $8 million a year, particularly for navel oranges.

Primary cause of this "delayed bitterness" in oranges, lemons, tangerines, and some other citrus fruit is formation of intensely bitter limonoids, such as limonin and nomilin. (Bitterness in grapefruit and Natsudaidai comes mainly from formation of flavonoids, although nomilin is also found in grapefruit.)

Now a preharvest treatment that inhibits formation of limonoids in citrus fruit has been developed by scientists at the Fruit & Vegetable Chemistry Laboratory of the Department of Agriculture's Agricultural Research Service in Pasadena, Calif. Led by Shin Hasegava, the team includes Zareh Herman, Edward D. Orme, Peter Ou, and Chi H. Fong.

Furthermore, the team is elucidating the major biosynthetic pathways for formation of limonoids. It also has identified the sites of limonoid biosynthesis in fruit trees and has shown that limonoids are then translocated to other parts of a tree. Some of their results will be described in two papers which will be published in Phytochemistry. Their work also was discussed in part at the recent American Chemical Society national meeting in Anaheim.

Knowledge of biosynthetic pathways and sites has greatly aided the USDA team's search for a method of reducing or eliminating limonoids from citrus. Groups working in this field have taken several approaches to removing bitterness from citrus, most involve post-harvest fruit treatment or treatment of extracted juice. However, Hasegawa notes, pre-harvest treatment has many advantages.

The Pasadena scientists have found that auxins - plant growth regulators - are potent inhibitors of nomilin biosynthesis. In particular, an inexpensive synthetic auxin, 1-naphthaleneacetic acid (NAA), inhibits up to 95 per cent of nomilin biosynthesis in citrus seedlings. NAA inhibits nomilin biosynthesis in stems and hence reduces nomilin accumulation in the fruit. The USDA team also recently showed directly that NAA inhibits limonin accumulation in fruit.

The team plans a field test of its method next spring, in co-operation with a large private firm, California Citrus Producers Inc. They will spray NAA on a navel orange orchard while the fruit is small. (Limonin biosynthesis goes faster when fruit is small.)

No side effects on fruit or trees have been found so far. Moreover, Hasegawa notes, NAA is already widely used commercially to prevent apples, pears, grapes, and other fruit from dropping prematurely. (Abstracted with permission from Chemical and Engineering News, 27 October 1986, pp. 25-26. Copyright 1986, American Chemical Society)

Energy and environmental applications

Industrial effluent treatment by catalysis

Aquagenesis Promotion Center began the development of an industrial effluent treatment process whereby over 99 per cent of BOD (biological oxygen demand), COD (chemical oxygen demand), and SS (suspended solids) fractions are removed respectively. This new treatment process uses the first wet oxidation process in the world in which catalysts are used to recycle industrial effluent. Recycling industrial effluent is an issue directly related to factory relocations associated with Japan's Fourth Nationwide General Development Plan and the development of technopolis. The Center's goal is to assure high-quality industrial water and, using this retreatment technology as a lever, maintain harmony with environmental safety policies being advanced by autonomous bodies.

According to the plan, the Center will build a model plant during 1987 and aims for full scale application as early as 1990. In principle, the raw water (effluent) is heated to a high temperature of 250 degrees celsius under an elevated pressure of 70 atmospheres to incinerate the micro-organisms it contains and separate out water and carbon dioxide. The resulting water is used as industrial water after retreatment. However, the Center is aware of the necessity of finding a process for heating and pressurising below 10 atmospheres. Consequently, the wet oxidation process using special catalysts is considered promising and future research themes are expected to focus on development of these catalysts.

According to the Center, the major substances contained in the effluents will be efficiently and economically removable upon completion of this new technology. It is particularly suitable for industrial effluents where COD creates most of the problems. The Center's plan is to continue experiments with a model plant for about a year and aim for practical applications based on its data. (Extracted from Nihon Kogyo Shimbun, 30 September 1986)

Phenol solution detoxified biologically

Laboratory tests at Manville Filtration & Minerals, Denver, indicate that biodegradation might be a solution for companies needing to dispose of aqueous phenolic waste solutions. Pseudomonas putida organisms were immobilized by adsorption on Manville's custom R-630 carrier, which consists mainly of diatomaceous earth and has a pore structure optimized for immobilizing micro-organisms. In one laboratory test, 280 g of the biocarrier degraded phenol solution with an initial concentration of 1500 ppm to 15 ppm or less at rates up to 1.0 mg of phenol per hour per gram of carrier. The 103-day test showed that the system could successfully metabolize the waste if the phenol concentration alone was increased, though its capacity was overwhelmed if phenol concentration and influent flow rate were dramatically increased together. A second, 29-day test used Pseudomonas species immobilized on 30 g of carrier. With only p-nitrophenol (PNP) as an energy source, the system reduced an aqueous solution containing 300 ppm of PNP to 3 ppm at a rate of 0.6 mg of PNP per hour per gram of carrier. (Source: Chemical and Engineering News, 22 December 1986)

Industrial microbiology

The hopes for biopulping

Paper producers have long tussled with the high costs and environmental concerns associated with current methods of separating lignin from the cellulose in wood and have taken an active interest in scaling up and proving out a new method of turning wood into pulp - biopulping - that offers the lure of being both cleaner and more efficient than conventional methods.

The US Agriculture Department's Forest Products Laboratory and the University of Wisconsin's Biotechnology Center has suggested a plan for forming a research consortium that would sponsor an investigation of the commercial potential of biopulping technology. The technology utilizes the enzymes in a naturally occurring white rot fungus known as Phanerochaete chrysosporium, which separate lignin from cellulose in a selective manner.

To get the programme off the ground, the Forest Products Laboratory and the University of Wisconsin's Biotechnology Center estimate they will need at least $2 million to support a five-year research programme.

To drum up support, the promoters of the biopulping process point to the flaws of currently used methods of pulping - chemical delignification and mechanical pulping. Chemical pulping, they note, requires considerable capital investment. It produces toxic waste products and a lignin byproduct that has little value. Furthermore, officials at the Forest Products Laboratory and the university say that the mechanical process produces pulps that lack strength and that it requires the use of large amounts of energy.

The US Forest Products Laboratory and the Swedish Forest Products Research Laboratory have demonstrated that wood can be partly delignified using fungal species, or mutants that selectively remove lignin from wood. Their research shows that fungi can be used to partly delignify a mechanically produced pulp, resulting in a net 25 per cent savings in energy.

While representatives of the two laboratories tout the benefits of the biopulping method, they acknowledge that much more research must be done. (Extracted from Chemical Week, 5 November 1986)

E. PATENTS AND INTELLECTUAL PROPERTY ISSUES

Study urges more patent protection for biotechnology

According to the views of scientists, new developments and discoveries in biotechnology should in future be better protected with regard to patent rights than has been the case in the past. For this reason, the Max Planck Institute for Foreign and International Patent, Copyright and Competition Law in Munich has, at the request of the OECD, compiled a study which includes suggestions for reform.

By including biotechnological breakthroughs in patent protection, patent lawyers believe that on the one hand the flow of information from science and industry will increase and on the other hand, this will encourage industry to invest in the field of biotechnology, according to a statement made by the Max Planck Society (MPG) in Munich.

According to the proposals of the Munich scientists, in the future it should be possible in all countries to receive patent protection for micro-organisms (cell lines, plasmids, monoclonal antibodies) and macro-organisms (animals, plants), provided that they are new and have potential commercial applicability. Furthermore, the recommendations provide for patent protection for micro-organisms in the FRG to include the filing of samples and a description. In this way, the manufacturing process and the micro-organism can be protected by patent law.

According to a decision handed down by the Federal High Court of Justice in Karlsruhe, on the other hand, only the description of the manufacturing process for the micro-organism is valid. However, this description must be formulated in each case in such a way that any specialist familiar with the field would be able to reproduce the results in a variety of ways, the report continues. However, this point is regarded by scientists as a major obstacle to the generation of biotechnological organisms.

It was not always possible to give an exact description of procedures. For this reason, the possibility of filing a sample of the micro-organism has been introduced, which is intended to supplement, but not replace a description. Such a combination of description and sample is accepted in Japan, the United States and is in keeping with the practice of the European Patent Office. The Munich Max Planck Institute also suggested that in the future a grace period of one year be granted for new developments. This should make it possible for a scientist to publish his results within this grace period, without excluding the possibility of patent protection at a later date. (Source: Handelsblatt, 23 July 1986)

Parliamentary discussion on bill to protect Canadian drug patents

In December the Canadian Parliament heard its first reading of a new bill designed to clear the way for increased investment in biomedical manufacturing and research. The proposed legislation has major support from the Conservative Government, and from most of the country's biotechnology companies, but political opposition to it is so strong that passage is not likely before mid-1987.

At issue is a revision in the existing patent law, which provides for compulsory licensing of new proprietary-drug patents to manufacturers of generic-equivalent products. The revised patent act would grant innovators of pharmaceutical drugs from 7 to 10 years of marketing exclusivity.

Major pharmaceutical firms, small biomedical R&D concerns and government agencies involved in economic growth programmes all contend that Canada's current patent protection removes the economic incentive for research, innovation and investment. But consumer groups, and members of Canada's two opposition parties, are spearheading a drive to retain compulsory licensing, arguing that this has kept retail drug prices low.

Now that the development of new plant varieties is increasingly based on recombinant-DNA techniques, plant breeders and seed firms also want patent protection. (Extracted from McGraw Hill's Biotechnology Newswatch, 15 December 1986)

Cetus counter-sues Amgen over interleukin patents

A fortnight after Amgen, Inc., Thousand Oaks, Calif., challenged the interleukin-2 patents of Cetus Corp., Emeryville, Calif., in the US District Court in San Francisco, Cetus filed a complaint of its own charging Amgen with infringing those IL-2 patents. In its counter-claim, Cetus lists three US patents issued to it between May 1985 and February 1986 covering its protein-engineered "mutein" analog of the interleukin molecule, Proleukin®. This is "currently in advanced human clinical studies around the USA, involving over 700 patients", according to a Cetus press release announcing its new lawsuit. (Extracted from McGraw-Hills Biotechnology Newswatch, 6 October 1986)

Roche sues Genentech for infringing human growth-hormone patent

Genentech, Inc. has won a three-week delay in responding to the legal charges brought against it in September by Hoffmann-La Roche, Inc., Nutley, N.J. Together with its co-plaintiff, the Hormone Research Foundation, Berkeley, Calif., Roche accuses Genentech of "wilful, wanton and deliberate" infringement of US Patent #3,853,833, covering production of "Synthetic Human Growth-Promoting and Lactogenic Hormones" by chemical synthesis. This patent was issued in 1974 to the Hormone Research Foundation, which licensed it in exclusivity to Roche in 1982.

Meanwhile, Genentech constructed a recombinant human growth hormone, trademarked Protropin®, and brought it to market late last year.

Before suing Genentech, whose Protropin is the only human growth hormone available in the USA today, Roche had offered the firm a sub-licence, which it refused.

Several years ago Roche and Genentech had a research collaboration to develop alpha-interferon. The California firm cloned the molecule which Roche then developed into marketable form as Roferon®, approved for sale by the US Food and Drug Administration in June 1986. (Extracted from McGraw-Hills Biotechnology Newswatch, 6 October 1986)

Biogen patent challenged

Biogen's European patent relating to the production of recombinant alpha interferons may be revoked by the European patent office. Although four patent examiners, sitting as an opposition division of the office, conceded that Biogen's patent described and claimed a patentable invention, they objected to the scope of certain claims.

Ten biotechnology and drug companies are challenging Biogen's patent claims including Cetus, Hoffmann-La Roche, Ciba-Geigy and Hoechst. As the

rules of the patent office require either total acceptance of all claims within a patent or revocation of the patent, the opposition division has indicated that it intends to revoke the patent. A written opinion from the division is expected within the first half of 1987.

Biogen intends to defend the patent aggressively before the office's technical board of appeals. Biogen claims that the decision will not affect its patent position in the US or sales of Intron-A marketed by Schering-Plough. The whole patent situation is unlikely to be resolved for a further two years and may cause problems if any firm infringes the patent before a final decision is made. (Source: European Chemical News, 22-29 December 1986)

Damon Biotech wins US patent for cellular enhancer technique

Damon Biotech, Inc., a majority-owned subsidiary of Damon Corporation, claims the US Patent & Trademark Office has approved a patent for the company's cellular enhancer technique, a technology for large-scale production of new biological products.

Damon Biotech claims it has already applied its cellular enhancer technique successfully to the production of tissue plasminogen activator (t-PA) and pro-urokinase.

The cellular enhancer was discovered at the Massachusetts Institute of Technology and licensed exclusively in the United States to Damon Biotech.

A cellular enhancer is a sequence of genetic material, which, when combined with the gene for the desired biological product, significantly increases the production of that product from a mammalian cell. The patent will cover all tissue specific mammalian cell enhancers.

Mammalian cells are the most desirable production vehicles for many of the new biological products being developed by the biotechnology industry. However, these cells are difficult to grow in quantity and they produce a relatively small amount of product, which has made large-scale production difficult. (Extracted from Chemical Marketing Reporter, 29 December 1986)

Hybritech patent upheld by appeals court

A US federal appeals court reversed a year-old federal district court ruling that invalidated a patent held by Hybritech on one of the most commonly used technologies for monoclonal antibody-based diagnostic kits. With the appeal victory, Hybritech, now a subsidiary of Eli Lilly, will continue its now two-and-a-half-year-old patent infringement suit against Monoclonal Antibodies, of Mountain View, Calif., in the San Francisco district court. The new court ruling is a blow to Monoclonal Antibodies, which began reporting net income once the heavy costs of the initial litigation ended last year. (Abstracted with permission from Chemical and Engineering News, 29 September 1986, p. 9. Copyright 1986, American Chemical Society)

Genex files for patents

Genex Corporation has filed patent applications relating to the design and production of novel, single-chain antibodies developed using the company's proprietary protein engineering technology.

Genex believes that, once widely available, single-chain antibodies may revolutionise the use of antibodies in diagnosis, therapy, sensing devices, and separations technology. (Extracted from Chemical Marketing Reporter, 6 October 1986)

BioTechnica wins patent

BioTechnica International Inc., Cambridge, Mass., has been awarded a US patent for a novel method for the purification of phenylalanine, a major component of the artifical sweetener, aspartame. Corresponding patents covering the company's process are pending in other countries. (Source: Chemical Marketing Reporter, 17 November 1986)

Biotechnology patent tangles

About 6,000 biotechnology-related US patents are awaiting approval, and a wave of patent-infringement suits are expected. In recent months, patent infringement suits have been filed over two of the biotechnology industry's most promising drugs-tissue plasminogen activator (a blood clot dissolver) and interleukin-2 (an anti-cancer agent). As precedent in these cases, in September a federal appeals court upheld the patent for a fundamental diagnostic technique developed by Hybritech. That case could be the basis of patent law in an industry where many companies are trying to develop similar products. As a result, big firms like Abbott Laboratories and SmithKline Beckman, as well as numerous start-up companies, may be forced either to pay royalties to Hybritech or withdraw their products from the market. To many in the biotechnology industry, the Hybritech decision is a landmark case. It shows that biotechnology companies are willing to fight to protect their patents and signals an end to the US Government's lax enforcement of patents, but it also shows the riskiness of relying too heavily on a court decision, given the fact that the Hybritech decision was reversed once already before being changed in the appeals court. (Extracted from Business Week, 27 October 1986)

French and US Chiefs of State act to settle Pasteur AIDS lawsuit out of court

At a press conference in Paris on 27 November, France's Minister of Health, Dr. Michele Barzach, told the media that Dr. William B. Walsh, founder and head of Project Hope, the Virginia-based international health organization, had been requested to prepare an agreement to settle the patent-infringement litigation between the Pasteur Institute and the US National Cancer Institute.

One key suggestion both sides agreed upon was to reduce the considerable number of negotiators to a single legal representative from each Government.

The patent litigation pits Pasteur's chief cancer virologist, Dr. Luc Montagnier, who discovered an AIDS virus he named LAV, against the apparently identical HTLV-III claimed by NCI's Robert C. Gallo. Both viral variants, now known internationally as HIV - human immune-deficiency virus - are used commercially in kits for detecting exposure to AIDS, which are licensed respectively by Pasteur and NCI. (Extracted from McGraw-Hill's Biotechnology Newswatch, 15 December 1986)

F. BIO-INFORMATICS

New journal ... Molecular and Cellular Probes Published by the Academic Press on a quarterly basis.

The aim of the journal is to provide a forum for the presentation and technical and clinical evaluation of specific molecules which may be used in the diagnosis of disease processes. It will encompass the description of new or greatly improved strategies for the production of molecules potentially suitable as molecular probes and of new strategies for the generation and detection of signals from such probes. It is envisaged that these probes would most often be polynucleotides or

monoclonal antibodies and would be used for the detection and measurement (in vivo or in vitro) of specific polynucleotide or polypeptide sequences. T-cell clones and hybridomas with specificity for antigens in association with major histocompatibility complex (MHC) molecules can also be used for identifying the presence of their specific antigen in the appropriate MHC context. Although these cellular reagents, especially T-cell clones, are more difficult to handle and grow than hybridomas producing monoclonal antibodies, they are the only reagents that can be used for detection of certain antigens (e.g., minor histocompatibility antigens). They can be, and have been, exchanged between laboratories and can serve as very useful reagents. Other highly characterized and specific reagents are not excluded.

The need for a journal providing this coverage has become very apparent and is due to the spectacular advances in molecular biology, the production of hybridomas and the designing of new labelling and detection methods. Such advances do not observe the traditional boundaries of the diagnostic departments in medicine such as radiology, clinical biochemistry, haematology, immunology, microbiology and histopathology. New probes or approaches discovered by a worker in one of these departments are likely to be of relevance to workers in other departments. However, the journals sponsored by these disciplines are read by a necessarily narrow readership which may not, and certainly increasingly will not, reflect the wide applicability of advances in the production and use of molecular probes.

The phrase "molecular probe" is used here both with reference to the substance used as a reagent for detection and the substance to be detected. Thus the putative reagent for diagnosis should itself be well characterized at the molecular level. This could be in terms of its polynucleotide or polypeptide sequence, as a monoclonal antibody from a cloned hybridoma, or antigen and restriction specificity with respect to a T-cell clone or hybridoma. Likewise the molecular species capable of reacting with the probe should be reasonably well characterized thus endowing the method of detection or estimation with a high degree of specificity. The applications of the probe relevant to the scope of the journal include all those which pertain to diagnosis, including the monitoring of disease progression or remission. They include the detection and localization of tumours or infection in vivo and the detection or measurement of substances in body fluids, samples of tissue (e.g., histology) or inflammatory exudates. Animal studies in so far as they are clearly relevant as models or tests of techniques applicable to man also come within the scope of the journal.

In addition to accepting original contributions as full papers or short communications the journal will include reviews, technical evaluations of equipment, summaries of conferences and correspondence. A strong emphasis will be placed upon rapid publication.

For Instructions to Authors, subscription details or free sample copies please write to either of the addresses below:

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Molecular Microbiology, Edited by C.F. Higgins PhD, Department of Biochemistry, University of Dundee, DD1 4HN, UK

Molecular Microbiology will publish high quality research papers addressing any microbiological question at a molecular level. The journal will include papers describing the molecular biology, genetics and biochemistry of any micro-organisms, prokaryotic or eukaryotic. Articles in the area of molecular pathogenicity will be particularly welcome. Papers in the field of biotechnology will also be considered, but only where they address fundamental biological questions.

Short reviews will be published in areas where rapid advances are currently being made. Many, but not all, reviews will be invited; authors with an idea for a review should contact the Editor.

Molecular Microbiology is to be published bimonthly, starting in July 1987. Subscription rates will be £80.00 (UK), US$173.00 (North America) and £96.00 (elsewhere) post free.

MIRCEN Journal of Applied Microbiology and Biotechnology

The aim of this periodical is to provide an outlet for papers describing the results of original work in applied microbiology and biotechnology, on topics relevant to the needs of the developing world. The Editors wish to emphasize that the Journal is not restricted to the recording of experimental work from the MIRCENs and they hope to receive papers, in English or in French, from scientists in the developed as well as the developing countries who have a common interest in tackling the same problems.

The Journal will contain research papers of substantial length, short communications and review articles. Communications on the following topics will be well suited to this new journal: all aspects of biological nitrogen fixation with special emphasis on the Rhizobium-legume symbiosis in warmer climates, management of culture collections, microbiology of fermented beverages, foods and feeds, soil microbiology, single-cell proteins, fuel production from biomass, waste recycling and biogas production, pollution control, diseases of tropical food plants, public health and veterinary problems in the tropics.

Papers in English must be sent to:
F.A. Skinner, 5 Carisbrooke Road, Harpenden, Herts., AL5 5QS, UK; and papers in French to:
J.C. Senez, Laboratoire de Chimie Bacterienne, C.N.R.S., 31 Chemin Joseph-Aiguier, 13277, Marseille, Cedex 9, France.

Mushroom Journal for the Tropics

Mushroom Journal for the Tropics is the official publication of the International Mushroom Society for the Tropics, and is derived from the previous publication of the Society "Mushroom Newsletter for the Tropics".

The Journal will start in January 1987, as Volume 7, No. 1, in order to be continuous with the Newsletter, which was published between August, 1980 (Volume 1, No. 1) and May, 1986 (Volume 6, No. 4). The Journal is to be published quarterly in January, April, July and October. The editors invite contributions of articles dealing with both basic and applied research involving edible mushrooms,

particularly those which can be grown in tropical climates. Reports of research with other fungi will also be considered if it is clear that the findings have relevance to edible mushrooms.

The Journal will have two sections. In one section will appear those articles that have received acceptance after peer scientific review. In the other section will appear articles and comments of the "newsletter" type. Only members may submit newsletter items, but non-members as well as members may submit articles for publication via the review route.

Requests for information on subscription and submission of manuscripts should be directed to Prof. S.T. Chang, President, The International Mushroom Society for the Tropics, c/o Department of Biology, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong.

The Software Directory for Molecular Biologists by Christopher Rawlings

This single volume brings together the scattered information on software available to molecular biologists.

The Software Directory compares and critically appraises specialized software for molecular biology, and also provides concise descriptions of commercial and business software applicable to laboratory work.

Each entry covers functional features, machine type, computer manufacturer, operating system, and author or company. The book also contains a thorough index of all the software listed, under seven different headings (the five above, plus package name and keyword).

The all-new Software directory for Molecular Biologists gives information on all known software in the field - commercial or non-commercial. 300 pp. $80.00. 0-943818-37-0. April 1986. £40.00. 0-333-39821-1.

The Biomass Directory by J. Coombs

This new and authoritative directory offers the most practical, commercially-oriented guidance on the biomass industry yet available, with key information on more than 2,000 companies and non-commercial organizations. The Biomass Directory covers:

Products: Fuels and chemicals
Equipment: Biological and thermal conversions
Biomass: Raw materials and waste
Research: Public sector and commercial
Information: Journals and services

The directory also offers an easy-to-access Buyers' Guide which gives a detailed listing of the biomass products and services produced or supplied by these many organizations. £45.00. 0-333-39289-2.

Biogas Technology Resource Index

The Biogas Technology Resource Index is a comprehensive guide to the world biogas literature published up to early 1985. The topics covered include Anaerobic Fermentation, Feed Stock Materials, Plant designs and Utilization of biogas in addition to several non-technical topics such as promotion and extension, subsidies and country programmes. This publication is expected to be a useful reference guide to those institutions and scientists who are engaged in the development and diffusion of biogas technology.

Compiled by Dr. V. Vijayalekshmy of the Tata Energy Documentation and Information Centre, the resource index also contains valuable information on the rural applications and the environmental aspects of biogas technology. Interested readers should address their queries to the Tata Energy Research Institute, Bombay House, 24 Homi Mody Street, Bombay 400023, India.

Agricultural information: experiences and emerging issues

Agricultural information is a basic component of agricultural research and development. It is very important in the overall development process in developing countries because dissemination of research results is essential to bring about a change towards a more balanced economy. Agriculture is the way of life of more than 85 per cent of people in developing countries. It is the biggest employment sector and the most crucial earner of foreign exchange. For more than a decade, the IDRC has been supporting a variety of agricultural information projects in developing countries which have made significant contributions to overall development.

The Seventh Congress of the International Association of Agricultural Librarians and Documentalists (IAALD), held in Ottawa, 6-8 June 1985, presented an ideal opportunity to bring together the project leaders from the majority of on-going projects in agricultural information supported by the Information Science Division, IDRC. As a post-congress activity, a one-day meeting was held in IDRC which, for the first time, enabled project leaders from 33 projects and related activities to meet, exchange ideas and talk over various important project matters with IDRC staff.

Interested readers should address their enquiries for a copy of the manuscript report, Document IDRC-MR 116e, to the International Development Research Centre, Ottawa, Canada.

WAITRO - International Seminar

In conjunction with the biennial meetings of its General Assembly, the World Association of Industrial and Technological Research Organizations (WAITRO) has regularly arranged international seminars. These seminars have usually focused on themes aiming at improving the R&D infrastructure in developing countries, and identifying technologies which are best suited to the conditions within the respective countries. Thus, in 1982 the theme of the seminar (in Venezuela) was "Appropriate Technology through Co-operative Arrangements".

The 1984 seminar, held in New Delhi, India, from 6-8 November, was in pursuance of the objective of furthering this co-operative process in the are of "emerging" or advanced technologies appropriate to developing countries. The seminar focused on two major fields of advanced technology, viz: Biotechnology and Informatics. A number of themes within each field were chosen for detailed emphasis, and for the identification of specific co-operative projects. These themes included food processing; bioenergy; fermentation; automation in industry; and computer development and applications. The seminar also devoted time to the methodologies for need assessment, especially in the small-scale and rural sectors in developing countries.

Readers interested in obtaining copies of the final seminar report and of the proceedings should address their enquiries to: WAITRO, Grev Turegatan 19, S-11438 Stockholm, Sweden.

Protein Engineering: Technical Perspective and Strategic Issues

Prepared by SRI International, this is a comprehensive, 360-page analysis of both the technological and the business aspects of protein engineering. The interrelationships among the scientific disciplines (molecular genetics, protein physical chemistry, and computational chemistry) and technologies (in vitro mutagenesis, X-ray crystallography, NMR, AI-based structure prediction algorithms, computer graphics, molecular mechanics) and their potential impact on future developments are analyzed. Commercial applications, strategic issues, and current R&D efforts are discussed. Inferences about crucial problems and limitations are offered for consideration by planners of research and investment strategies. Details: Paul Johnson, Director, Molecular Biology Department, SRI International, 333 Ravenswood Avenue, Menlo Park, CA 94025.

Fourth National Congress of Culture Collections and Industrial Microbiology - Turkey

The Fourth National Congress of Culture Collections and Industrial Microbiology was organised by the Turkish Society for Culture Collections and Industrial Microbiology (KUKEM), the Turkish Centre for Culture Collections (KUKEWS) and the Scientific and Technical Council of Turkey (TUBITAK), 16-18 September 1985, on the theme "Hospital Infection and its Control". Main sessions dealt with: antiseptics, disinfectants and their use; hospital acquired infections; role of culture collections in biotechnology; micro-organism in industrial production; genetic manipulation of industrial micro-organism; and biotechnology in food production.

Readers interested in the published proceedings should address their enquiries to: Dr. Gülsen Aktan, Istanbul Tip. Fak. Mikrobiyoloji Anabilim Dali, Temel Bilimler Binasi, Capa, Istanbul, Turkey.

IBA survey shows maturing US bioindustry

One indication that the biotechnology industry is now "coming of age" is the expanded 1986 Industrial Biotechnology Association/Radford Associates Biotechnology and Benefits Survey just released in the USA. This new survey has doubled the number of job descriptions as well as doubling the company participation base over the 1985 study. A total of 126 biotechnology companies took part, with 31 located in the San Francisco area and 46 on the East Coast. The survey covers compensation data for 100 benchmark positions, broken down by company size and geographic regions. Additional information is supplied on long and short term incentive programmes, benefits and general personnel practices. Details from: Industrial Biotechnology Association, 2115 East Jefferson Street, Rockville, MD 20852, USA or on (301) 984 9598.

Directory of British Biotechnology 1987/88

Produced in conjunction with the Association for the Advancement of British Biotechnology (AABB) and covers British companies, laboratories and academic groups active in biotechnology. This new edition of the Directory of British Biotechnology 1987/88 has been extensively updated to include:

- Detailed company and academic profiles
- Review of British biotechnology, its achievements and progress
- Breakdown of venture capital companies with interests in biotechnology
- Outline of the establishment and aims of the Association for the Advancement of British Biotechnology (AABB)
- New easy-to-use larger format

Activities represented range from monoclonal antibodies to bioelectronics; topic areas include agriculture, commodity and speciality chemicals, environment, waste disposal and pharmaceuticals. Coverage is also given to equipment manufacturers producing apparatus specifically for microbiological and chemical engineering applications.

The Directory of British Biotechnology 1987/88 provides an essential link between British industry and academic institutions, allowing companies ready access to researchers working in relevant areas and enabling academic researchers to identify their opposite number in industry.

Industrialists will find the directory particularly useful as a contact book, outlining market size and providing profiles of competitors and potential customers.

In addition the Directory of British Biotechnology 1987/88 will prove a valuable reference tool for overseas companies interested in British collaboration, venture capitalists, information officers, librarians, journalists and job seekers - in fact all those interested in who is doing what in British biotechnology. Price £65.00. For further information contact: Alison Cowley, Longman Group UK Ltd, Westgate House, The High, Harlow, Essex CM20 1NE, United Kingdom.

Latin American Association of Rhizobiology (ALAR)

With support from FAO and the Comisión Honoraria del Plan Agropecuario, ALAR has produced an information booklet on the actual state of Rhizobiology in Latin America and the Caribbean. The booklet provides valuable information on: the availability of legumes and their types, species of Rhizobium; the production of inoculant materials (type of inoculants, species used and volume produced); quality control of imported and locally-produced inoculants; rural extension work; basic research and academic activities in Argentina, Bolivia, Brazil, Colombia, Costa Rica, Chile, Ecuador, El Salvador, Honduras, Mexico, Panama, Peru, Puerto Rico (USA territory), Uruguay and Venezuela. Copies of the booklet can be obtained from: Secretaría de ALAR, Bulevar Artigas 3802, Montevideo, Uruguay.

The Second Edition of the Rhizobium Catalogue for Latin America, 1982-1984, has been prepared and released by the Latinoamerican Association of Rhizobiology. Copies and accompanying ALAR Bullatins can be obtained directly from: The Secretary, ALAR Secretariat, Bulevar Artigas 3802, Montevideo.

Engineered organisms in the environment: Scientific issues

The American Society for Microbiology (ASM) announces publication of the proceedings and a lay summary of the cross-disciplinary symposium "Engineered Organisms in the Environment: Scientific Issues, Proceedings of a Cross-Disciplinary Symposium, edited by Marlys O. Halvorson, David Pramer and Marvin Rogul, and Engineered Organisms in the Environment: Scientific Issues, Lay

Summary, by Bernard Dixon, can be ordered from the ASM Publications Sales Office, 1913 I Street, N.W., Washington, D.C. 20006, at a cost of $18.00.

The cross-disciplinary symposium on "Engineered Organisms in the Environment: Scientific Issues" was organized by the ASM in collaboration with seven other scientific societies and was sponsored in part by funds from eight federal agencies. The objectives of the symposium were to review what is known relevant to the introduction of engineered organisms in the environment, to identify areas of uncertainty that require attention, and, by encouraging discussion, to elicit a synthesis of thinking on scientific issues that will assure advances in molecular biology will be used wisely to maintain environmental quality and improve human well-being.

The proceedings convey both the substance and spirit of the symposium. The book includes the text of all formal presentations by distinguished ecologists, geneticists, microbiologists and molecular biologists, as well as informal discussion from the floor. The volume follows the symposium sessions: A Perspective of the Problem, State of the Art: Case Histories, Genetic Variation and Gene Transfer, Evolutionary Considerations, Other Introductions into the Environment, Biological Responses to Perturbation: Genome to Ecosystem, and Future Trends: Toward a Predictive Capability.

Genetically engineered organisms, their development and wise use, are the concerns of many fields ranging from macroecology to molecular biology. A free flow of information among related scientific disciplines is essential for progress. Engineered Organisms in the Environment: Scientific Issues is a significant contribution to an important ongoing dialogue.

Maintenance of micro-organisms

Information on culture maintenance is sparse and scattered widely through the literature. This volume, edited by B.E. Kirsop and J.J.S. Snell, fills an immense gap by bringing together methods for the preservation of a wide range of micro-organisms which have been developed and tested by recognised authorities.

To ensure that the manual is easy to use each chapter is devoted to a particular group of micro-organisms rather than to a method. An assessment of shelf life and suitability for different organisms is provided for each method. General information on the service culture collection has been included, together with comprehensive lists of suppliers, useful addresses, and over 1,000 references.

Topics covered are:

Service Collections: Their Functions; General Introduction to Maintenance Methods; Maintenance of Bacteria by Freeze-drying; Maintenance of Bacteria on Glass Beads at -60°C to -76°C; Maintenance of Bacteria in Gelatin Discs; Maintenance of Anaerobic Bacteria; Maintenance of Leptospira; Maintenance of Industrial and Marine Bacteria and Bacteriophages; Maintenance of Methanogenic Bacteria; Maintenance of Fungi; Maintenance of Yeasts; Maintenance of Algae and Protozoa; and Maintenance of Parasitic Protozoa by Cryopreservation.

Enquiries from MIRCEN laboratories and other interested researchers should be addressed directly to Academic Press, London, U.K.

Directory of Departments and Collections in the Nordic Register of Microbiological Culture Collections

In 1984 the Nordic Council of Ministers formed a Policy Group for Nordic Co-operation on Microbiology, which amongst other tasks, would supervise the build-up of a computerised register of micro-organisms relevant to agriculture, forestry and horticulture. In addition, the group would also keep pace with the international developments in the field of computer registration of microbiological strain data. As a result, the Nordic Register of Microbiological Culture Collections (NORCC) started its activities in April, 1984, and in an initial step, an extensive contact campaign concerning collection of information about microbiological departments in the Nordic countries was begun.

This first Directory of Nordic Microbiological Departments is the result of that initial work. The Directory contains addresses as well as general information about 119 departments in Denmark, Finland, Norway and Sweden. Of these departments, 90 maintain some kind of a culture collection.

The Directory also provides information on departments from many areas within the field of microbiology. From the information that has now been collected, the Nordic Register of Microbiological Culture Collections will be able to identify the collections that maintain organisms relevant to agriculture, horticulture and forestry.

As a result of the development of the computer technique within recent years, registers on micro-organisms are currently being developed in many parts of the world. A large international project aimed at the development of the co-operation and the usage of these registers has been started. The Nordic Register of Microbiological Culture Collections has been involved in this Microbial Strain Data Network-project since its beginning. Through this activity, the Nordic Register will soon be able to offer large amounts of data on micro-organisms maintained in other parts of the world to its Nordic users. Simultaneously, the Nordic microbial collections will be presented outside the Nordic countries.

The Nordic Register of Microbiological Culture Collections is now in a very dynamic phase of development, and views and opinions from the users are extremely important to help develop its activities and best fulfill its tasks and responsibilities.

Further information can be obtained from: The Secretary/Project Manager, Nordic Register of Microbiological Culture Collections, Department of Microbiology, University of Helsinki, SF-00710 Helsinki, Finland.

Isotopes in studies on nitrogen-fixation

A technical document (IAEA-TECDOC-325, 1985) has been issued on the "Role of Isotopes in Studies on Nitrogen-Fixation and Nitrogen Cycling by Blue-Green Algae and the Azolla-Anabaena Azollae association. The document summarizes the proceedings of a consultants meeting organized by the joint FAO/IAEA Division of Isotope and Radiation Applications of Atomic Energy for Food and Agricultural Development that was held in Vienna, October, 1982. The topics covered were: Nitrogen fixation by the Azolla-Anabaena Azollae symbiosis; establishment and management of Azolla in rice fields; environmental conditions and field assays concerning the growth and

nitrogen fixation of Azolla pinnata var. africana; annual reproduction of Azolla species; blue-green algae in rice fields; use of isotopes in nitrogen-fixation by blue-green algae and in paddy soils at the International Rice Research Institute; effects of blue-green algae and Azolla on the yield of rice; and the ecology of blue-green algae.

Readers interested in acquiring a copy of the document should address their enquiries to: IRIS Clearinghouse, IAEA, Wagramerstrasse 5, P.O. Box 100, A-1400, Vienna, Austria.

International microbial strain data network

The needs and specifications for an international strain data network have been described in a UNEP publication that summarises the contents of a workshop held at Brussels, Belgium (November, 1983) and of a Working Group Meeting held at Bangkok, Thailand (November, 1984). Edited by L.R. Hill, and N.I. Krichevsky, the publication covers presentations at the workshop, i.e. ability of a decentralized system designed to meet the requirements of an international microbial strain data network; co-operative scientific and technical information networks; development of a biological data bank; the establishment of a Nordic register of microbial culture collection; a microbial strain information system (MICRO-IS) and computer-assisted conference systems for the exchange of microbiological information. In addition summaries of several Panel discussions are included. Policy responsibilities and methodology of the operations of the network are contained in appended summary in the publication.

Interested readers should address their enquiries to UNEP, P.O. Box 30552, Nairobi, Kenya.

Microbiological Resource Databank

A Microbiology Resource Databank containing information of scientific and biotechnological importance on animal cells, plant cells and viruses has been set up. In future catalogues micro-organisms, bacteriophages, plasmids, vectors and genes are expected to be covered. The data stored for each organism is designed to contain sufficient information to enable users to carry out preliminary screening of available material to show WHO HAS WHAT. Mirdab provides an up-to-date means of exchanging vital information on various aspects of microbiology, using modern methods of data collection, storage and dissemination.

The information received through relevant Contributor's Input Forms is stored in the databank, providing individuals, researchers and organizations with the means to locate sources of material which would not be readily discovered by currently available search procedures.

Being refereed by an editorial board and regularly updated by feedback from users, Mirdab is considered an extremely valuable library reference.

The name, address and telephone number of the holder of each cell line is provided to stimulate interlaboratory contact between interested scientists. Since data input is computerised, machine-readable output can also be considered a viable option.

Interested readers should address their enquiries to: MIRDAB, P.O. Box 1527, 1000 BM Amsterdam, The Netherlands.

Microbial Cultural Information Service (MiCIS)

The U.K. Department of Trade and Industry has been identified as the "lead" Government Department on Biotechnology and the Laboratory of the Government Chemist (LGC) has been given the task of administering a biotechnology support scheme for industry. It also has an in-house research group working on biotechnology projects for industry. In its long term support programme for biotechnology, the Department of Trade and Industry has made provision for enhancing the contribution of the national culture collections by encouraging stable funding and relevant R&D as well as responding to the demand from industry for a central information system on the holding of the national as well as some private collections. A survey of industry showed that industry needed an on-line facility to find:

- The source of supply of a named organism
- The known properties of a named organism
- An unknown organism displaying particular properties

The database, to be known as MiCIS, will be housed on a GEC 4190 minicomputer based at LGC.

The database management system employed is Logica's RAPPORT TM which provides an interactive query language, back-up and recovery facilities, multi-user access and data security. This is a relational database which, while being easy to understand, is capable of being extended to meet subsequent user needs.

Communications will be handled by LGC's GEC 4160. Subscribers and curators will be able to link up to the database through either a packet switch stream (PSS) or the public telephone network (PTN). Connection to EUROMET DIANE will enable both data from mainland Europe to be added and non-UK subscribers to use the database. A postal and telephone enquiry service will also operate.

The proposed database has been designed to enable both regular and occasional subscribers to use MiCIS with ease and takes account of the multi-disciplinary audience in biotechnology. Over 250 European based companies have already registered an interest in MiCIS and these are to be kept up-to-date with MiCIS and culture collection developments via a quarterly newsletter "MiCIS NEWS".

Further information can be obtained from: Mrs. Geraldine Allinton, Biotechnology Group, Laboratory of the Government Chemist, Cornwall House, London, U.K.

Biosym Technologies gets $500,000 for computer aided molecular design

The US National Institute of General Medical Sciences of the National Institutes of Health has awarded a $500,000 grant to Biosym Technologies for the development of improved computer methods for molecular simulation in protein design. The funds will pay for a two-year programme headed by Dr. Donald MacKay, the Company's vice president of engineering and co-founder. The objective is to enhance the computational efficiency of existing molecular mechanics/dynamics software and to develop new algorithms to address design needs specific to proteins. Details from: Dr. David H. Klipstein, president, Biosym Technologies Inc., 9605 Scranton Road, San Diego, CA 92121, USA or on (619) 458 9900.

BioCommerce data's new database

BioCommerce Abstracts is now available through the San Francisco-based database host, Dialog Information Services Inc. The file (286) contains over 20,000 abstracts indexing more than 70,000 biotechnology business news reports since 1981, and is updated twice monthly with references from major

newsletters, business magazines, trade journals and newspapers published worldwide. Details from: BioCommerce Data Ltd., Old Crown Building, Windsor Road, Slough, Berks SL1 2DY or on 0753 74201.

BICEPS bio-informatics workshops

In the build-up to the European Community's BICEPS (Bio-Informatics Collaborative European Program and Strategy) Programme, a series of workshops will be held on such subjects as artificial intelligence, data capture technology, databases, high resolution graphics, networks, and fermenter process control. Details from: Leif Kvistgaard Jakobsen, Computer Resources International, Vesterbrogade 1A, DK-1620 Copenhagen V, Denmark or on 0045 1 131166.

European Bank of Computer Programs in Biotechnology

Funds are currently being raised to set up a European Bank of Computer Programs in Biotechnology (EBCB), according to the European Biotechnology Information Project (EBIP). The EBCB will offer a means of exchanging and collecting computer programmes in the fields of microbiology biochemistry and bioengineering, as well as providing an advisory service. The Bank, to be hosted by the Laboratory of Biotechnology at the University of Technology, Delft, The Netherlands, will be under the direction of Prof. K. Luboun, and will adapt programmes to other operating systems, extending their applications. Details from: EPIB, British Library, 9 Keen Street, London WC2B 4AT or on 01 379 6488.

Genetic information software and database

CD/Biotech is a software and database package supplied on a read-only compact laser disk. The disk contains GenBank, the Protein Identification Resource, the Yale University Human Gene Map Library, a selection of biotechnology and biochemistry abstracts, DNA sequence manipulation software, and several scientific software packages in the public domain. CD/Biotech requires a standard CD/ROM reader and an IBM PC or compatible personal computer; software provided with CD/Biotech makes the CD appear as a hard-disk drive with a large number of directories. The system will be updated and expanded with new sequence information and software twice a year. International Association for Scientific Computing.

New products

Software packages. Bio-Tek Instruments (Winooski, VT) announces support for its microplate readers with a new series of menu-driven software packages for use with IBM and Apple computers. Software includes data storage and retrieval, statistical analysis, regression analysis, and kinetics.

G. MEETINGS

16-20 March 1987. Recombinant DNA, Rockville, MD, USA. (Contact: American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD 20852-1776, USA or on (301) 881 2600).

17-19 March 1987. Biotech 87 Transfer. (Contact: BIOTEC 87, Dusseldorfer Messegesellschaft mbH, NOWEA, Postfach 32 02 03, Stockumer Kirchstrasse 61, D-4000 Dusseldorf 30, Federal Republic of Germany).

7-10 April 1987. Canada-OECD Biotechnology Workshop. The Ministry of State for Science and Technology in conjunction with the Biotechnology Secretariat of the OECD is sponsoring a policy workshop in Toronto, Ontario, Canada, involving invited senior biotechnology delegations from the OECD countries. The major topics of discussion will centre on national policies and strategic priorities, the commercialization of university and government research, training and mobilization of human resources, and international co-operation. Dr. John Evans, Chairman of Canada's National Biotechnology Advisory Committee, will chair the event which constitutes the first international review of biotechnology programmes and policies adopted by member countries.

22-23 April 1987. Protein Structural Analysis. Piscataway, NJ. Course. (Contact: Edward V. Lipman, Jr., Cook College, Rutgers, The State University, PO Box 231, New Brunswick, NJ 08903. Phone: 201-932-9271).

27-28 April 1987. Biotechnology Patent Conference. Rockville, MD. (Contact: Doug Drabkowski, Workshop Co-ordinator, American Type Culture Collection, 12301 Parklawn Dr., Rockville, MD 20852. Phone: 301-231-5566).

5-8 May 1987. 9th Symposium on Biotechnology for Fuels and Chemicals, Boulder, Colorado, USA. (Contact: Charles D. Scott, Oak Ridge National Laboratory, PO Box X, Oak Ridge, Tennessee 37831, USA).

11-15 May 1987. 3rd International Symposium: Toxicity Testing Using Microbial Systems, Valencia, Spain. (Contact: Prof. P. Vasseur, Centre des Sciences de l'Environnement, L rue des Recollets, 57000 Metz, France).

12-14 May 1987. Biotech 87. The fifth event in this series, this meeting is to be held at Wembley, London. It will feature a larger exhibition plus a conference split into modules on international business, bio-systems, agriculture, healthcare, bio-transformations and processing. Further information from Pam Howard, Online International, Pinner Green House, Ash Hill Drive, Pinner, Middlesex HA5 2AE, UK. Telephone 01-868 4466; fax 01-868 9933; telex 923498 online g.

13-14 June 1987. 1st Meeting of Scientific Committee of Biotechnology. Amsterdam, The Netherlands. Further information from Dr. Jorge E. Allende, Co-chairman, Interim Steering Group for COBIOTECH, Departamento de Bioquímica, Facultad de Medicina (Norte), Universidad de Chile, Casilla 70086, Santiago 7, Chile. Telephone: 56/2/376 320 Telex: UNESCO 340258.

14-19 June 1987. Fourth European Congress on Biotechnology. The 4th European Congress on Biotechnology, will be held in the International Congrescentrum RAI in Amsterdam, The Netherlands and will cover all aspects of biotechnological research and development in Europe. Special attention will be given to the most recent breakthroughs and possibilities in several important fields of basic biotechnology in Europe as well as to the most recent developments in the European biotechnological industry.

In poster presentations and a number of special sessions, this congress further offers a unique meeting and working place for biotechnologists from universities, institutes and industry all over the world. The combination of the congress with the commercial exposition "Amsterdam Biotechnology 87" that will be held in the RAI Exhibition Centre in Amsterdam during the same period, ensures the integration of science and application which is so important for biotechnology.

The fields to be covered by this congress are: Biocatalysis, Animal Cell Culture, Plant Cell Culture, Measurement and Control, Molecular Genetics, Downstream Processing, Bioreactors, Microbial

Physiology, Environmental Biotechnology, Pharmaceuticals: vaccines, diagnostics, therapeutics, Raw Materials, Food & Feed, Fuel/Energy, Fine Chemicals, and Amino Acid Fermentation. A special plenary meeting will be devoted to "The Biotechnology Race" with invited speakers from the USA, Japan and Europe, followed by a forum discussion. A satellite symposium will be organized to celebrate the 30th anniversary Amino Acid Fermentation under the auspices of the International Committee on Economic and Applied Microbiology (ICEAM).

For futher enquiries please contact: Congress Secretariat ECB6, Organisatie Bureau Amsterdam bv, Europaplein 12, 1078 GZ Amsterdam, The Netherlands.

20-26 June 1987. Incheba: chemistry in agriculture. The British overseas trade board has agreed to support British companies wishing to exhibit at the Incheba fair in Bratislava, Czechoslovakia. This means that companies can reduce the cost of exhibiting by approximately 50 per cent besides getting a trade subsidy and being relieved of much of the administrative tasks. Incheba, which is regarded as the most important fair of its kind in Eastern Europe, offers companies the opportunity to reach markets in the Socialist bloc. Czechoslovakia is spending a significant amount of money now on updating its chemical industry to produce added value products as well as buying equipment for inclusion in plant sales to third countries, making it a particularly good time for companies to get an entrée. Emphasis of the 1987 event will be on chemistry in agriculture. Further details from David Ford, Denis Cox Public Relations, 8 Crucifix Lane, London SE1 3JW, UK. Telephone 01-378 7778.

23-25 June 1987. Getting Into Biotech Business. Cambridge Conference. Churchill College, Cambridge, organized by the Biotechnology Centre Wales sponsored by Cambridge Life Science Plc. This three day Conference has been designed to introduce academics, entrepreneurs and businessmen to the many aspects of commercial Biotechnology. An Overview of the UK situation will be made and illustrated by case histories of successful "Start-ups". This will be followed by innovative seminars on aspects of Biotech Business. Christine Roberts, Conference Secretary, FREEPOST, The Biotechnology Centre Wales, Singleton Park, Swansea, SA2 922. Tel: (0792) 296396. Telex: 48358 ULSWANG.

28 June - 2 July 1987. Boulder, Colo. Frontiers in Bioprocessing. (Contact: Subhas Sikdar, Center for Chemical Engineering, National Bureau of Standards, 325 Broadway, Boulder, Colo. 80303 (303/497/5232)).

6-8 July 1987. Surfaces of Biomaterials Biotechnology, Cambridge, UK.
(Contact: Mary Kornsdorffer, Biomaterials, Butterworth Scientific Ltd, PO Box 63, Westbury House, Bury Street, Guildford, Surrey GU2 5BH or on 0483 31261).

7-10 July 1987. World conference - chemical accidents. This conference is to be held in Rome and will cover all types of chemical accidents. Sessions will comprise papers on prevention of accidents, contingency planning, emergency response, rehabilitation following chemical accidents and case studies and surveys. Contributed papers are welcome within the themes outlined. For further information contact the World conference on chemical accidents, secretariat, CEP Consultants Ltd, 26 Albany Street, Edinburgh EH1 3QH, UK. Telephone 031-557 2478.

9-15 August 1987. Eleventh North American Rhizobium Conference, to be held at Laval University. For further information, queries should be addressed to Dr. H. Antoun, Département de Sols, FSAA, Pavillon Paul-Comtois, Université Laval, Québec, G1K 7P4, Canada.

25-28 August 1987. 7th Australian Biotechnology Conference, University of Melbourne, Australia. (Contact: K. D. Kirby, The Secretariat, 7th Australian Biotechnology Conference, CSIRO, Division of Chemical and Wood Technology, Private Bag 10, Clayton, Victoria 3168, Australia).

21-25 September 1987. International Congress of Plant Tissue Culture, to be held in Bogotá, Colombia. Further information from Antonio Angarita-Zerda, General Co-ordinator, Congress Secretarial, Apartado Aereo No. 057303, Bogotá 2, Colombia.

6-8 October 1987. Washington DC. First International Symposium on Bio-Processing Safety Standard Guidelines and Practices to Insure Worker Safety in the Bio-Processing of Industrial Chemicals, Foods, and Waste Products. Contact: Warren C. Hyer, Jr., Hytech Development, Trenton, NJ. (609/896/2437).

9-12 November 1987. Bioreactors and biotransformations. This international conference will be held at Gleneagles Hotel, Perthshire, Scotland. The organizers are inviting papers on all technical and economic aspects of bioreactors and biotransformations; the deadline is 16 January 1987. Further details from Elspeth Gibson, Organizer, Bioreactors and biotransformations conference, National Engineering Laboratory, East Kilbride, Glasgow G75 OQU, Scotland, UK. Telephone 035 52 20222; telex 777888 nelek; fax 035 52 36930.

B. REPRINTED ARTICLE

Genetics and the forests of the future by Gene Namkoong (Reprinted from Unasylva, FAO, Rome. Vol. 36, No. 152, 1986/2).

One of the greatest challenges awaiting foresters in the future - especially those working in tropical forests in developing countries - is genetics. It is in the tropical forests that most of the world's animal and plant species are located. Many of these species, at present, are virtually unknown. As knowledge of the resources contained in these forests increases and as the emerging field of biotechnology opens new possibilities for management and development, foresters will be presented with a wide new set of questions - scientific, economic, ethical and ecological. The first part of this article deals with these questions in general terms; the second examines, in detail, some of the concrete implications they might have for forest management.

Part one

Management objectives

The well-being and productivity of forests are dependent on the structure and dynamics of their genetic foundation. Their inherent capacities for growth and development are under strong genetic control and can be improved through breeding. The focus of this article, however, is not on breeding techniques but on the deeper question of how to maintain or generate useful genetic variation for the continued evolution, improvement and adaptation of forests to human and environmental demands. Methods for selective breeding and genetic manipulation of trees will be addressed, but the main concern will be the quantity and pattern of genetic diversity needed to inhibit the dangers arising from uniformly susceptible stands. We are seeking ways to ensure the diversity needed both for immediate benefits and for future generations - for new economic goals; for adaptability to changing sites and climates; and for survival within the ever-evolving living community of pathogens, pests, competitors and mutualists.

For these issues, we need to look beyond the trees we use for today's breeding to the past populations that gave rise to them and to the populations we will have to construct for future forests. We must consider populations that are at present of peripheral interest but that may contain variation that will be useful under other conditions in the future. We must also consider some species that may have little present commercial value but may have future value either in themselves or as sources of genes for use with other species. The conservation of genetic resources is a complex task, in which problems and solutions vary according to the immediacy of commercial use and the amount of knowledge about and manageability of the species involved.

It is apparent that issues affecting forest genetic resources are not qualitatively different from those affecting agricultural genetic resources. The problems differ in detail and emphasis, but the array of conservation and management issues is similar for many species. The identification and conservation of new species is as much a concern for medicinal and agricultural species as it is for forest tree species. Ecogeographic surveys of wheat are as new as provenance studies of tropical pines, and the evaluation and enhancement of maize varieties are similar in design to testing radiata pine. It is therefore appropriate for us to consider forest genetic resource issues within the context of general plant genetic resources, and to clarify management objectives where more than one species and more than one objective may be involved in any operational decision. In addition to discussing management objectives, this article will describe genetic management for three types of species: (1) those of current commercial significance; (2) those of clear potential value; and (3) those of unknown value given present technology. Problems of investing in more intensive and complete programmes are considered, a basis for deciding on programme investments is proposed, and mechanisms to support gene conservation and management are suggested.

Measuring objectives

Decisions about conservation of species or ecosystems depend on value judgements. We must therefore ask who benefits from conservation efforts and establish the measures by which values will be judged by the people on whose behalf we operate. For commercial species, the interests of local growers and users are not necessarily the same as those of large industries, even if they are in the same country. Furthermore, people other than those directly affected by our broad definition of commercial use (see below) derive benefit from, and therefore are concerned about, commercial and non-commercial species and the land they occupy. In addition, there are future generations of people whose welfare depends on how well we manage the genetic resource.

One critical factor affecting all available alternatives is underinvestment in genetic conservation and management programmes. The International Board for Plant Genetic Resources estimates that worldwide expenditures on all forms of genetic conservation and development for all animal and plant crops total US$50 million per year. While the danger of genetically ameliorable famine increases annually, worldwide investment has not grown in the last five years. Hence, in addition to describing the management options that are available, we must consider the values placed on genetic resources. Who benefits? Who invests in programmes affecting those resources? How can a conservation management programme be supported?

It is clearly possible to ensure the continued evolution and availability of plant and animal populations. However, it is also clear that only very meagre funding is available for any but the most important commercial species in industrialized forestry. Even the execution of such projects as an ecogeographic survey of world wheat genetic resources, which would require funding of $10 million each year for several years, is by no means certain. If only the major commercial food and fibre species are considered, investments of an order of magnitude much greater than the present level would be needed to conserve and develop the genetic resource base adequately. While such funding is not large in relation to the international trade in agricultural and forestry products, there is an obvious gap between needs and investment. That gap has not been reduced in recent years.

The situation is not qualitatively different between forestry and agronomic crops. It is particularly obvious in forestry that investments in genetic resource development come primarily from industrialized country sources, while the needs for that development exist over a much broader area. The dangers inherent in this situation are that the overall global good may not be best served if development is restricted to the interests of a small segment of the public. While it is not necessarily true that the wider public interest is not well served by industrial development, it is also not necessarily true that it is. It is essential to allocate costs fairly, to decide who pays for programmes, and to determine who is to benefit from gene resource management.

I am assuming that a just solution to this central problem would lead to reasonable but much higher investment in genetic management. The interests expressed by agribusinesses, by governments and by United Nations agencies - FAO most notably - indicate that there is a recognition of the need for investment and development. The disagreement is over means. The immediate dangers in the present situation are that the genetic resources of most crop species are being threatened by a severe reduction, that potential progress from breeding is foregone, and that the genetic and ecological vulnerability of our food and fibre crops is increasing.

One of the features of the current global economy is the unequal distribution of resources and of the benefits to be derived from them. Even within nations, the interests of rural agriculturists or wood-users differ from those of urban consumers or timber merchants. Many genetic resources lie in remote areas or in isolated, scattered populations which may have to be extracted and tested elsewhere. While the present value of at least some of those populations may be due to past policies and practices, including protection of the populations, it also seems clear that modern genetic technologies can more rapidly develop their potential and expand their utility and benefits.

Developmental technology itself, however, can be considered to be yet another resource which is not uniformly distributed, either within or between nations. Technological centres are commonly concentrated in urban areas, supported by industries or central governments, and staffed by professionals educated in these same technological centres. There are substantive reasons for these concentrations, but the results are often unfortunate. Maldistribution of technological capability leads to a concentration of technical efforts on species and for products of immediate commercial value to those who support those centres.

Another potential problem is the dependence of powerless future generations on the genetic endowment left by previous generations. The materials we leave and the technology we develop are our endowment to future generations. This endowment can be diminished or enhanced. Management objectives, even by government agencies, seldom explicitly consider future wishes. Obviously, industrial concerns must heavily discount future values, since only present investors can voice preferences. In fact, the perspective of present investors is often the only one in economic analysis of alternatives by government or privte industry. This total reliance on market forces to determine investment priorities implies that political or ethical concerns for future generations are secondary.

Capitalists might argue that only the free market can ensure such fairness, while socialists would argue otherwise. In any case, neither could argue that the only objective should be industrial profit. Free-market motivation may arguably result in economic fairness, but it does not necessarily represent justice. Management objectives are properly set by political and ethical considerations, only one of which is industrial profit.

Investments in developing and managing the genetic resources are now made largely by industrial interests, either directly or indirectly through support for government policies and technologies. I emphasize that this is not a condemnation of the maldistribution of power, but an observation that there are inequalities in the distribution of genetic technologies, resources and power which affect management plans. If we accept that it is feasible to consider various levels of genetic management to ensure the productivity of future forests, the main question to consider is how to generate the investments needed to do so with some sense of justice.

Given the assumption that current industrial investment in genetic management is that which can be justified by expected financial returns under present conditions, far greater investment needs nevertheless do exist and greater inducements for investment by industries and governments must be sought. Since private industrial interests cannot be expected to invest in programmes that provide few returns, there is considerable debate over how the necessary exchange of genetic resources should be managed. A focal point for the debate is the concept of genetic resources as the "common heritage" of all people.

A libertarian view might consider the genetic heritage something available to everyone - and thus to anyone with the means to develop it. Investors therefore use technological and other resources to develop a varietal product of higher value or lower cost for sale to potential buyers. By such means as patent rights, the initial investment can be protected and the investor can obtain returns for those efforts. Furthermore, by this view, all people eventually benefit as the profits from the better varieties trickle down to society in general. People lucky enough to possess gene resources of unrealized potential value in their own countries benefit by private development of that potential, possibly by the sale of improved varieties back to their own people.

An egalitarian view of genetic resources would see them as a "common heritage" from which all people have a claim to any benefits derived. By this view, the fact that one nation may have a particularly valuable genetic population while another may have the testing facilities and analytical capabilities for developing a new variety gives neither of them exclusive rights of ownership or profit. The unequal distribution of resources is viewed as the result of a kind of natural global lottery. A proper function of governments is to support the co-ordination of resource use for maximum total benefit, while allowing each to receive profit from his or her investment.

The conflict between these two views inhibits what I believe to be a justifiable need for larger investments in gene management. Industrialized nations, together with forest and agribusiness industries, are the primary sources of investment capital, and they largely subscribe to the "libertarian" view. The Third World nations, which house many of the genetic resources, largely subscribe to the egalitarian view. In this situation, private investors are reluctant to capitalize long-term development programmes without at least some assurance of varietal protection while developing countries seek programme support for the development of their own research and training facilities. Meanwhile, some agricultural seed companies and industrial co-operatives such as CAMCORE (Central America and Mexico Coniferous Resources Co-operative) are beginning breeding and conservation efforts on an international scale. Other agencies, like the Commonwealth Forestry Institute and the Danish International Development Agency, have had international conservation and breeding programmes funded by governments for philanthropic reasons. As more private and governmental agencies enter the arena, conflicting objectives may preclude efficiencies in co-operation and mutual support. Indeed, the role of international assistance agencies is not clear, given the multiple objectives of genetic management programmes.

A programme proposal

When the objective of management is simple and unequivocal, such as financial profit, and the subject is merely a single agency or investor, determining optimal investments and programmes is relatively easy. However, when the subjects who can be harmed or benefited by genetic management do not share the same political and economic status, may not even be in the same generation, and may have a multitude of different needs, programme evaluations will be quite different. Whereas the costs of ecological destabilization may be viewed mainly as an externality to a timber investor, a local community dependent on the land for other products may view it as an "internal risk" - as may the global community, which may be hurt indirectly. Private investments made for the benefit of future generations risk that future generations may or may not want certain forest products as at present defined. Public bodies, however, may wish to reduce such risks greatly by making certain assumptions about the anticipated needs of future generations.

Various systems of public subsidies can probably achieve gene management objectives, but not without substantial problems. There are problems in achieving public awareness of the significance of the issues involved, and problems in adjudicating the responsibilities of the interested parties. While most parties may agree on the desirability of sharing costs and benefits, it is not clear how to do that. How, for example, can we best bear the costs of conservation programmes in this generation while future generations reap the benefits? How can the people of Amazonia justly bear the costs of maintaining, or not otherwise using, natural areas - a policy that may benefit the global environment and future generations, but not themselves? How can the gene-rich but technology-poor developing nations trade with the gene-poor but technology- and capital-rich industrialised nations? Can the

philanthropies of certain groups support programmes that may profit private entities such as seed companies but not the general public? How can national programmes of foreign aid equitably allocate funds among programmes or evaluate benefits among government agencies, private investors and other governments? Finally, how should subsidies be derived in the first place, and which segments of the affected people should be expected to bear the costs?

I believe that justice for future generations of people requires protection of evolutionary potential, and I believe such protection is feasible (Namkoong, 1982). This goal can be accomplished in a programme of genetic conservation (Namkoong, 1984a) that includes directional selective breeding in at least one and preferably in multiple populations. It would also include conservation in multiple populations when direct management intervention is not feasible. For species with high market value, private investment may sometimes be sufficient for the development of commercially valuable varieties and for the protection of the interests of all affected people. Obviously, for species or varieties at the edges of commercial utility, and for those without known commercial benefits, private investment cannot be expected. The values to be derived from the genetic management of species with little or no commercial value are generally of such long-term and diffuse global value that the general global public is the prime beneficiary. In that case, international agencies such as the International Union for the Conservation of Nature and Natural Resources and the Nature Conservancy may be needed to invest in such programmes. In one sense, these organizations would be subsidizing the later development of more immediate and exploitable commercial values. This is similar to the functions of state and federal agricultural research stations in the United States, which support the development of breeding populations which they or others may use for commercial variety development. For the vast majority of less directly useful species, however, public and non-governmental investments will be required. If some commercial products are eventually realized, payment of royalties to these organizations would seem proper.

Perhaps the greatest conflicts are associated with commercial or near-commercial species that require some research and development. Developing nations may resist the notion of granting Plant Breeder Rights (PBRs) and protecting the privileges of developers, but they lack the capital and technological capacity to develop varieties on their own. I suggest that since the varietal developments that may occur in an industrial country are not likely to be useful in a Third World country, PBRs can be granted without harm to developing countries. However, since the materials used for varietal development are affected by the people in the nations of origin and by the ecosystems that supported their evolution, some royalty is owed to the nations of origin. To this extent, royalties on profits and fees for use of such materials might appropriately be deposited in a trust agency for the development of technologies deemed useful for gene management by the people in those nations. A special United Nations-FAO fund might be created and supplemented by governmental and non-governmental agencies for the development of local options in the use of the genetic resource and for the long-term development of the resource itself. These could then be integral parts of a larger gene management programme and would fit into an effective system for ensuring genetic diversity.

The issues involved are complex, and the difficulties in fine-tuning any broad programme proposal are substantial. Nevertheless, there seems to be substantial room for agreement on a global policy towards the development of the genetic resource.

We have the opportunity to make much progress while protecting the interests of the powerless in present and future generations. Can we afford to do less than to seek just agreements?

Part two

Three types of genetic management

1. Management for commercial development

In this article the term "commercial" is not meant to distinguish between capitalist and socialist economies or between market and peasant exchange values. Its function is rather to indicate the status of various species as resources that return direct value on some form of investment. Value may come from the sale of a highly manufactured forest product or from direct consumption of fuel. The concept encompasses values that may be measured differently by different managers. In the analyses that are envisioned, indirect effects of forestry practices on soil, water or socio-economic consequences are not considered as commercial returns.

The commercial objective of breeding is to produce a genotype or set of genotypes that will return an economic yield sufficiently higher or more assured than the current level of yield to satisfy management's definitions of "good". This definition is solely in terms of the manager's organization, and the interests of outsiders and of the resource itself may be ignored. The "manager" involved can be a private owner or a stockholder in a private corporation, or just as easily a peasant in a developing nation. The only requirement of this manager is the investment of personal time, effort or capital with the expectation of some economic return.

Breeding theory. The typical forest tree-breeding operation includes a finite number of selections (from 10 to 300) made from a population that usually contains more than a few thousand individuals. General yield improvements are thought to be caused by many different genetic "loci", or by genes within a chromosome. Each locus may have several "allelic" variants of a given gene. Increases in, for example, the quantitative yield of wood from a species are thought to be a consequence of an accumulation of alleles positively affecting this characteristic; such alleles can occur at many different loci. In forest trees, where clear estimates of single gene effects are difficult to obtain, it may most generally be necessary to treat inheritance as a quantitative phenomenon. In any case, the assumption is usually made, and often borne out, that careful selection results in heritable improvement in the next generation. Hence, the focus of research in tree-breeding has been on obtaining precise estimates of the breeding quality of potential parents and on developing several aids to selection. In the initial generation, several source populations are often screened and the best of these used as the initial population.

In subsequent generations, the breeding population is effectively closed. Even if the initial selections were numerous, it is naïve to assume that the effective population size will remain large. In general, commercial breeding can be expected to reduce drastically the effective population size. In spite of the best intentions to maintain a large base population, a corporate tree breeder may find that the immediate gain achievable by using, for example, the five best rather than the 10 to 20 best parents outweighs the long-term risks of loss of genetic variance. This is true for simple recurrent selection programmes as well as for any hybrid recurrent selection programmes.

Reduced population sizes, in addition to inbreeding depression, cause a loss of genetic variability and a consequent loss of the ability to

respond to shifts in selection objectives. These are related to shifts in economic or management objectives or to changing requirements for ecological adaptability. Reduced effective population sizes also reduce the ability of populations to respond cumulatively to reiterated selection pressure, or to reverse selection. The problem seems less acute than when applying new selection to an entirely independent trait. The loss of genetic variation also precludes selecting for qualitative trait genes if they were lost from the breeding population, and precludes the possibilities of selecting for new environmental response functions or resistances if that variability is lost (Dudley, 1977).

One answer to reduced breeding population size is maintaining a hierarchy of relatively large, less highly selected populations (Kammenberg, 1984). For agronomic crop plants, this approach requires large pools of unimproved varieties and source collections and perhaps one or two large populations that are partially tested and selected for some levels of adaptability. From these more or less enhanced populations, breeders can develop commercial varieties. These processes, however, are often difficult, expensive, and time-consuming (Stuber, 1978), and in forest trees they may only involve one base level of selected populations (Namkoong et al., 1971). However, owing to the nature of tree-breeding operations, such base populations would be useless unless substantially improved and, if substantially improved, might better be bred selectively in multiple populations for useful diversity (Namkoong, 1984c).

Breeding in multiple populations for genetic diversity is also potentially useful for traits where the adaptability of individual trees is not infinite and there is a range of economic or environmental variability (Namkoong et al., 1980). When breeding base populations for immediate commercial use, it is theoretically more cost-effective to improve yield or value in different populations that are adapted to different environments. By applying simple breeding procedures within each, an adaptable array of foundation populations can be developed as easily as a single large hierarchical base population, and the resulting array is more readily incorporated into advanced varieties. Such an array can also serve as part of a gene conservation programme, since intraspecies diversity can be maintained and may often be enhanced (Namkoong, 1984a).

Either of the above methods permits use of advanced biotechnology, including cloning and gene transfer. Tissue cultures or other clonal material can be generated as easily in population arrays as in single breeding populations. Thus, cloning does not directly affect the gene management programme. It is merely a special way of using the end-products of the programme.

Similarly, controlled gene transfer need not alter gene conservation programmes, though it would certainly alter the breeding programmes themselves. At the moment, there are many obstacles to the use of gene transfer, but it is theoretically possible to transfer an operational gene from one organism to another. It is also theoretically possible to alter such genes if enough is known about them. Eventually, after a long period of rather tedious experimentation, gene exchanges may become feasible.

However, problems remain in the use of this technology since we must still know far more than we do now about specific genes and the alleles we wish to transfer. Genes capable of causing qualitative changes must be structured simply enough to be transferable and to be able to operate in the host genotype with the desired effect. Therefore, as in traditional breeding with single gene traits, we are limited to those few genes about which we can develop some clear idea of qualitative effects. Since gene exchanges allow otherwise impossible transfers and potential alterations, it will undoubtedly expand our vision of what it is possible for single genotypes to do; it will also be of direct commercial value; and it will teach us about inheritance. At this time, however, it can be viewed only as an intriguing supplement to traditional breeding methods of gene management (Sederoff et al., 1985). Certainly, we cannot rely upon direct gene transfer as a usable technique for gene conservation any time soon.

Managing breeding populations. Obviously, all breeding methods require greater investments than those needed to manage an unimproved forest. A breeding programme can involve elaborate testing, estimation and breeding for different kinds of gene effects for several different commercial objectives in several different geographical areas. However, it is also possible to scale operations down to very simple systems that produce some genetic gain in the short run - within one or a few generations. In a breeding programme with no testing and no base populations other than the commercial one, genetic variation is lost rapidly and only additive gene effects for, for example, general average growth in one kind of environment can be exploited. In elaborate breeding systems, far more flexibility is created, and information is generated to improve future gains, without loss of genetic variation. Various levels of compromise exist between these two extremes. Each agency thus requires a decision-making strategy for each species concerned. When only one species is involved, the allocations involve choices of the number of populations to develop, their size, range of adaptability, etc.

Agencies could organize affordable long-term development programmes for the various subpopulations and consider the collection of breeding populations a metabreed with the objective of ensuring the overall utility and improvement of the species (Namkoong, et al., 1980). However, for multiple species programmes, an allocation of effort among them must be determined. For commercial needs, it is unlikely that all species would be of equal importance, and for biological potential it is unlikely that all species would be equally likely to generate gains. Therefore, to maximize commercial profit with finite resources, particular sets of traits in particular sets of environments for a limited array of species could be programmed. For example, Ohba (1984) proposes to subdivide Japan into zones with different sets of priority selection criteria that dictate the intensity of breeding to be followed.

Assuming that some method of allocation is chosen, each agency is likely to derive a list of species, each with a different assigned priority. Many agencies will probably arrive at a highly skewed distribution of effort with one species developed intensively in many multiple populations and all the rest relegated to the simplest level possible. Even if several species are given some attention by several different agencies, it is likely, even considering those species at present commercially useful, that many of them will not be bred intensively by any one agency. These species may therefore never be developed as a collection of populations in a cohesive metabreed. Almost all of the commercial angio-sperms and the fire, the larches, the cedars and most pines of North America fall into this category of moderate neglect. For such species, interagency efforts may be required to conserve and deve[illegible]ulations in low-intensity programmes to enh[illegible]ir potential use for future generations.

While some commercial species can be expected to be well developed, either within government or private organizations or by efforts such as the International Union of Forestry Research Organizations working parties, many commercially useful species will not. Future users of forests will likely find that opportunities for enhancement were lost, and that the genetic resource was eroded to some extent. In North America, Europe and East Asia, the main problem is expected to be the lack of enhancement programmes while elsewhere both conservation and enhancement programmes are underfunded.

Unfortunately, there is no general forum in which to discuss a global strategy to identify species that can be safely neglected. Hence, there are no rational choices being made for an optimum programme of research and development except the present, narrowly contained economic criteria. Recommendations of the Panel of Experts on Forest Gene Resources, an FAO statutory body meeting every three to four years, include lists of priorities by region, species and operation; this is a useful first step in identifying global priorities for action.

2. Management for potential commercial use

There are generally good biological and economic reasons for the primary commercial species to occupy our immediate interest and for us to devote major efforts to improving species that are already economically and ecologically well adapted. Nevertheless, as product requirements and the physical and biotic environments of forests change, it is not unreasonable to expect that the list of commercially important species will change. In the United States, for example, a small change in wood prices, or in the location of commercial forestry sites, or in planting techniques, could make some species of Alnus, Prunus or Quercus much more likely candidates for commercial development. The need for reserve or substitute species and varieties as a safety net is obvious. This need becomes more critical as the genetic base of the primary varieties narrows. There are, of course, abundant examples in forestry around the Pacific Basin and from North America and Europe where native species are displaced by other commercial species, populations or provenances.

Testing has been extensive for some species, and trials will undoubtedly continue to be established. The objective of most of these past trials has been to replace whole populations or species with others that better meet present-day needs. They are, however, similar to tests designed to evaluate specific traits of populations for possible back-crossing or gene transfer of given traits into established varieties or populations. These trials often have two principal objectives: (1) discerning and sampling the distribution of genetic variation; and (2) analysing and discriminating useful differences between genes, individuals or populations. These two objectives are discussed below.

Genetic variation. The first objective is to understand the present distribution of genetic variation produced by the combination of natural forces and human activities. Fundamental questions need to be answered about the structure of species, the ways in which different genes and gene combinations may be common in some areas and rare in others, and the extent to which such patterns are related to the species' survival strategy. A few species such as Pinus resinosa contain relatively little genetic variability; samples from adjacent trees or from different ends of the distribution of the population are alike (Fowler and Lester, 1970). Most tree species, however, seem to contain high levels of genetic variability, of which the proportions located within stands are great - at least in relation to most other plant species (Hamrick, 1983). However, it also seems that there are finely tuned heritable adaptations to environmental gradients even in species such as Pseudotsuga menziesii (Campbell, 1979) which generally do not display much discernible variation between stands (Yeh, 1981). The lack of high genetic variability among stands therefore does not necessarily indicate the absence of genes that confer special adaptations. Furthermore, there is substantial evidence of significant levels of differentiation among conifers in Europe (Muhs, 1981) and in Japan (Sakai et al., 1974).

One of the problems we have in studying the existing levels and patterns of allelic distributions is that we can sample populations only within a very narrow slice of time. While the changes in forest gene patterns that influence adaptability may take many years and several generations to equilibrate, studies of gene variations have generally been limited to one or two decades and often to samples from one or two years. Longer patterns of generational changes in stand structure are easy to miss with limited sampling. Thus, the pattern of allele dispersal sampled in eastern North American forests, for example, may reflect only the dispersal conditions extant at the time of stand establishment; they may reflect the socio-economic milieu of the 1930s and 1940s more than any biological steady-state condition. Humans may strongly influence the genetic structure of forest trees directly by selection effects and indirectly by changing pollen and seed dispersal and seedling densities. Thus, as detailed elsewhere (Namkoong, 1984b; 1985), the genetic dynamics of our forest species may be undergoing substantial changes, and it is not at all clear that even the temperate conifer species are at present in a steady state. For example, in Pinus taeda (Roberds and Conkle, 1984) and Pinus sylvestris (Tigerstedt, 1984), the populations are not in equilibrium. Similarly, in southern pine beetle (Dendroctonus frontalis Zimmermann), the populations are not at a stable equilibrium (Namkoong et al., 1979). Furthermore, if tree species are in a state of transition, so too are associated species as well as their pest and pathogen populations (Namkoong, 1983). It is especially important for us to recognize that states of disequilibrium may have been caused by human impacts on the genetic structure of interacting species. As a result, we must exercise caution when extrapolating from present conditions to any assumptions that the present population structures are optimal, equilibrium states.

For tropical species, with more complex and restricted reproductive modes (Stern and Roche, 1974) and more complex stand structures (Ashton, 1976; Bawa, 1976), ecological and genetic structural complexity may be important for species adaptability and continued evolution. Forest populations may have evolved in the tropics with fine, stable subdivisions of populations. Temperate forests, while not stable, may be adapted to wide variations on population size and distribution. In the tropics, however, multiple small populations appear to be the normal structural mode for tree species, perhaps buffering species against pathogen epidemics.

A problem in using such species is our nearly total ignorance of their genetic structure. In the absence of knowledge of the coevolution of competitors, pests and pathogens, it is necessary to save a greater diversity than may be ultimately needed until such variations as may be redundant can

be safely eliminated. Thus, the first objective of provenance trials is the study of natural population structures.

Useful populations. The second objective of provenance trials is to identify populations for use. It does not necessarily conflict with the first objective - understanding the distribution of genetic variation - but it is oriented towards practical breeding decisions about initial gain and immediate gene conservation. Assuming that we know what traits or genes are desirable, the direct problem is to estimate the probability that a resampling will achieve sufficient additional gain to be worth the attempt to find such better populations. We must feel not only that such populations exist but also that the tests are designed to locate and sample better populations in a timely manner. If there is little evidence of large population differences, little benefit will result from new population samples (Namkoong, 1978). Similarly, even if differences do exist but are random with respect to any measurable feature of the environment, we will have little chance of directing a population search with a reasonable probability of achieving additional gain. Furthermore, any expected gain from population reselection may not equal the gain achievable by ordinary breeding with previously established breeding populations. However, until the distribution of alleles for all traits of potential value is known, we cannot know the costs of forgone opportunities to incorporate particular traits or levels of trait performances.

Hence, the search for populations useful as sources of genes for producing subsets of desired traits is directed toward finding genetic variation. The design and analysis of such tests require no new statistical theory: multiple regression techniques can be extended to multivariate analysis (Namkoong, 1967). For these purposes, several regression variables can be identified as causal variables or variables useful for identifying the location or identity of populations. The analysis of association between a dependent response variate, such as growth, and independent variables, such as altitude of origin, is then carried out with several response variates as well as with the correlated relationships among the variates. It can then be determined whether variations are other than random, and the size and utility of those variations can be estimated for any single trait or combination. In this way, we can determine the usefulness either of any previously sampled population or of unsampled but potentially usable populations.

Advances in the design and analysis of such tests have made the achievement of these objectives attainable in moderate-sized plantings. However, for pests and pathogens, which can evolve relatively rapidly, estimates of types and effects of resistance have to be made within the context of their population and their evolutionary dynamics. Testing and estimation procedures for them differ from those for responses to physical environmental variables. Testing is directed to discerning genetic variations in forms of resistance or reaction phenomena. Dynamic analysis is then required to predict the effects of introducing resistance types into a forest ecosystem.

Similar testing procedures are needed to conserve and develop agronomic species and varieties not currently in commercial use. Often, little is known of the present or natural distribution of traits or alleles, of the location of potentially useful populations, or of especially useful trait expressions. Therefore, studies of wild relatives of crop plants are directed to understanding the evolution of the crops and to finding sources of genes for introduction into commercial varieties. The ecogeographic studies of non-commercial varieties are directed primarily to finding genes that may be useful in established varieties and in new breeding populations. For many of these crop species, with their short breeding cycles and long histories of breeding, concern has focused on preservation. Once endangered sources of germ-plasm are secured, geneticists trust that the testing and enhancement stages of selection can be carried out at some leisure. The organization of such programmes is not well defined or fixed (Kannenberg, 1984), and the difficulties of breeding and back-crossing are not trivial (Frey et al., 1984). Nevertheless, I believe that success will be achieved. Thus, while specific breeding techniques and the organization of breeding populations may differ (Namkoong, 1984c), the problems in testing tree and agronomic crop species are similar for species or varieties not currently in commercial use.

Two kinds of programmes are needed to realize the potential value inherent in preserved secondary populations: testing, and development. Testing is generally required to judge inherent capabilities; the testing efforts needed are those outlined above for provenance testing. The developmental or enhancement efforts are those outlined for the creation of hierarchical or multiple populations.

The source materials for testing and development must be some ex situ or in situ sample of the available gene pool. As a minimum, such a sample must be large enough to have a reasonable chance of saving the useful genes. Even with the best sampling efforts, however, this minimum may miss many alleles if they are present only in small quantities at the time and in the place where the sampling is done. That is why it is so vital to determine patterns and structures of variation. To reflect the structural diversity which may exist in populations, samples are needed from different areas, stands and individuals. While difficult, such programmes are feasible.

3. Management of non-commercial populations

The vast majority of forest plant species have little recognized current or future commercial value, or no function that is not otherwise served by other species. They may be useful only for some elements of ecosystem stability, or they may be considered to be potentially useful, but only for unforeseen future possibilities. For such species there exists no effective concept of "improvement" for human use. Hence, merely ensuring the continued existence of a sample of such populations or species may be the only management objective. The sample should have some minimum number and a reasonable distribution.

There are at least two reasons, however, for considering somewhat more intensive management than that which is implied only by the need to conserve such species. The first is the direct utility of such populations for the study and understanding of essentially natural population processes. The second is the possibility of uncovering uses at present unknown, such as medicines or insecticides. Since our understanding of the evolution of forest ecosystems, and even of the most valuable commercial species, is so tenuous, there is clear advantage to maintaining at least a sample of the evolutionary system. For species in some rough state of equilibrium, it is important to know if their genetic and ecological features are simple or complex, if viability selection factors or mating habits and fecundity interact to conserve or dissipate genetic variation. If species are not in a stable equilibrium, their ability to return to an original equilibrium or to shift to new equilibria or limit cycles, or to go extinct, is an important consideration.

We would like to know also what features of evolution have conspired to create such stable or unstable behaviour. By learning about the possible behaviour of systems, we can inform ourselves of the possible ways in which the commercial species and forests in general can function. The design of future forests would undoubtedly be better informed and would likely lead to more stable forest ecosystems with populations more broadly adaptable to variable environments. There are, of course, the further benefits inherent in simply understanding how the world really operates, whether this leads to increased human utilization of forests or not.

Other contributions of non-commercial species to ecosystem functioning and stability cannot be lightly dismissed. While highly complex and interdependent webs of association may often be fragile and easily degenerated with high extinction rates of component species (May, 1973), the existence of fragility does not imply that species or systems should be allowed to die. Rather, for our own benefit, we must recognize that the various functions of non-commercial species include the long-term productivity of all other parts of the ecosystem.

The management options for these populations are more restricted than for commercial species and stands. Some form of in situ conservation seems best, even though it may be neither the most secure nor the least costly option. Since species values are likely to be associated with community functions, conservation is perhaps most easily assured by area management as in reserves, parks or natural areas. The requirements of population size and multiple population dispersal remain the same, and since little direct control of each species in any one area can be expected, some redundancy is needed in size of individual populations and in numbers of populations. For species in which population size is a driving factor in evolution, the multiple populations should be of variable sizes. For species that respond to known environmental variables, including the co-evolution of other species, sampling from the range of those variables is an efficient method for capturing significant genetic variability.

For many species, however, even such recommendations are futile, since so little is known of the species distribution or even of their existence. For these, targeted sampling in centres of diversity such as outlined by Pires (1978) may be the only realistic hope of their conservation. Obviously, where known centres of diversity exist within a species, those would be prime targets for sampling. Supplementary sampling from more extreme populations is desirable (Namkoong, 1980). Similarly, we should not rely exclusively on natural reserves in centres of origin or diversity, but should also reserve areas of more extreme habitat for the various biotypes to ensure sampling the genetic diversity of the contained species. There is, in fact, reason to believe that there is a substantial degree of independence between measures of biological diversity and the adaptive variations that exist within species. While certain types of species interaction may tend to increase intraspecific genetic variation (Leonard, 1984); Futuyama, 1983), other types may reduce it. Thus, in order to conserve the viability of an ecosystem and to ensure the availability of genetic variation, the dynamics of species evolution will require multiple population sampling.

Whether we consider a species and its associates to be of commercial value or not, we know that genetic and ecological variations are not likely to be in an evolutionarily static state. While some may have impoverished gene pools, and some may contain all genetic variations within single large populations, most must be considered to be in some transient evolutionary state. Whether they have been stable in the recent past or not, human activities have probably at least changed many of their equilibria. For managers of genetic resources, the goal is not to conserve a static state but to contain a dynamic system, even though our understanding of its dynamics is very meagre.

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