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Vol.1, No. 3, 1994

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UNIDO's *Genetic Engineering and Biotechnology Monitor* is established as a mechanism of current awareness to monitor developments in the genetic engineering and biotechnology sector and inform governments, industry and academia, primarily in developing countries.

The *Monitor* is issued four times a year and distributed free of charge to readers in developing countries. It is not a formal document and has been reproduced without formal editing. Opinions expressed here do not necessarily reflect the views of UNIDO. Mention of the names of firms and commercial products does not imply an endorsement by UNIDO.

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To our readers

The publication of the Genetic Engineering and Biotechnology Monitor was initiated by UNIDO in response to a recommendation by a group of experts that met in Vienna in February 1981 to review the implications of genetic engineering for developing countries. The experts were of the view that genetic engineering and biotechnology hold significant potentials for developing countries and requested UNIDO to collect and disseminate information on technological developments and institutions in this field, for the benefit of developing countries.

The concept of monitoring technological advances as such stems from the Vienna Conference on Science and Technology for Development held in the summer of 1979 and was further considered by UNIDO's General Conferences and the Industrial Development Board, its governing body. Consequently, UNIDO has been engaged in implementing a programme of technological advances in which activities related to genetic engineering and biotechnology form an important part. The aim of this programme is to sensitise developing countries as to the potentials and limitations of technological advances for developing countries and to help them strengthen their technological capabilities, as appropriate.

UNIDO began this task by issuing first the *Microelectronics Monitor* in December 1981, followed by the *Genetic Engineering and Biotechnology Monitor* in February 1982 and later on by the *Advances in Materials Monitor* and the *Marine Industrial Technology Monitor*. Eventually the series will include monitors on high technology spin-offs and on environment technology. The Monitors purport to be no more than bulletins of current awareness aimed at a target audience in industry, government and the scientific and technological community in developing countries. As such, information of potential interest to developing countries is presented without evaluation or recommendation.

In the current global reckoning, investments and technology are viewed in tandem, understandably so because of the intrinsic relationship between these two elements, particularly in the manner in which they influence industrial growth in all countries. For developing countries in particular, investment and technology play a vital role in their integration into the international economy; hence the need for an integrated approach in their efforts to improve investment and technology flows.

It is for these reasons that UNIDO, in responding to the requirements of developing countries, views the need to generate investment flows in parallel with the need to secure technology flows. Readers will notice under the section on UNIDO News in this issue of the Monitor that there is information on one of the Organization's activities in this respect, entitled TECHMART. Within UNIDO's mandate to promote and assist industrial development, the Organization provides a cluster of integrated services that relate to industrial information, technology management, feasibility studies, investment promotion, direct technical assistance and project development and management. TECHMART is an example of such a service.

Through the Monitors, we hope to continue to play a key role as one of the avenues through which access to information, ideas and opportunities concerning technology and investment matters are facilitated. We will indeed welcome contributions and information from readers concerning industrial and technology development projects, government policies and programmes, regulatory issues, environmental issues, and other subjects of relevance.

Malee Suwana-adth
Scientific Editor

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A. NEWS AND EVENTS

UNIDO News

Biosafety Information Network and Advisory Service (BINAS)

Industrial countries have addressed biosafety with a number of regulatory approaches varying greatly in terms of scope and administrative detail. In some cases, regulations have been outdated by current experience with the handling of genetically modified organisms (GMOs) and have resulted in reduced industrial competitiveness. In developing countries, the lack of standards for the development, handling and commercialization of biotechnology products not only compromises human and animal health and environmental safety but, in addition, raises a major barrier to accessing technologies and products.

UNIDO, through the Biosafety Information Network and Advisory Service (BINAS), facilitates regulatory harmonization and thus the flow of technology to the developing world without compromising human, animal health and environmental safety.

BINAS is a technical assistance service providing national authorities with advice on the formulation of biotechnology regulations; it strengthens institutional capability in biotechnology by information support and advanced training in biological risk assessment

The service is a comprehensive data resource for biotechnology regulations, field releases of GMOs and experts. It is accessible via Internet and/or X.25 Public Data Networks.

BINAS facilitates regulatory harmonization by allowing referral to and cross-correlation of existing national regulations and administrative procedures, thus simplifying identification of regulatory conflicts. As such, it provides a decision support environment for the formulation and/or refinement of biotechnology regulations. It strengthens institutional capability through information support, advisory services and training in risk assessment methodologies.

The service is cost-effective. It builds on established UNIDO services, such as the Referral Database on Energy and Environment (REED) and the Industrial and Technological Information Bank (INTIB). Integrated with the research, training and infrastructure support services of ICGEB, it goes a long way towards meeting some of the major objectives of Agenda 21, Chapter 16 of the Earth Summit on "environmentally Sound Management of Biotechnology".

BINAS strengthens institutional capability in biotechnology and at the same time provides an industrial service. It helps industry identify regulatory trends worldwide, reach competent regulatory authorities directly and partake in the regulatory harmonization.

UNIDO was the first amongst the UN agencies to promote biotechnology and take active steps to strengthen the capability of developing countries in gene technologies through the establishment of the International Centre for Genetic Engineering and Biotechnology (ICGEB). In parallel, realizing that regulatory issues play a key role in the dissemination and commercialization of biotechnology, UNIDO as early as 1984 took the initiative of forming a UN Interagency Working Group on Biosafety. The group, comprising UNIDO, the United Nations Environment Programme (UNEP), the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO), endorsed in 1991 an International Voluntary Code of Conduct for the Release of Genetically Modified Organisms into the Environment.

Information support includes:

Databases of:

- National biosafety regulations/guidelines;
- Experts in risk assessment and evaluation;
- Addresses and regulatory mandates of national authorities;
- Field releases of GMOs.

Interactive tools for:

- Molecular sequence and bibliographic databases;
- Electronic mail and bulletin board services;
- Access to other relevant biotechnology information resources.

Extension services:

- By designated National Network Nodes (NNNs).

Human resource development—Training in:

- Risk assessment methodologies for releases of transgenic organisms; information requirements for field trials and commercialization of GMOs; data access and management.

Expert advice—To Governments:

- What are their regulatory options; what are the institutional requirements to monitor compliance with regulations; how to set up Institutional Biosafety Committees; what needs to be known for issuing commercialization permits for biotechnology products;

To institutional biosafety committees:

- What procedures to follow; how to gain data access.

To industry:

- What is required to obtain permits for field trials and commercialization of transgenic products.

The BINAS information resource is totally unbiased. All database entries are primary material from original sources. Data are regularly updated and validated by dedicated BINAS national and/or regional network nodes (NNNs). The system design is modular permitting expansion to cover country-specific information on intellectual property legislation, available technologies, products and venture capital. NNNs serve as referral points for general information on biotechnology in their respective countries and regions.

BINAS is guided by an international Steering Committee. It does not provide advice on individual field releases and commercialization of transgenic products.

Network access information is available from: the United Nations Industrial Development Organization (UNIDO), Biotechnology and Genetic Engineering Unit, Vienna International Centre, P.O. Box 300, A-1400 Vienna, Austria. Tel. 43-1-21131 Ext 4336; Fax 43-1-230 7355.

Meeting on biotechnology regulation: Towards the establishment of intergovernmental co-operation in Central and Eastern Europe

The increasing demand for industrial and environmental applications of biotechnology in Central and Eastern Europe and the almost total lack of regulatory oversight capacity requires urgent measures aimed at facilitating indigenous industry and promoting the transfer of genetic engineering technologies.

The Biosafety Information Network and Advisory Service (BINAS) established by UNIDO with the support of the International Centre for Genetic Engineering and Biotechnology (ICGEB) has been requested by government authorities in Central and Eastern Europe to convene a meeting with the objectives of capacity-building for regulatory oversight of biotechnology-derived products at the national level; harmonization of biotechnology regulations and implementation of an information exchange system at the regional level; and the establishment of a regional biotechnology forum mandated to monitor international developments and interact with respective supranational organizations.

Participants at this meeting, which will be held at UNIDO Headquarters in Vienna on 22 and 23 September 1994, will be from Bulgaria, the Czech Republic, Hungary, Lithuania, Poland, Russian Federation, Slovenia, ICGEB and UNIDO, with invited observers from Austria, Agriculture Canada, Environment Canada, European Commission, Germany, Switzerland, EPA, USDA, OECD, SAGB, IBF and GIBiP.

The meeting will review international regulatory frameworks and their potential adaptability to the situation in Central and Eastern Europe and ways and means of formalizing relations with established intergovernmental bodies dealing with biotechnology regulation. A review will be made of the status of biotechnology regulations in the region, as well as consideration of the industrial sectors to be covered under regional cooperation (e.g. environmental, industrial, agrifood biotechnology, etc.).

Also to be covered are regional notification schemes and information exchange with a review of established systems (e.g. mandates, operational modalities, potential to cover needs in the region). The need to obtain intergovernmental endorsement of a regional information resource will be considered.

Based on consensus conclusions, a workplan will be defined leading to the preparation of a detailed report to inform Governments of the need, merits and operational modalities of an intergovernmental group dealing with biotechnology regulations.

Techmart

After its successful beginning in China in December 1991, Technology Market (Techmart) was held in Zimbabwe and India in 1992 and 1993, and is to continue in up to two different locations each year. For 1994 Techmart is planned for Viet Nam in November and India in ....., which will be concentrating more on the investment side of TT.

Techmart is a business forum where the rights to manufacture and upgrade existing products and processes can be bought and sold through direct contacts between technology seekers and technology suppliers from developed and developing countries, with special emphasis on the needs of small- and medium-scale industries (SMIs).

The rights offered may cover machinery, tools, patents, designs and the use of recognized trade marks and names to promote the business, or it may involve finding a source of expertise, investment opportunities and capital to stimulate business activity. The technologies for sale will include both well-tried and newer technologies, especially where their application may bring economic or environmental benefits or improve the quality and acceptability of a product or process.

Techmart, which is specifically aimed at the needs of SMIs in developing countries, also serves to market the technologies produced by SMIs themselves. It is a unique forum organized by the United Nations Industrial Development Organization (UNIDO) and associated national development authorities and financial institutions, with the assistance of consulting firms specializing in technology transfer. The experience gained in many developing countries, through modifying and adapting technologies to suit local conditions, has resulted in the creation of many sources of low-cost but well-tried systems of manufacture that closely match the needs of entrepreneurs in developing countries.

Techmart permits the display of technologies by means of sample products, drawings, process flow diagrams, photographs and product catalogues covering various industrial sectors. A comprehensive, indexed compendium of the technologies offered and requested by companies and organizations world-wide is always available in advance of the event to enable potential customers to select and compare technologies of interest. The entrepreneur who purchases this compendium of technologies and examines its contents before attending Techmart may be able to transform his or her business to achieve faster growth through technical collaboration arrangements. Expert legal advice on technology acquisition and the negotiation process, one-to-one prearranged business meetings, plant visits and seminars on emerging technologies and the UNIDO technical assistance programme are essential components of each Techmart.

Techmart is aimed at the business person, the manufacturer and the buyer or seller of technology who wishes to generate productive new business. It represents an important opportunity for technical universities and research institutes to seek outlets for the results of their work and to identify new areas for research and development. Techmart will also able them to highlight their ability to provide training resources needed by industry. Investors should likewise attend Techmart to promote their interest in financing new business opportunities. Manufacturers' associations, trade associations, chambers of commerce, development banks and agencies and national governmental organizations responsible for implementing economic, industrial and technology policies should attend Techmart

together with leaders in the development of new and existing manufacturing operations in their own countries.

Techmart is a meeting place where technological resources and the latest developments in manufacturing industry are brought together and new business opportunities are offered to the leaders of manufacturing businesses in both developed and developing countries. It provides a unique setting for the conclusion of practical business arrangements focusing on technologies and including the financial, legal and investment advice required to produce a powerful solution to technical and entrepreneurial problems. More than this, Techmart is the only event that enables entrepreneurs to identify required technologies before deciding to attend. To facilitate the process of matching technologies with needs, UNIDO compiles and publishes a technology compendium that describes thousands of technologies currently available for transfer to developing countries. Technologies may be offered and requested by completing the attached compendium entry forms. A copy for dispatch immediately on publication can then be purchased to enable the entrepreneur to indicate which offers or requests he or she would like to discuss at the Techmart.

Companies and organizations offering licensing opportunities may reserve an exhibition booth at the Techmart to display their technologies by means of sample products, drawings, process flow diagrams, photographs and product catalogues. The normal sizes of the display booths are 6 and 9 square metres, and the cost of renting a booth is quoted on each Techmart leaflet, which will be forwarded upon receipt of the attached order form, duly completed.

Companies, organizations and individuals seeking technologies or partners for cooperation may register their interest in Techmart. Potential visitors can order and pay in advance for a copy of the technology compendium by using the attached order form. They will be dispatched by airmail prior to the event.

Purchasers of the technology compendium will be encouraged to visit Techmart and to participate in the seminars on technology transfer, industrial cooperation and emerging technologies that are scheduled to take place at that time.

Attendance at Techmart will generally be at the participants' expense. However, UNIDO may offer limited financial assistance to selected entrepreneurs from developing countries to attend Techmart, provided they initiate business contacts with technology suppliers and requesters before the event, and can show a serious interest in cooperation by meeting the concerned parties at Techmart. Similar assistance may also be sought from the development banks, industries and international, regional and national development agencies willing to sponsor participation in Techmart.

Offers of, and requests for, technology may be submitted by companies, organizations, exhibitors, visitors and others for inclusion in the technology compendium (entry form attached), which will contain only entries that describe a specific product or process. General offers of service, manufacturing, consultancy etc. will not be included. Each entry should clearly describe what is being offered, its potential uses and the claimed advantages.

The assistance rendered by UNIDO during Techmart will enable entrepreneurs to select and compare alternative technologies offered by developed and developing countries to improve or refine products and processes in various industries to meet specific technological needs.

As a condition of participation in Techmart, detailed information on the results of contacts made through Techmart must be submitted to UNIDO to enable it to plan and provide follow-up project support.

Subject to the availability of funds, follow-up assistance to Techmart participants may include prefeasibility and feasibility studies for selected projects, continued expert advice on technology negotiation and the investment process, identification of high-level technical expertise for projects, as well as agency support for project implementation and equipment procurement. On the basis of specific requests for follow-up assistance, the involvement of other UNIDO departments may be required to satisfy demand and to ensure cost-effective project implementation.

Further Techmart are planned for 1995 in Lusaka, Zambia in March or April, and Sao Paulo in November. More information about Techmart events may be obtained from: Technology Service, Investment and Technology Promotion Division, United Nations Industrial Development Organization (UNIDO), Vienna International Centre, P.O. Box 300, A-1400 Vienna, Austria. Fax: 43-1-232156 or 2307584; Telex: 135612 uno a; Tel.: 43-1-21131, Ext. 3693; Cable: unido vienna; E-mail address: GE QUIK-COMM:AAQ001IB@UNIDO.

Viet Nam Techmart '94

Since 1986, when Viet Nam began an ambitious reform programme, the country has been making a steady transition from a centrally planned economy to a market-based system. The main elements of this reform include opening the economy to foreign investment and technology and encouraging the development of the private sector; the equitable distribution of wealth and income; and rural reforms.

UNIDO, in cooperation with Viet Nam's Ministry for Science, Technology and Environment (the National Centre of Science and Technology Information and Documentation), is organizing VIET NAM TECHMART in Hanoi from 1 to 4 November 1994.

At VIET NAM TECHMART technologies will be displayed by means of sample products, drawings, process flow diagrams, photographs and product catalogues. The following industrial sectors will be represented:

- Food processing, including food preservation;
- Light industry (plastics and textiles);
- The electronics industry (microcomputers, electronic equipment and household electrical appliances);
- Chemicals and pharmaceuticals;
- Advanced materials.

The business opportunities available at VIET NAM TECHMART will be of interest to individuals and organizations, such as:

- Manufacturers, buyers and sellers of technology;
- Manufacturers' associations, trade associations, chambers of commerce;
- Investors;
- Development banks and agencies;
- Technical universities and research institutes.

Companies, organizations and individuals looking for technologies or offering partnership for cooperation can register their participation in VIET NAM TECHMART. The programme will include technology displays; pre-arranged business meetings, plant visits, technology information, negotiation and acquisition seminar; seminar on technology legislation in Viet Nam; advisory services on technology negotiations and sectoral seminars.

More information about VIET NAM TECHMART may be obtained from the Technology Service, Investment and Technology Promotion Division, UNIDO, Vienna International Centre, P.O. Box 300, A-1400 Vienna, Austria. Tel.: 00431 21131 ext. 3693; Fax: 00431 232156 or 2307584; Telex: 135612 uno a; E-mail: EARN:S568568@UNIDO1.BITNET

A few examples of technologies offered and requested by participants in VIET NAM TECHMART are described below.

Offers

BACTERIAL INSECTICIDE PRODUCTION—This bio-insecticide is based on local materials and *Bacillus thuringiensis var. Kurstaki 3a, 3b.* The insecticide, code named "BIOTOX", has been successfully and widely used to control lepidoptera in several Vietnamese provinces. It can be kept at room temperature for 6-12 months. Ecologically clean technology. Production capacity is 100 tons per annum. The technology is commercialized and is offered for manufacture under licence or joint venture.

PRODUCTION OF GLUCOSA from starch derived from cassava, maize, rice or potatoes using enzymes from *Bacillus subtilis* and *Cispergilbus sp.* The glucosa produced possess the foliowing properties: moisture, 8 per cent; reducing sugar, 96 per cent; ash, 0.06 to 0.08 per cent; anpha, D:52:53. The technology is at the laboratory stage and is offered for manufacture under licence.

LYSINE PRODUCTION—The technology of lysine production is based on main raw materials such as molasses, peanut cake and urea. Through the activity of certain bacteria isolated by the Food Industries Research Institute, lysine is produced. Simple process and equipment. The technology is commercialized and offered for manufacture under licence.

Details available from: Dr. Ngo Thi Mai, Director, Food Industries Research Institute, Km. 8, Nguyen Trai Road, Hanoi, Viet Nam. Tel.: 844 244318/244551; Telex: 411417 UNDP VT.

HIGH YIELD GLACILARIA CULTURE—Appropriate technical methods of high yield glacilaria cultures such as breed choice technique, pool size, culture, cultivation, protection from wild water plants and the creation of suitable environment for growth acceleration. Raw materials: glacilaria breed, cattle manure, urea fertilizer, phosphate fertilizer and lime. Production capacity is 2-4 tons of dried glacilaria per year. The technology is available and commercialized, and is offered for manufacture under licence; training and technical assistance is available.

Details available from: Dr. Nguyen Xuan Ly, Deputy Chief of Algae Department, Institute of Sea Product Research, 170 Lelai Street, Hai Phong, Viet Nam. Tel.: 84-31-46656

PRODUCTION OF SPIRULINA PLATENSIS FROM WASTE WATER OF BIOGAS HOLD—Technology includes the tank system where waste water and gas from the biogas hold are collected, treatment, algal tank, harvesting and processing for animal feed (pigs, chicken, fish and shrimp). Also extraction of algae for medicinal purposes. Ecologically clean technology. Production capacity: 300 kgs per year. The technology exists in the form of a working model which is available and commercialized and is offered in the form of a turnkey operation.

Details available from: Dr. Dinh Van Sam, Head of Environment Technology, Hanoi University of Technology, 1 Daicoviet Road, Hanoi, Viet Nam. Tel.: 844-291466.

Requests

PRODUCTION OF HORMONE LH-RH STIMULATING ARTIFICIAL REPRODUCTION OF FISH—Production of LH-RH (luteinizing hormone-releasing hormone), which stimulates the process of the maturing and dropping of ova in fish. LH-RH is used for substitution of hypophysis and makes the initiative in fish breeding. The technology sought should be in production and already on the market. Sought is a partner for joint venture, training, design, formulation and technical assistance.

The request for technology comes from: Dr. Nguyen The Anh, Director, National Aquaculture Service Company, NASCO, 57 Ngoc Khanh, Ba Dinh, Hanoi, Viet Nam. Tel.: 844-243186, 243190.

FRUIT AND VEGETABLE PROCESSING—Technologies for processing of mushrooms, various kinds of tropical vegetables and fruits that are abundant in Viet Nam. The technology should include freezing, canning, or drying and dehydration. The products must be of high quality for export. Estimated capacity 3,000-5,000 tons of product per year. The technology should already be on the market. Sought is a joint venture partner, turnkey operation and production equipment.

The request for technology comes from: Dr. Tran Quang Nhung, Tan Binh Foodstuff Export Factory, 1/1 Cach Mang Thang 8, Dist. Tan Binh, Ho Chi Minh City, Viet Nam. Tel.: 848-643042/645900; Fax: 848-640291.

AQUATIC PRODUCT FREEZING EQUIPMENT for processing of marine shrimp and Japanese shrimp using the IQF method. Product should have high grade quality and be suitable for supermarkets. The technology should already be on the market. Turnkey technology and joint venture sought.

The request for technology comes from: Dr. Tran Van Con, Director, Ben Tre Frozen Aquatic

Products Export Company, Tan Thach, Chau Thanh, Ben Tre, Viet Nam. Tel.: 84-0175-60261/60265; Fax: 84-0175-60346.

UN and other organizations' news

New industry group for in vitro testing

An "Industry Platform" has been established in the area of *in vitro* pharmacotoxicology testing. The primary purpose of the group will be to benefit from the results of two new large EC R&D projects on developmental and immunological *in vitro* toxicity tests. The group will also have a role in advising on future EC R&D in this area. The new "*in vitro* Testing Industry Platform" (IVTIP) was established on 1 December in Budapest at the initiative of ACTIP, an industry platform set up in association with the EC research activities in Animal Cell Technology. The meeting which formed IVTIP was attended by companies from the chemical, pharmaceutical and cosmetic sectors.

IVTIP is actively seeking further members for the group. A second meeting to formalize IVTIP and elect its officers was planned to be held in Dublin (Ireland) in early 1994.

Further details on IVTIP can be obtained from: Dr. Helma Hermans, IVTIP Secretariat, Scientific Writing & Consultancy, P.O. Box 23 161, 3001 KR Rotterdam, The Netherlands. Tel.: (31) 10 4 36 37 35; Fax: 10 4 36 10 04. (Source: *Irish Biotech News*, January 1994)

New biotherapeutic contract development association

Four British companies offering contract development services—Huntingdon Research Centre (HRC), Q-One Biotech (formerly Quality Biotech Ltd., Kent and Glasgow, UK), M-Scan (Sunninghill, Berks., UK) and Leicester Clinical Research Centre (LCRC)—have formed a marketing association to offer integrated services to the world-wide biopharmaceutical industry.

Cell-bank characterization, product purity testing and production-method validation will be conducted by Q-One Biotech; product integrity by M-Scan; preclinical safety testing by HRC and Phase I and II clinical testing will be covered by HRC's sister company, LCRC.

"Project management will play a vital part in the service, especially where clients wish to place whole packages or work with the association", says Malcolm Brattle, director of Q-One Biotech. "This should allow the design of an integrated package and efficient and easy contract monitoring by the client." (Source: *Genetic Engineering News*, 1 January 1994)

A CBDC programme for Africa

The Community Biodiversity Development and Conservation Programme is an (initial) four-year enterprise which began in January 1994, linking formal research institutes with farmers' organizations, and NGOs to conserve and enhance germplasm within communities. In Africa, PGRC/E acts as regional coordinator with the first projects being in Ethiopia, Sierra Leone and Zimbabwe; and others expected shortly from Kenya, Botswana, Mali and Côte d'Ivoire. About US$1 million is earmarked for the African work over the four-year period. The donors include DGIS, IDRC and SIDA. (Source: *African Diversity*, No. 8. February 1994)

New directions for biotechnology at the OECD

For more than a decade the OECD Group of National Experts for Safety in Biotechnology (GNE) has worked to establish the scientific concepts and principles that underlie the safe development and use of biotechnology. Its work has been internationally recognized as outstanding. The principles it has developed have been adopted world-wide as the conceptual basis for safety assessment.

Its work done, the GNE held its final meeting in January 1994. It will be succeeded by a group focused on science, technology and innovation policy issues in biotechnology. The application of the safety principles it developed will become the province of OECD sectoral committees that deal with specific product categories, such as agriculture or environment.

The booklet *Biotechnology in the OECD Committee for Scientific and Technological Policy: Evolution and main events 1980-1993* is an excellent summary of the work of the GNE and a guide to the complex OECD committee system. The OECD has published a long series of useful documents on biotechnology that have been prepared by or for the GNE. The following is a list of the most recent releases:

- Safety Evaluation of Foods Derived by Modern Biotechnology: Concepts and Principles (1993);
- Field Releases of Transgenic Plants,1986-1992: An Analysis (1993);
- Safety Considerations for Biotechnology: Scale-up of Crop Plants (1993) B;
- Traditional Crop Breeding Practices: an historical review to serve as a baseline for assessing the role of modern biotechnology (1993);
- Aquatic Biotechnology and Food Safety (1994).

OECD publications are available from: OECD Publications Service, Chateau de la Muette, 2 rue André-Pascal, F-75775 Paris, CEDEX 16, France. (Source: *Australasian Biotechnology*, Vol. 4, No. 1, February 1994)

OECD: transgenic trials up

The number of field trials of transgenic plants approved by members of the Organization of Economic Cooperation and Development (OECD) nearly doubled each year between 1986 and 1992. The US leads the way, having completed 492 trials, followed by Canada with 302 trials, the UK with 122, France with 117, and Belgium with 89. About 40 per cent of all trials involved plants modified to tolerate weed-killers. (Source: *Chemicalweek*, 9 February 1994)

Bamboo and rattan network

A new International Network for Bamboo and Rattan has begun operations. The network grew out of projects funded by the Canadian International Development

Research Centre (IDRC) in South-East Asia and Africa. The UN International Fund for Agricultural Development (IFAD) is also supporting the new initiative. The network provides regional coordination for research and offers information on projects, meetings, publications and news in the field in the *Bamboo/Rattan Network Newsletter*. For a free copy of the newsletter and further information, contact: International Development Research Centre, South Asia Regional Office, 11 Jor Bagh, New Delhi 110 003, India. Tel.: 91-11-619411, Fax: 91-11-4622707. (Source: *Ceres*, January/February 1994)

New biotech rice network

There was good news from the Manila-based International Rice Research Institute (IRRI). Germany has joined with the Asian Development Bank to fund a US$ 2.28 million Asian Rice Biotechnology Research Network coordinated by IRRI, China, India and Indonesia—the world's largest rice-producing countries—the Philippines and Thailand will take part. "The establishment of this research network is a major achievement and signals the application of a new tool to contribute to rice research in the next decades", IRRI Director-General Klaus Lampe said. (Source: *Ceres*, January/February 1994)

Eurotech Capital and Eurotech Innvest: a simple route to finance

Small and medium-sized enterprises (SMEs) may find it difficult to secure private capital investment for their activities in the field of high technology. In order to encourage capital investment in such high technology developments on a pan-European basis, the Eurotech Capital initiative has been established by DGXVIII of the Commission of the European Communities.

A network of European financial institutions have agreed to invest approximately 150 million ECU primarily in SMEs involved in high technology. The SMEs should be registered in a member country of the EC and should have a product or process which is aimed at a transnational market. Enterprises are required to provide information concerning the management team as well as financial details of the firm. This information is treated in the strictest confidence by the Eurotech Innvest management team, who screen, select and process the data before presenting it to the investors by means of a confidential database.

For further information please contact: Longman Cartermill Ltd., Technology Centre, St. Andrews, Fife KY 16 9EA, Scotland, United Kingdom. Tel.: (44) 334-77660; Fax: (44) 334-77180, or: J. Berger, EEC-DGXVIII. Tel.: (352) 4301-36246; Fax: (352) 4301-6322. (Source: *EBIS*, Vol. 3, No. 2, 1993)

AMFEP—Association of Microbial Food Enzyme Producers

The AMFEP is a European industry association founded in 1977. The members of AMFEP produce and sell enzymes for, among other things, food processing. The main objectives of AMFEP are:

- To provide a common basis for representing the interests of its members in negotiations with the Commission of the EC;
- To ensure a free flow of information between members about developments related to the regulatory status of food enzymes in Europe.

AMFEP has published a report about the production of enzymes and their use in a variety of industries, particularly the food industry. Other short publications are also available from AMFEP:

- Regulatory aspects of microbial food enzymes;
- Regulatory aspects of food enzymes produced by recombinant microorganisms;
- Classification and labelling of microbial enzyme preparations.

Details: AMFEP Secretariat, Avenue de Cortenberg 172, B-1040 Brussels. Tel.: (32) 2-73558170, Fax: (32) 2-736 81 75. (Source: *EBIS*, Vol. 3, No. 2, 1993)

BIOLAC

BIOLAC is a Biotechnology Programme for Latin America and the Caribbean of the United Nations University, an academic and autonomous institution, with its coordinating centre in Tokyo, organized on a network basis. BIOLAC started when the university signed an agreement with the Venezuelan Government; its coordinating office is in Caracas. The general objectives are: to carry out research in specific area of biotechnology and genetic engineering; to serve as a focal point for training and dissemination of knowledge; and to provide the infrastructure for regional networks. The Programme is financed by an endowment granted by the Government of Venezuela. It emphasizes three areas: vaccine development and improved diagnostic methods of human and animal diseases; plant biotechnology, stressing the improvement of the nutritional quality and pest resistance; and microbial fermentations for industrial purposes. BIOLAC has already established several networks involving scientists and their laboratories, such as: the Brucellosis Network, coordinated by Dr. Julius C. Frank, from Ontario, Canada, with the participation of eight countries: Argentina, Chile, Peru, Ecuador, Colombia, Venezuela, Mexico and Canada; the Plant Genetic Engineering Research Network, coordinated by Dr. Rubén H. Vallejos, of the National University of Rosario, Argentina, with the participation of Brazil, Mexico, Argentina and Spain; the Diagnostic and Vaccine Research Network, coordinated by Dr. J.C. Mandible, of Central University of Venezuela, involving Peru, Uruguay, Bolivia, Venezuela and the Netherlands; and, finally, the Network of Microorganisms of Industrial Interest, which is being developed under the coordination of Dr. Rafael Almudi Villen of Brazil. The Programme provides research grants to the researchers involved in the networks and support for annual workshops and/or specific training courses. It also offers fellowships for research and training, in leading laboratories in Latin America, with a duration between three to 12 months. (Source: *Boletin de Biotecnologica*, Vol. 10, No. 2, December 1993)

International Service for National Agricultural Research (ISNAR)

The mandate of the International Service for National Agricultural Research (ISNAR) is to assist developing countries in bringing about lasting improvements in the performance of their national agricultural research systems and organizations. It does this by promoting appropriate agricultural research policies, sustainable research institutions, and improved research management. ISNAR's services to national research are ultimately intended to benefit producers and consumers in developing countries and to safeguard the natural environment for future generations.

ISNAR offers developing countries three types of service, supported by research and training:

- For a limited number of countries, ISNAR establishes long-term, comprehensive partnerships to support the development of sustainable national agricultural research systems and institutions;
- For a wider range of countries, ISNAR gives support for strengthening specific policy and management components within the research system or constituent entities;
- For all developing countries, as well as the international development community and other interested parties, ISNAR disseminates knowledge and information about national agricultural research.

ISNAR was established in 1979 by the Consultative Group on International Agricultural Research (CGIAR), on the basis of recommendations from an international task force. It began operating at its headquarters in The Hague, the Netherlands, on 1 September 1980.

ISNAR is a non-profit autonomous institute, international in character, and apolitical in its management, staffing and operations. It is financially supported by a number of the members of the CGIAR, an informal group of donors that includes countries, development banks, international organizations and foundations. Of the 18 centres in the CGIAR system of international centres, ISNAR is the only one that focuses specifically on institutional development within national agricultural research systems.

ISNAR's Research Report series presents the findings of research conducted by the institute and its partners in the areas of agricultural research policy, organization and management. (Source: *International Service for National Agricultural Research (ISNAR)*)

The Intermediary Biotechnology Service

The Intermediary Biotechnology Service (IBS) was established by an international group of donor agencies to act as an independent adviser to national programmes in developing countries on matters of biotechnology research management and policy. The IBS is headquartered at ISNAR, where it represents a continuation of activities begun in 1988 under a four-year programme of ISNAR, the World Bank and the Australian Government, titled Agricultural Biotechnology: Opportunities for International Development.

The establishment of the IBS resulted from a recommendation of the Biotechnology Task Force (BIOTASK) of the Consultative Group on International Agricultural Research (CGIAR). BIOTASK conducted an extensive investigation into the problems and potential benefits of applying biotechnology to agricultural research in developing countries. It recommended that a demand-driven, problem-oriented advisory service be established to make available the expertise of advanced biotechnology institutes to the developing countries. The Government of the Netherlands provided funding to implement this recommendation in late 1992.

The IBS is guided by a Steering Committee composed of representatives from client countries, contributing donors and the implementing agency, ISNAR.

The current programme of the IBS has three main functions:

- To assist national agricultural research systems in developing countries with biotechnology research programme management and policy formulation;
- To carry out country studies to identify priority problems amenable to solution through biotechnology;
- To identify international biotechnology expertise and enhance its availability to national programmes in developing countries.

The IBS also advises bilateral and multilateral development agencies on biotechnology issues affecting developing countries. Further information is available from: Dr. Joel Cohen, Project Manager, Intermediary Biotechnology Service, ISNAR, P.O. Box 93375, 2509 AJ The Hague, The Netherlands. Tel.: (31) (70) 349-6100; Fax: (31) (70) 381-9677.

Social Issues

New therapies face ethical dilemmas

Genetic illness is more widespread than most people think: about a half of all infant deaths in the West are caused by genetic disease. Each individual's genetic code determines their susceptibility to heart disease and certain types of cancer. During a normal life-span, two-thirds of all people will suffer from an illness with a genetic component. Even more surprisingly, every human carries between ten and 15 potentially lethal genetic abnormalities. These are usually harmless to the carrier, as all cells have two copies of most genes. However, the children of parents who are unlucky enough to have matching genetic abnormalities may inherit both copies of a mutated gene and develop the full-blown condition.

Advances in genetic medicine, unimaginable a mere two decades ago, have made it possible to determine the root causes of some genetic illnesses. In a few cases it has even led to possible cures. However, the capability to alter parts of the genetic code can bring with it many dilemmas.

Some scientists forecast that genetic therapies will totally revolutionize medicine within the next decade. The driving force for the acceleration has been the advances in computing: a decade ago, it would take a whole laboratory

10-15 years and millions of dollars to identify a possible target for gene therapy; now, a single researcher can do this task in days or weeks at a cost of about $1,000/target. Medical care could turn from its current pattern of "diagnose-and-treat" to one of "predict-and-prevent". Doctors will have at their fingertips an armoury of selective therapies based upon genetic targets, tailored to the type of disease.

Once again, it will be information processing technology that will enable the changes to take place. By 2003, advances in information systems will allow everyone to carry a "smart card" holding extensive health records—from foetal heart rate to phenotype—which will allow 360° care. However, the speed of advances brings with it problems over how the technology is perceived.

Of particular concern is how such information might be used it if were available so freely. Many people fear that there may be a "genetic underclass" who, because of an inherited susceptibility to certain diseases, would through no fault of their own be unable to get insurance or employment. The Nuffield Council on Bioethics, a working group set up by a British charity, the Nuffield Foundation, recently published a report calling for insurers to declare a moratorium on questions relating to genetic tests.

Such a moratorium would be temporary, the Council stresses, pending talks between insurers and government on how such information might be used.

Part of the problem is that the techniques are new, and this always causes uneasiness—organ transplantation was greeted with extreme scepticism when the first operations were carried out in the 1950s. But gene therapy carries much more ethical baggage—for example, are we treating humans like machines? Should these techniques be used only to improve health? And is it acceptable to patent genetic sequences, which implies motives other than altruism?

The pace of research may be increasing, yet out of 4,000 known genetic diseases, there are currently only five for which genetic therapies are available. (Extracted from: *Chemistry & Industry*, 3 January 1994)

Genetic screening should be kept in the family

Screening for certain genetic diseases will bring benefits that outweigh the risks, according to Max Perutz, the Nobel prizewinner who discovered the structure of the blood protein haemoglobin, when he addressed an international conference. Genetic screening would be acceptable if the law guaranteed a family's right to keep the information private.

Speaking at the Seventeenth International Congress of Genetics in Birmingham in August 1993, Perutz acknowledged the widespread fear that genetic screening could be misused by insurers and employers. And, he outlined the arguments of Neil Holtzman, a paediatrician at Johns Hopkins University in Baltimore, whose book *Proceed with Caution* "conjures up the nightmare of the state imposing eugenic birth control on its citizens".

By contrast, Perutz said he was "haunted by the opposite nightmare, a democracy so scared of science that it may accede to the shrill demands and intimidation by those who want termination of pregnancies to be banned together with genetics and all its works".

Research into certain genetic disorders, such as cystic fibrosis, has already improved the prospects for their treatment. Other disorders, such as thalassaemia, have been understood for a time but still lack really effective treatment. Families at risk, and especially those who already have an affected child, are afraid of bearing more children with the disease and are keen to have antenatal diagnosis and termination of the pregnancy if this is possible.

He acknowledges the complexities of screening for diseases where genetic defects predispose, but do not guarantee, the onset of life-threatening disease in the future—such as forms of Alzheimer's or breast cancer.

Perutz, who at 79 years of age still works at the Laboratory of Molecular Biology in Cambridge, believes the British Government should set up a committee to explore the possibilities of legislation to protect the privacy of genetic information. Others, such as the philosopher Mary Warnock, have already made such calls. (Source: *New Scientist*, 21 August 1993)

Regulatory Issues

Battling over biotech milk

The genetically engineered growth hormone for cows, bovine somatotropin (BST), can now be sold in the United States. A temporary ban on BST ended after a government report found BST to be safe for humans and animals and concluded that dairy products containing BST would not need labelling. But anti-biotechnology campaigns to boycott these products are already in full swing.

The developers of the hormone, Monsanto, first took BST to the Food and Drug Administration (FDA) almost ten years ago, finally receiving approval last November. However, Monsanto was banned from selling BST—which boosts milk production in cows—for 90 days while the Clinton Administration compiled a report on its implications for consumers, the economy and the dairy industry.

The Administration's report estimates that BST will have a positive net effect on the US economy of $656 million over the next six years. This is worked out from increased consumer savings (from cheaper dairy products) minus higher federal government costs (incurred in dairy and domestic nutrition programmes) and lower net farm income.

However, The Pure Food Campaign (PFC)—"an international boycott of genetically engineered foods"—is back on the offensive, threatening an unprecedented national consumer boycott of products from BST-treated cattle. It is also filing a federal lawsuit charging the FDA with gross negligence in approving the drug without requiring long-term studies of its human and animal health impacts.

Meanwhile, the European Union, a major dairy producer, has extended its series of moratoriums on BST by one more year instead of the anticipated seven years. The ban, which is due to expire at the end of 1994, does not

affect imports into the EU of milk, dairy products and meat from BST-treated animals. (Source: *Chemistry & Industry*, 7 February 1994)

BST, biotech products accepted by US public

As supplemental bovine somatotropin (BST) and other early products of biotechnology near marketplace introduction, the US public is expressing strong acceptance of the entire category, according to a new survey of consumer attitudes.

Overall, the survey found that two out of three (66 per cent) consumers support the use of biotechnology in agriculture, compared with eight out of ten (82 per cent) who support its use in the development of human medicines.

Consumers gave the use of biotechnology to develop human medicines an acceptability rating of 7.2 on a scale of 1 to 10, while awarding the technology's use in developing insect-resistant crops and herbicide-resistant cotton ratings of 7.1 and 6.9 respectively.

The survey also indicates that the use of BST by dairy farmers is not an issue of concern for the vast majority of consumers and will have virtually no effect on the public's consumption of milk. (Source: *Chemical Marketing Reporter*, 7 February 1994)

Protection asked for rare plants

Greater protections are needed in the Endangered Species Act to preserve increasingly rare plants which have medicinal value, say conservationists. Plants—which are the origin of one quarter of all prescription drugs used in the US—constitute the fastest growing category of endangered species listings.

The Pacific Yew tree, from which the drug Taxol is derived and has shown positive results in the treatment of breast and ovarian cancer, is an example of a US plant with proven medicinal value that has been "put at risk due to irresponsible human activity". At one time the Pacific Yew, a part of the endangered ecosystem of the ancient forests of the Pacific Northwest, was burned as scrap. (Source: *Chemical Marketing Reporter*, 7 February 1994)

Highlights of proposed amendments to German law regulating genetic engineering

Production facilities working with Group 1 (no risk) organisms will only need to notify authorities, but there would still be a shortened delay before use.

Time delays for research work with microbes in Group 1 and Group 2 (low risk), currently 90 days, would be shortened by 30 days, and the obligatory review by the Central Commission for Biological Safety would be dropped in certain cases.

Renewals of permits to work with organisms in higher safety classes (Groups 2, 3, 4) will require only notification, and the time delay will be dropped.

Public hearings for authorization of a production facility producing organisms in Groups 1 and 2 would be dropped, and construction can proceed before a permit is received.

It would be possible to incorporate the simplified procedures outlined in EEC Directive 90/220 without a public hearing. (Source: *Genetic Engineering News*, 1 October 1993)

General

PGR training workshop in Ethiopia

The Fifth International Training Workshop on Plant Genetic Resources was held in Addis Ababa from 15 November to 3 December 1993. Twenty participants mostly from Africa and Asia were given theoretical and practical training on the conservation and utilization of crop genetic resources. The practicals included laboratory and field tours to various regions in Ethiopia. In the field participants were able to visit the on-farm landrace conservation activities which the Plant Genetic Resources Center/Ethiopia (PGRC/E) together with the Seeds of Survival Programme/Ethiopia (SoS/E) has been undertaking since 1988/1989. As in the previous workshops, the participants were able to gain first hand experience on how farmers collaborating with the SoS/E project were conserving and multiplying their seed. The participants, most of whom come from governmental agencies and the NGOs working in related fields in rural communities, are expected to undertake activities similar to the ones they experienced in Ethiopia and will be provided with consultation through a follow-up programme. From the North, two Canadian organic growers were able to participate in the training, and will share their experience with Canadians upon their return. The workshop also provided a unique opportunity for a number of grass-root workers (especially from Kenya and India) to formulate or further develop programmes similar to the one which, based on the Ethiopian experience, SoS is promoting in Africa.

Readers interested in more information about the Training Workshop and possibility of applying for the next one, due in November 1994, may contact SoS/E, P.O. Box 5760, Addis Ababa, Ethiopia. (Source: *African Diversity*, No. 8, February 1994)

Biodiversity and PAHO

At the XXVI Annual Meeting of the Advisory Committee for Research on Health (ACHR), in Rio de Janeiro in 1987, a recommendation to elaborate a programme on the area of biotechnology applied to health problems, was made to the Pan American Health Organization (PAHO), and consequently, a specific subcommittee was appointed. It recommended the training of manpower, the support of research in priority areas and the strengthening of institutions. As a consequence of this, PAHO started the support of 12 projects of R&D on malaria, HIV and hepatitis B. Eleven institutions were strengthened in four countries and two biotechnological products were obtained; also, three panels of monoclonal antibodies for malaria and hepatitis, two panels of sera anti-HIV, and three banks of strains of HIV were started in Mexico, Brazil and Argentina.

In 1991 ACHR emphasized manpower formation, regional courses and fellowships, and recommended attention to other topics such as quality control, ethics, biosafety and molecular information networks. (Source: *Boletin de Biotecnologica*, Vol. 10, No. 2, December 1993)

New products boost US biotech

The rapidly maturing US biotechnology industry survived a decidedly mixed 1993. Good sales growth and key product approvals contrasted sharply with financing problems and growing uncertainties over President Clinton's proposed health care reforms.

The good news going into 1994 is biotech sales are expected to continue to soar as a slew of new products hit the market. The Pharmaceutical Manufacturers Association (Washington) estimates 132 biotech drugs are undergoing human clinical trials, while 11 more await final approval from the Food and Drug Administration.

Significant US approvals in 1993 included a beta-interferon drug for treating relapsing multiple sclerosis and a recombinant factor VIII blood-clotting agent for treating haemophilia A. The FDA is expected to approve several more biotech drugs in 1994, including Genentech's (south San Francisco) DNase cystic fibrosis treatment, which received the go-ahead from an FDA scientific advisory panel. The agency is also likely to approve Genzyme's (Cambridge, Massachusetts) recombinant Ceredase to treat Gaucher's disease.

An initial crop of agricultural products—including biotech tomatoes developed by Calgene (Davis, California) and several novel biopesticides—is hitting the market. Perhaps most notably, Monsanto received FDA approval in November for its bovine somatotropin (BST) hormone to boost milk production in cows.

Capturing capital financing continues to be a critical problem for biotech firms, particularly smaller companies without major product sales. Biotech companies raised $5.2 billion between July 1992 and June 1993, but much of the 1993 money came from private financing, including strategic alliances and venture capital, as the biotech stock market remains tepid. How the economic and political climate will affect the industry's deal making and acquisitions in 1994 is uncertain. (Extracted from: *Chemicalweek*, 5/12 January 1994)

Growing UK biotech sector seeking funding

The most comprehensive report on the long-term strategies and financial position of the fledgling UK biotechnology sector was launched in February. Compiled by accountants Arthur Andersen in conjunction with the UK Bio-Industry Association, *UK biotech '94—the way ahead* confirms the underlying strength of the UK product pipeline and the high potential growth prospects for the sector. But to fuel the growth the sector will require £1.1 billion ($1.6 billion) of new equity funding over the next three years—considerably more than the £878 million equity raised by the sector to date. The report is based on responses from 68 out of 166 companies surveyed.

With external factors—particularly the relaxation of the London stock exchange listing rules and the DTI's deregulation initiative—now favouring the biotech sector's development, "all the signs and indications look good", according to the BIA.

According to the report, over the next three years the sector's turnover is expected to increase by 79 per cent to £878 million, but the strength of the sector's product development pipeline indicates even faster growth could follow, particularly when recombinant drugs and plants progressing through clinical and field trials reach the market in 1996 or beyond.

The report makes no allowance for the new start-up companies which will inevitably be created, so is "probably conservative".

In terms of product development, the estimated average number of products in development per company was 23 for both the agbio and biopharmaceuticals segments in 1992-1993. By 1995-1996, this is expected to rise to 35 for the agbio and 31 for the biopharmaceuticals segments.

Much of the sector's growth will come from the biopharmaceuticals companies which expect sales to increase by 64 per cent to £319 million although it is the agbio companies that expect to see the fastest rate of growth with a 274 per cent increase—to £116 million—over the next three years.

Across all segments, strategic alliances are expected to be important, the majority initiated by the UK biotech company. Biopharmaceuticals expect their primary partners will continue to be pharmaceuticals companies, while agbio companies expect to form links with agriculture and chemicals companies.

Over the next three years, agbio and diagnostics companies expect to place more emphasis on US alliances, whereas biopharmaceuticals companies and suppliers expect to concentrate on European alliances. The sector also expects to treble the number of Japanese partners. (Extracted from: *European Chemical News*, 28 February 1994)

Biotechnology industry critical of price control

Biotechnology research into breakthrough drugs and therapies for cancers including breast, lung, ovarian and prostate, has been cut back due to a lack of investment, according to an industry survey.

The reason most often cited by biotech companies for the cuts is the decline in investment due to uncertainty over the Clinton Administration's proposals for indirect price controls on new breakthrough drugs.

In the survey, conducted by the USA's Biotechnology Industry Organization, 44 per cent of companies say their cancer research has already been delayed or curtailed and 62 per cent predict these activities would face further reductions should the Administration's proposals become law.

The industry spokesman observes that new therapies and cures for various cancers, AIDS, and other afflictions will come from biotechnology medical research.

The survey says biotech therapies not only provide improved health, but can also be a critical component in reducing future medical costs. Biotechnology, according to the industry official, can "ultimately be the most cost-effective and efficient way to deal with many diseases". However, declines in medical research in biotech laboratories have already begun, which could mean "longer waits for medical help for millions of Americans".

The Administration's health care plan would create a drug advisory council which would review introductory prices of new breakthrough medicines. In addition, the secretary of Health & Human Services Department would be allowed to require payment of special rebates for new drugs and to "blacklist" them if their prices are deemed too high. The biotech industry believes these proposals amount to price controls. (Source: *Chemical Marketing Reporter*, 21 February 1994)

Trends in biopharmaceutical product development and commercialization

The road to commercialization in not easy for biopharmaceutical products. The Pharmaceutical Manufacturers Association (PMA) survey of the industry estimates that, on average, it takes $231 million and 12 years to bring a pharmaceutical product from early-stage research to regulatory approval. A large pool of capital, whether comprised of private or public funds, is thus crucial to the success of this industry.

While health care reform is virtually inevitable in the 1990s, the biotechnology community is particularly concerned that measures implemented by the Clinton Administration may result in price controls on drugs, threatening the industry's development. Whatever the outcome of the Clinton Administration's health care reform initiative, some observers believe that all industries, including the pharmaceutical industry, will become increasingly concerned with controlling costs. One method of controlling costs is through industry consolidation; a second will be through re-engineering the drug development and approval process.

Workable government regulatory policies are the key to the continued prosperity of the biopharmaceutical industry. In response to industry and investor concerns about the inefficiency of its drug review policies, the FDA has made a number of changes designed to streamline the review process.

The accelerated approval policy for breakthrough drugs was designed to expedite the approval of therapies to treat patients suffering from serious illnesses. Other reforms included the early 1993 reorganization of the Center for Biologics Evaluation and Research (CBER). As part of this reorganization, CBER designed a new process to increase its efficiency in reviewing the ever-growing number of applications for biological products. In addition, the 1992 passage of the Prescription Drug User Fee Act provided funding for additional staff to help facilitate the biological review process.

A number of biopharmaceutical products to be approved for marketing in 1994 could include:

- DNase, a new cystic fibrosis (CF) treatment being developed by Genentech. When approved, Pulmozyme, the trade name for DNase, will represent the first new CF treatment in 30 years;
- Ceredase, used to treat patients with Gaucher's disease, a rare genetic disorder.

In the long term, approval of several other products is expected. Selected examples include:

- Hirulog, a rationally designed drug based on a natural leech protein. Regulatory approval for Hirulog may be in 1996;
- Platelet-Derived Growth Factor (PDGF), as a treatment for chronic skin ulcers in diabetic patients. Expected regulatory approval for PDGF is in 1996;
- Consensus Interferon, a novel, non-naturally occurring protein. Results from early clinical trials indicate that consensus interferon may be useful in treating hepatitis C. Regulatory approval for this product is expected in 1997.

The technologies used to develop biopharma-ceuticals have evolved considerably since the industry's inception in the late 1970s. Many biopharmaceutical products currently on the market, including insulin and erythropoietin, are made via protein synthesis. Rational drug design, oligonucleotide and carbohydrate synthesis are some of the second-generation technologies that are currently being used in drug development.

- Rational drug design: rational drug design refers to the use of computers and techniques, such as X-ray crystallography, to design therapeutic compounds. A number of computer hardware and software companies are also involved in developing this technology.
- Oligonucleotide synthesis: a number of oligonucleotides are currently being evaluated as therapeutic treatments, including products with potential use in antisense therapy. The goal of antisense drug therapy is to specifically inhibit target messenger RNA, thus preventing the production of harmful proteins.
- Carbohydrate synthesis: carbohydrates, which are often connected to proteins in the body, frequently play a vital role in regulating various bodily processes. A number of biotechnology companies are focused on the development of therapeutic carbohydrate products.
- Molecular diversity: several companies are developing a group of technologies called molecular diversity, or combinatorial chemistry, which enable scientists to rapidly synthesize and screen large numbers of novel compounds. Examples include the use of phage libraries "mimotope" methods of producing and screening large numbers of peptides.

Each of the above technologies, along with gene therapy, neuroscience and the greater use of computers, will help to propel the biopharmaceutical industry into the twenty-first century. Regardless of health care reform, those with the creativity to find the proper blend of resources, the ability to fund drug development and the

patience to gain regulatory approval, will continue to reap attractive rewards. (Extracted from *Genetic Engineering News*, 1 January 1994)

Space shuttle to conduct microbial biopesticide study

Astronauts on the space shuttle Discovery will carry out an experiment to determine if certain microorganisms grown in near-zero gravity can be used to make better performing biopesticides.

The microbial experiment was developed by Novo Nordisk Entotech (Davis, California) and Penn State's (University Park, Pennsylva Center for Cell Research (CCR). In 1990 the compan covered that bigger protein crystals could produce a be secticide. Working with a biopesticide strain of *Bacil. thuringiensis* (Bt), variety *tenebrionis*, the company f d that by exposing the Bt crystals to radiation, the c als would grow larger. The space experiment will test hypothesis that exposure to near-zero gravity could alte e size, shape or quantity of crystal production, perhaps easing the bioinsecticide's toxicity further.

The experiment will b conducted in a computer-controlled device called the Penn State biomodule, which was developed and patented by the university's CCR. The biomodule fits into a containment vessel which is sealed and placed in a refrigeration/incubation unit that controls and monitors temperature. (Source: *Genetic Engineering News*, 1 February 1994)

Growth hormones ban

A decision to ban all artificial growth promoters in the European beef industry moved a step closer in February. The European Parliament's environment committee approved a report by its chairman, Ken Collins. The report was an assessment of the Commission's proposal for controls on the use of "certain substances having a hormonal or thyrostatic action and of beta agonists".

If approved by the Council of Ministers, the regulation will curb a black market in illegal growth-promoting substances, which was estimated to be worth £700 million in 1992. The wording of the proposal was kept deliberately vague to avoid the risk of a new generation of products filling the gap left by controls on specific substances.

However, the main target of the regulation is the beta agonist, clenbuterol. This compound is a smooth muscle relaxant used legitimately in treating respiratory diseases and problems at birth in horses and cattle, but given in higher concentrations, the compound known as "angel dust" acts as a repartitioning agent, increasing the production of muscle at the expense of fat.

If an animal is slaughtered soon after treatment, residues of the compound can be present in edible tissue. The drug is toxic, causing muscle tremors, palpitations and dizziness. Several food poisoning incidents around Europe have been caused by these residues, including one in Spain in 1990, in which 135 people became ill after eating cows' liver. The drug also poses a hazard to those using it; deaths of three Irish farmers have been attributed to their handling of treated feed.

In Belgium, it was estimated recently that 80 per cent of beef cattle are treated with illegal growth-promoting substances. Substantial markets also exist in Spain, Germany, Italy, France and Ireland. A major monitoring programme on the British mainland has shown no evidence of misuse, but residues have been found in Northern Irish cattle.

Clenbuterol emerged as a growth promoter only after the Commission decided to ban three natural hormones (oestradiol, testosterone and progesterone) and two synthetic hormone analogues (zeranol and trenbolone) in 1985. The ban took effect in 1988 despite a report by the Commission's own panel of experts, which said that the hormones posed no threat to consumers.

However, following legal challenges by the British Government in 1987 and the European animal health industry association in 1990, the Commission acknowledged that the ban was introduced for political and economic reasons: to curb the growth of Europe's beef mountain rather than to protect public health.

Under the proposed regulation on beta agonists, clenbuterol would only be allowed for therapeutic use in horses and pet animals. Collins has added amendments proposing that the Commission operate a list of producers of the raw materials for growth promoters and that manufacturers keep a detailed register of production and sales. (Extracted from *Chemistry & Industry*, 21 March 1994)

People, patents and human genetic diversity

The Human Genome Organisation (HUGO) and an informal consortium of North American and European universities and scientists have set up the five-year Human Genome Diversity Project, to cost US$ 23-25 million.

Blood, hair roots and oral scrapings will be collected from 15,000 people, members of 500 genetically distinct human groups across the globe who are near extinction. Sampling has begun along the Nile, in South-East Asia, and in Chile, though the official project launch will be later this year. The tissue samples are sent to Virginia, USA for storage and the white blood cells "immortalized" as cell lines in the American Type Culture Library. Many human cell lines already in the collection are under patent application.

Population geneticists and molecular anthropologists have long known of the rapid erosion of human genetic diversity. For example, 90 of Brazil's indigenous communities have become extinct since 1900 and over two thirds of the remaining 180 groups each have less than 1,000 surviving members.

A human genetic hit-list came out of the Second Human Genome Diversity Workshop held at Penn State University, 29-31 October 1992. Among the peoples identified for genetic immortalization are the Yukaghir of Siberia (about 100 people), the Dorasque of Panama (50 people), the Amazon's Akuriyo (50 survivors), the Salsia of Taiwan, Samaritans in the Near East (480 people

left) and the Delaware and Sarcee of North America (each around 600 people).

A list of the 722 most endangered indigenous communities includes—Africa, 165 groups; Asia, 212; South America, 114; Oceania, 101; North America, 107; Europe, 23.

With money expected from the US National Institutes of Health (NIH) and the governments of other industrial countries, researchers hope ultimately to draw blood samples from all 7,000 to 9,000 distinct human populations believed to exist now.

Aside from the basic sampling of 15,000 people, the researchers will collect inner cheek cells and hair roots from as many other humans as possible at each collection site, for short-term study. These specimens provide less DNA than blood but are more durable. As human blood can only survive for 48 hours outside storage, HUGO (Human Genome Organization) calculates that "One person can bleed 50 people and get to the airport in one day".

The profit potential in indigenous germplasm was brought home to drug companies this year when 30 people in the isolated Northern Italian town of Limone, on the shore of Lake Garda, were found to have a unique gene that codes against many cardiovascular diseases. Swedish and Swiss companies and the University of Milan have applied for patents. If the gene produces a marketable therapy, big profits are likely.

The US Patents Office could decide that the Genome Diversity samples are patentable, without further research or manipulation. Such patents may outlive the indigenous groups from whom they are drawn. The NIH has already applied to patent more than 2,800 genes and DNA fragments from the Human Genome Project's study of brain tissue, and HUGO teams in England and Japan plan to file for patents.

Finance allowing, a duplicate of each group's DNA will be left with their national government or a regional institute.

The meeting conceded that indigenous peoples would get little value from such storages or genetic screening services. The working group concluded that, "The study of the human genome, including elucidation of its diversity, should not detract in any way from the need to address the health problems of the Third World, the bulk of which could be solved by the wide-scale application of knowledge already available; what is needed is the will to do so and the commitment of adequate resources." (Source: *The Gene Report*, No. 3, 1993)

Team building in biosafety: The ABSP internship programme

Most developing countries currently lack the biosafety regulatory framework and appropriate policies to safely utilize new and promising biotechnologies. To build a sound biosafety regulatory framework, there is a critical need for a pool of well-trained people. Realizing this, the Agricultural Biotechnology and Sustainable Productivity (ABSP) project has sponsored an internship programme in biosafety.

The first session of the ABSP biosafety internship programme was organized from 10 May to 2 July 1993, with seven participating scientists from Egypt, Indonesia and Kenya.

The main objectives of the internship programme were:

1. Review the current biosafety regulations and guidelines, including permit application procedures, used in the United States and other countries;
2. Become familiar and gain "hands on" experience with various biosafety issues related to the safe handling of transgenic germplasm in laboratory, greenhouse and field settings including the movement of transgenic seed and plant materials;
3. Develop a draft set of guidelines and regulations for the participants' countries to be used by regulatory agencies and policy makers while modifying existing or formulating new guidelines and regulations;
4. Learn about perceived risks and benefits of a biosafety regulatory framework.

The internship programme commenced with a reporting of the biosafety regulatory status in their home countries and involvement in the work group activities at the USAID-sponsored Latin America and Caribbean Region Biosafety Workshop in Jamaica. The workshop provided interns with theoretical background on various issues regarding the safe use of biotechnology and the opportunity to interact with scientists and regulatory persons who have a broad base of experience in the area of biosafety.

Additional information on the ABSP internship programme may be obtained from either Bruce Bedford or Karim Maredia, Department of Crop and Soil Sciences, Michigan State University, East Lansing, MI 48824-1325, USA. (Source: *BioLink*, 1993)

Biosphere project reaches milestone

A long-term scientific project in which researchers have been living inside the world's largest closed ecological life-support system has passed a significant milestone. The Biosphere II crew completed its two-year mission in September 1993, successfully sustaining themselves and approximately 3,500 species of plants and animals without using toxic pesticides or chemical fertilizers. The experiment is the first phase of a 100-year study of the interdependent ecology of Earth.

Biosphere II, built between 1987 and 1990 near Oracle, Arizona, makes extensive use of computer systems for administrative support, communication, and monitoring of ambient conditions (*Computer*, May 1989, p. 11). Except for personal and scientific journals, and the Biospherians' library, the eight-member crew operated virtually without paper.

While the nearby Mission Control building received electrical power from the local utility, the biosphere itself used power generated from natural gas at a separate energy centre. The centre produced enough energy to heat and cool the biosphere and even to sell some excess power to the utility company. Moreover, project officials report that the Biospherians recycled 100 per cent of the human

and domestic animal wastes and 100 per cent of the water in their environment. (Extracted from *Computer*, October 1993)

Scientists join world genetic research pool

Chinese scientists hope to find genetic information that may lead to the treatment of thousands of hereditary diseases as well as cancers and heart problems.

The National Natural Science Foundation of China has decided to join international efforts to study the human genome in order to analyse the total chromosome content of human genetic material.

By launching the "China Human Genome Project," the Foundation hopes to obtain a complete data bank of genetic information which will help the early diagnosis and treatment of more than 5,000 hereditary diseases.

"The Chinese account for more than one fifth of the world's population, and the country has 56 ethnic groups", said a Foundation official. "Because of this, no one can claim to have established a complete data bank of human genetic information without a thorough study of the Chinese human genome."

The studies of the Chinese genome will focus on:

- The collection and preservation of the genomes of ten Chinese ethnic groups.
- The development of new technology for the study of local mutations, large-scale separation of DNA fragments and the structure of genetic banks.
- The genes liable to cause diseases peculiar to China's ethnic groups.

(Source: *China Daily*, 29 June 1993)

Brassica Germplasm Bank

A *Brassica* oilseeds germplasm bank will be established at Agriculture Canada's Saskatoon Research Station. About 800 *Brassica* lines will be moved from the present seed bank in Ottawa and consolidated with the several thousand lines already in storage as part of Saskatoon's canola breeding activities.

This change is the result of decentralizing Canada's national seed bank collection, to locate with the major breeding programs of specific crops, i.e. canola in Saskatoon. Funding for this initiative is from Canada's Green Plan Program. The conservation of crop breeding lines for future generations is a component of this plan.

The first job will be to produce seed of each line in order to have sufficient seed for field testing. The second job will be to evaluate all lines under field conditions in comparison to Canadian varieties adapted to Western Canadian conditions. The final task will be to describe the successful lines and enter them into storage at the Saskatoon Station for use by canola breeders throughout Canada. Ottawa will remain as a backup to Saskatoon.

For further information contact: Dr. Gerhard Rakow, Saskatoon Research Station, Tel.: (306) 975-7014. (Source: *The AgBiotech Bulletin*, Vol. 1, No. 2, March/April 1993)

B. COUNTRY NEWS

Brazil

Biotechnology Centre of the Butantan Institute

The Biotechnology Centre at Butantan Institute, São Paulo, Brazil, concentrates its efforts in the development of technologies for the production sector of the Institute itself. Its main activities are: the production of antivenoms and antitoxins in an enclosed plant system, which handles 400 litres of plasma per run; the manufacturing of bacterial vaccines (diphtheria, tetanus and pertussis).

Some processes under development are: the production of a vaccine for meningitis B, and the transfer of cholera toxin epitopes to *Salmonella* for the production of a vaccine. The Centre also produces albumin, enzymes and other proteins from human placenta, and monoclonal antibodies in large scale. Together with the University of São Paulo, a Master's degree in Biotechnology is offered. (Source: *Boletin de Biotecnologicia*, Vol. 10, No. 3, December 1993)

Canada

Dechlorinating bacteria

Canadian Biotech News reports that the University of Toronto research group has identified declorinating bacteria normally present in pulp mill treatment systems. They intend using these bacteria to improve the treatment of waste from pulp and paper mills. Many mills have biological treatment systems and elimination of organochlorines from mill effluent is known to occur. What the Toronto researchers have done is to isolate three species of bacteria—*Ancylobacter acquaticus*, a Pseudomonas species and an unidentified methylotrophic organism—from a pulp mill's biological treatment system. These organisms break down simple chlorinated substances. They found that there were 100 times more bacteria in the treatment system than in the influent river. Two of the isolates were found in abundance in the mill treatment system, but not in the river. They intend using these isolates to improve treatment of organochlorine containing wastes.

Further details can be found in a paper by G. Allen, R. Fulthorpe and S. Liss in the *Canadian Journal of Microbiology*. (Source: *Australasian Biotechnology*, Vol. 3, No. 6, December 1993)

China

Amgen in China

Amgen, the US biotechnology company, has opened offices in three Chinese cities, Beijing, Guangzhou and Shanghai, to provide promotional and technical support for sales of the company's pharmaceuticals products in China. The company, which established Amgen Greater

China in Hong Kong in August 1992, claims to be the only biotechnology company actively operating in China. (Source: *European Chemical News*, 21 February 1994)

Biotechnological cooperation agreements signed with Cuba

The involvement of Cuban organizations in exporting Chinese medical products to Latin America is imminent. This was stated in Beijing by participants in a joint meeting on cooperation in the sphere of medical products and biotechnology. This intention is expressed in one of the five accords that were signed by the two countries on 2 February. Another two accords were signed on 1 February.

Jose Luis Fernandez, head of the Cuban delegation to this bilateral conference in Beijing, also stated that this cooperation will result in the creation of new Cuba-PRC joint enterprises in the medical and biotechnology sphere. In the specific case of the Cuban Immunology Testing Centre, one of the agreements signed includes plans to produce biotechnological equipment and reactives. (Source: *Havana Radio Rebelde Network*, 2 February 1994)

Anti-cancer vaccine: human trials in China

A vaccine that prevents infection by virus implicated in a common Asian cancer has been tested by German scientists in China. Although other countries, including Britain, have developed vaccines against the Epstein-Barr virus, this is the first trial on people.

The Epstein-Barr virus is present in about 95 per cent of adults in the world, and is believed to be a key causal factor in certain types of cancer, especially nose and throat cancer which each year kills 40,000 to 50,000 people in Asia. In the West, the virus causes glandular fever (infectious mononucleosis), a 'flu-like illness which, though usually mild, can sometimes be incapacitating.

Hans Wolf of Regensburg University in Germany reported the Chinese trial of an anti-EBV vaccine at a recent international meeting in Annecy, France. Out of nine children given the vaccine, six were protected against natural EBV infection over a 16-month period. However all 10 children who were not vaccinated were infected.

The German-Chinese group tested their vaccine on humans before testing whether it could protect animals from infection, a choice that raised a few eyebrows at the Annecy meeting. Wolf defended this by saying that animal tests do not reliably predict how an anti-EBI vaccine will perform in people. When questioned about the ethics of the trial, Wolf said: "I am not using the Chinese as guinea pigs. This is a Chinese vaccine and it was approved for human trials by a Chinese ethical committee".

The vaccine used in this trial was made in China from a prototype designed by Wolf's group in Germany. It consists of a vaccinia virus genetically engineered to produce an EBV protein called gp 220-340. The vaccinia virus multiplies in the body, continuously releasing the immunizing protein. The British vaccine uses the same protein but without a virus "carrier". Presumably, it will need to be coupled to an immune-stimulating "adjuvant" substance to produce strong immunity.

Wolf notes that "one advantage of working in China is that the Chinese live with the constant threat of EBV-induced cancer and desperately need a vaccine against it". But not everyone is convinced that the vaccine is effective against cancer. Guy de The, a viral epidemiologist at the Institute Pasteur in Paris, is sceptical about an anti-EBV vaccine protecting against cancer because the virus is only one factor contributing to the disease. Salted fish in the diet, for example, is also known to play a role. De The also says that the vaccine's anti-cancer potential will take decades to measure. (Source: *New Scientist*, 1 May 1993, p. 16)

WHO advocates using Qinghaosu derivatives for malaria treatment

According to the World Health Organization (WHO), the malaria epidemic is now spread over more than 100 nations with 270 million people being infected, and each year the disease incidence is expected to reach 110 million cases while more than 1 million people will die of malaria. Unlike most high incidence areas in the world, where *Plasmodium falciparum* are resistant to chloroquine, *Plasmodium falciparum* obtained from South China, South-East Asia, South America, and Africa are resistant to sulfadimethoxine (SDM) and pyrimethamine. Since *plasmodia* are found to have gradually adapted to the chemically-synthesized drugs, the world is turning its attention to drugs derived from natural plants, such as Qinghaosu (arteannuin) and its derivatives—artether, artemether, artesunates—which were recently developed by Chinese researchers. Results from clinical trials conducted in China, the Netherlands, Viet Nam, Nigeria, Kenya, and Papua New Guinea indicated that the malarial infection mortality went down from 20-30 per cent to 10 per cent when arteannuin and its derivatives were used instead of conventional drugs. The Development and Planning Agency of WHO and the World Bank have jointly advocated the further development of the three arteannuin derivatives. (Source: *Chinese Science News*, 19 May 1993)

Costa Rica

Cell and Molecular Biology Research Centre of the University of Costa Rica

The Cell and Molecular Biology Research Centre (CIBCM) was established in 1977 as a new inter-disciplinary organizational model to gather researchers and equipment from several schools and departments of the University of Costa Rica. The model has proved valuable, as CIBCM has grown from an initial staff of 10 to more than 50 members. It is now constituted by 12 senior and 13 junior researchers coming from the Schools of Agronomy, Medicine, Microbiology. Biology and Chemistry. With the support of 25 technicians, assistants, undergraduate and graduate students, this group conducts 22 research projects in three main areas: Molecular Biology of Plants and its Viruses, Human and Animal Genetics, and

Immunology and Infectious Diseases. Projects in these areas include: genetic variability and characterization of plant populations, molecular and epidemiological studies of plant viruses in major basic and export crops, and plant transformation for virus resistance; chromosomal localization and molecular studies of two human inherited disease and genome organization studies in eukaryotes; search for anti-viral activities in natural products (in cooperation with INBIO) and studies of the immune response to bovine leukosis and immunodeficiency viruses.

Projects are being conducted in cooperation with research groups in the USA and Europe, and more than two thirds of the Centre's budget comes from foreign funding. An important activity of CIBCM is the organization of regional and international courses and the training of graduate students from Latin America.

CIBCM is an Associated Centre of the International Centre for Genetic Engineering and Biotechnology (ICGEB), is a member of the Latin American Plant Sciences Network and is an active participant of the Latin American Biosciences and Biotechnology Networks. (Source: *Boletin de Biotecnologicia*, Vol. 10, No. 2, December 1993)

Denmark

Danish Biotech Centre

Denmark is planning to set up a biotechnology research centre, which it hopes ultimately could become a leading unit in Europe.

Initially, the publicly-funded centre would require capital investment of around $30 million and money for running costs of around $18 million a year, which would initially come from the Danish Government. In the long term, total investment could exceed $1 billion, with funds from member States of the European Union.

The proposed centre has the backing of biotechnology companies in Denmark and neighbouring southern Sweden, though they do not intend to fund it directly.

The idea for the centre, which would be located in Copenhagen, fits in with suggestions by some leading researchers in the European Union that centres of scientific excellence should be established within the Union. DSM proposed last year that the Netherlands should have a European research centre for fine chemicals. (Source: *Chemical Marketing Reporter*, 24 January 1994)

European Community

Biofuels directive accelerates

The European Parliament (Strasbourg, France) last week adopted the European Commission's proposal for a biofuel directive that would cut excise duties on biofuels such as methanol, ethanol, and vegetable oils by about 90 per cent. The directive now goes before the European Council of Ministers, which should pass it by year end, Brussels sources say. If that happens, the directive would most likely become law in the European Union by mid-1995. The Commission says that using crop-derived biofuels instead of diesel fuels and gasoline in motor vehicles would cut vehicle emissions substantially and would help absorb some of Europe's severe agricultural oversupply. (Source: *Chemical Week*, 16 February 1994)

The proposed biocides directive

The European Commission has recently published a proposal for a new directive intended to establish a single market in biocidal products. The proposed directive aims to introduce a harmonized scheme for allowing biocidal products on the market. It is one of a number of single market directives aimed at setting Community standards based on a high standard of protection for people and the environment. If adopted it would inevitably involve some harmonization of existing arrangements in individual member States.

In the proposed directive the term biocidal product is defined very widely; in essence it covers any substance or product that kills harmful or unwanted organisms. The detailed definition as it appears in the draft directive is set out below. It introduces a key distinction between the formulated biocidal product as supplied and its active substance, that is, the ingredient that gives the product its biocidal action. Around 400 active substances are thought to be used in biocidal products presently on the Community market.

The proposed directive on biocidal products follows in the wake of Community agreement on a uniform approach to the control of agricultural pesticides as set out in the Plant Protection Products Directive. Some of the active substances used in biocides are also used in plant protection products, and biocidal products such as rodenticides, insecticides, avicides and molluscicides will be essentially the same as their plant protection product equivalents. The proposal on biocides is modelled on the Plant Protection Products Directive which has already been adopted. The scope of biocidal products covered by the proposal extends to, for example, household cleaners for which germicidal properties are claimed. The proposal, therefore, raises important issues on the nature of the controls that are appropriate to such a wide diversity of products.

Negotiations are likely to start in the second half of 1994 and agreement is by qualified majority voting. Following the Maastricht agreement the opinion of the European Parliament will also be influential on the eventual outcome. As the proposal is complex and ambitious, agreement is perhaps unlikely until 1995, with implementation in 1996 or 1997.

Whatever the details the final outcome will, of course, be important to manufacturers, suppliers and users of biocides. Industry sectors affected by the proposals have rightly been actively lobbying, either directly or via their national and European trade associations.

Detailed definition of biocidal products:

- Biocidal products are defined as "active substances and preparations containing one or more active substances, put up in the form in which they are supplied to the user, intended to destroy, deter, render harmless, prevent the action of, or otherwise exert a controlling effect on any harmful organism".

- Active substances are defined as "substances, fungi and micro-organisms including viruses having general or specific action on or against harmful organisms".
- Plant protection products and other biocides that are already covered by Community requirements are excluded from scope.

(Extracted from: *Chemistry & Industry*, 21 February 1994)

EU Council for patents on plants and animals

On 7 February, the EU Council of Ministers decided to adopt the so-called "directive on legal protection of biotechnological inventions" (after having voted on a "common position" on 16 December 1993)—but only with a very bare majority. Denmark, Spain and Luxembourg voted against; Italy had strong doubts. In this directive patents on plants and animals are basically accepted. Human genes and genes of plants and animals shall also be subject to patent claims. According to the directive, every living being—all of life—is viewed as "biological material". The common position still has to be formally adopted by the Parliament.

As a result of the strong opposition to patents on life in the Parliament, the Council took up one additional point: the so-called "farmer's privilege" shall be guaranteed—in a very narrow scope. European farmers shall be allowed to use part of their crop as seed for the next year, even if the crop is patented. They have to use it exclusively for their own purpose though; they cannot exchange it with other farmers. For animals the farmer's privilege does not hold (so that farmers will have to pay royalties for each calf from a patented cow). The equally important "breeders privilege", which would allow breeders to exchange seed for breeding purposes, was not taken up in the common position. Thus, the free exchange of seed and genetic resources, which is the very base of traditional breeding, will be severely limited.

In two other international treaties the patent issue is playing a crucial role. The finally signed GATT treaty implies that the patent system of Northern countries shall be imposed on all countries (so-called "Dunkel agreement"). Regarding the ratification of the Biodiversity Convention, the EU Council decided on 26 October 1993 that the EU member States shall only ratify this Convention together with an "interpretative statement". This statement basically says that genetic resources of biodiversity (of third world countries shall be patentable. (Source: *Mail out*, No. 19, February 1994)

Progress in Fourth Framework Programme

The Fourth Framework Programme is the European Union's overall plan and budget for science and technology in the period 1994-1998.

This Programme is currently in the process of discussion and approval by the European Council and Parliament. The discussions have now reached the "Common Position" stage at which the Council and Commission agree on the programme content and budget. An overall budget of 12 billion ECU has been proposed. The agreed document will now be put before the European Parliament for its approval. It is hoped that this proposal can be obtained before the parliament is dissolved prior to the 1994 elections.

If the Programme is not approved before the current Parliament is dissolved, there is likely to be a long delay in starting the individual R&D Programmes. The Life Sciences component or "Action" of the Programme consists of the Biotechnology, Agro-Industry and Bio-medical S&T activities. According to the Common Position document, the Life Sciences will receive 1.572 million ECU or 13.1 per cent of the funds.

The area of biotechnology will receive 552 million ECU, a significant increase on the 186 million ECU spent in the Third Framework Programme. The priority areas for R&D are:

- Cell factory (i.e. production of substances by cells);
- Plant molecular biology;
- Genome sequencing;
- Cell communication in neurosciences.

A lower level of funding of research on other topics will also be included. The Bio-medical and Health Research Programme will receive 336 million ECU. The priority areas are:

- AIDS and cancers;
- Anti-viral drugs and vaccines;
- New clinical tests and trial models;
- Brain research.

Agriculture and Fisheries will receive 684 million ECU, a significant increase on the 486 million ECU spent in the Third Framework Programme. The priorities are:

- Integrated production and processing chains;
- Scaling-up and downstream processing;
- Generic sciences and advanced technologies for nutritious foods;
- Agriculture/fisheries/forestry and rural development.

(Source: *Irish Biotech News*, January 1994)

EP dashes hopes of anti-biofuels lobby

Opponents of the EC's controversial biofuels directive are picking up the pieces of their long-fought campaign, after a flurry of European parliamentary activity dashed hopes that the issue would go away quietly. The full plenary session of Parliament, which passed the draft legislation, also overturned amendments won only two weeks earlier from the EP's economic, monetary and social affairs committee.

The 18-month deadlock at EP committee level was overcome in late January, and the proposals returned to the Parliament with three key amendments: that measures should be optional for each country rather than mandatory across the Community; the tax break gained by users of bio-derived fuels should be 50 per cent of current fiscal takings, rather than the 90 per cent proposed by the EC; and industry should be protected via a provision that any producer supplying the subsidized market could not in the same year participate in the free market.

Of these, only the first survived the passing of the EP plenary session, leaving battle-weary opponents wondering

what the last 18 months of costly procedure and painstaking lobbying have been all about. Now, only a failure by the council of finance ministers to unanimously rubber stamp the proposals stands between the opposing lobby and defeat. In any case, the diminishment of the proposals to optional rather than mandatory status effectively removes most of the anticipated ministerial opposition. (Source: *European Chemical News*, 28 February 1994)

Three moves to boost biotech

Europe's bioscience community has started 1994 in a better position than it may have anticipated, following three 1993 year-end moves by the European Union. The EU's Council of Ministers (CoM), which contains a ministerial representative from each of the EU's 12 member countries, rejected a proposal from the EU's European Commission (EC), the EU's civil service, for a seven-year ban on the sale of bovine somatotropin (BST). Also, European trade ministers, sitting in the EU's Internal Market Council (IMC), have drafted a proposal on new patent rules to protect biotechnological inventions in Europe. And, finally, officials at the EC amended a proposal to regulate novel foods and novel food ingredients that contain genetically modified components. (Extracted from *BioTechnology*, Vol. 12, March 1994)

Finland

Finland considering far-reaching biotech rules

A new far-reaching law to regulate all aspects of Finnish biotechnology—including medical, agricultural, environmental and industrial applications—has been drafted by a special working group appointed by the Finnish Parliament. The so-called Biotechnology Working Committee (BWC) recently presented its first draft of the new law to the Ministry of the Environment (Helsinki). The eventual law will likely not conflict with European Community policy on biotechnology. Though Finland is not an EC member, it is presently applying for such membership.

The BWC noted that Finland has 70 organizations—both public and private—actively pursuing biotechnology. Their main focus is on plant and animal research, with the main players being the wood-processing, waste-disposal, and food industries. An increasing number of medical-biotech firms are being established, however, particularly in the areas of hereditary disease and vaccines.

The BWC has recommended establishing a permanent Gene Technology Authority (GTA), a supervisory board that would operate as an independent body within the Ministry of Health and Social Welfare (Helsinki). The GTA would have broad powers of supervision to make biotech organizations accountable for their actions. Each organization conducting biotechnology research would have to inform the GTA of all ongoing and planned activities. The GTA would assess this research, as well as its impact on society and nature.

The BWC proposes two levels of regulation for biotechnology experimentation and production. The aim is to make it easier for organizations to conduct "legitimate" research projects, while curtailing them from conducting "ambiguous" projects. For level I activities, organizations will need to notify authorities of their work, but authority approval of new projects or changes to existing projects will be virtually automatic. Public hearings for level I activities will not be necessary.

For level II activities, public hearings will be held in the event that the activities involve installations that require approval under emission-control laws. Ideally, the waiting period between organization notification and authority approval will be three months.

The BWC proposal calls for a central register of all level I and level II activities. After the proposal receives input from interest groups, however, the betting is that the register will contain only level II activities.

The BWC proposal has a good chance of becoming law by the beginning of 1995. (Source: *BioTechnology*, Vol. 11, December 1993)

Mammalian protein protects potatoes against viruses

Creating plants resistant to a large spectrum of viral infections rather than to a single virus is exactly what Finnish and Estonian researchers are trying to achieve. Their idea is to create transgenic plants incorporating 2'-5' oligoadenylate synthetase, a protein produced by mammals in response to viral infections.

When activated by double-stranded RNA, the most frequently found replicative form of viral RNA, this enzyme acts as a catalyst in the polymerization of ATP [adenosine triphosphate] into 2'-5' oligoadenylates. In turn, these oligonucleotides go on to activate the endoribonuclease, RNase L.

Mart Saarma (Biotechnology Institute of Helsinki) and his colleagues have transformed potato plants, via *Agrobacterium tumefaciens*, with the c-DNA [complementary deoxyribonucleic acid] of the rat's 2-'5' oligoadenylate synthetase gene. These plants, planted on small parcels of farmland, were inoculated with potato virus X (PVX). In three of the clones tested, no viral particles were detected. The virus was detected in the tubercules and leaves of the other clones, but in two cases, in concentrations below those found in non-transformed control plants and in transgenic plants expressing the capside protein of PVX. These results would suggest that a mammal protein can protect potato plants from infection by PVX. Is this protection equally effective against other RNA viruses? And is it, as in the case of mammals, general and non-specific? These are questions currently being addressed by the researchers.

For more information, contact Mart Saarma, Biotechnology Institute, P.O. Box 45, Karvaamokuja 3A, 00014 Helsinki University, Finland. (Source: *BIOFUTUR*, November 1993)

France

France considers comprehensive bioethics legislation

Prompted by the serious ethical and policy dilemmas raised by new biomedical technologies, France is considering a comprehensive set of regulations intended to "ensure the inviolability and inalienability of the human body". At time when the United States continues to react to bioethics dilemmas on an ad hoc basis, this French legislation represents a concerted effort to ensure that federal public policy keeps apace with technological developments in genetics and medicine.

The proposed legislation strongly condemns "any eugenic practice tending toward the selection of the genes, the sex, or the physical or racial traits of human beings".

Appearing at a Suffolk University Law School symposium on biomedicine and the law, Justice Noelle Lenoir said that medical interventions should be restricted to cases of therapeutic necessity.

If this legislation is approved reproductive technologies such as *in vitro* fertilization and pre-implantation embryo selection would be allowed only for cases of infertility or when the offspring are at high risk for serious and incurable genetic diseases. The techniques could not be used to determine a child's sex or other non-medical characteristics. Similarly, gene modifications would be permitted only for life-threatening genetic conditions. Genetic interventions prompted solely by social conventions would be outlawed.

The statute would also outlaw the sale of human body parts and products. Sperm and egg donors would be barred from receiving payment, and the donations would have to be anonymous in all cases. All contractual reproductive arrangements, such as surrogate motherhood or the sale of embryos, would be outlawed. Patents on human genes would be prohibited.

The proposed French legislation also addresses the problem of genetic discrimination. If passed, it would prohibit prospective employers or insurance companies from using the results of genetic testing to screen job applicants or assign risk categories. (Source: *geneWATCH*, Vol. 9, Nos. 3-4, January 1994)

Germany

Germany eases controls on gene experiments

Germany has introduced a new law covering research in genetic engineering, overcoming a threat from the left wing of the opposition Social Democrats to block its passage through the German Parliament.

The law eases procedures for the authorization of genetic experiments. In particular it reduces substantially the amount of paperwork required for no-risk and low-risk genetic experiments, long considered a powerful disincentive for the development of biotechnology and genetic engineering in Germany.

The Social Democrats (SPD), concerned that the law would reduce public accountability, has demanded more control of genetic experiments, particularly for field experiments with genetically modified organisms which may now proceed without a public hearing, but 14 proposed amendments were overruled by their more conservative colleagues in the SPD-led *Länder*, who sit in the upper house, and who voted with the Government. (Source: *Nature*, Vol. 367, 13 January 1994)

Hoechst first gene field test

Hoechst has applied for permission to conduct its first field tests with genetically engineered plants at four locations in Germany between May 1994 and October 1996.

Tests with manipulated maize and rape-seed are to take place near Lingen, Mainz, Augsburg and Gotha. According to Hoechst, the tests are to facilitate the widening of applications for its broad-spectrum herbicide *Basta*. A gene introduced into the plants is designed to make these resistant to *Basta*.

The Hoechst launch, like all previous attempted field trials with genetically manipulated plants and organisms in Germany, is expected to face opposition from environmental groups. (Source: *European Chemical News*, 1 November 1993)

India

Seeds of discord

Even though India will gain from the opening of markets for its manufactures, many Indians persist in believing that the whole exercise is a foreign conspiracy to exploit the third world. Political parties are planning demonstrations and a farmers' protest is gaining strength in the southern state of Karnataka. The chief ministers of four opposition-run states say they will ask the courts to stop the Government ratifying the agreement.

Although the Government does not need parliamentary approval to sign the GATT Uruguay round, there are several provisions on intellectual property in the agreement that will require legislation on plant breeders' rights, drug patents, copyright and integrated circuits.

Some of the opposition to GATT is based on myth, some on reality. The main criticisms are:

- A new copyright law will raise the prices of seed, and farmers will be forbidden to sell patented seed;
- GATT will force the Government to cut subsidies for farmers' fertilizers, water and power;
- GATT will raise the price of drugs. Currently, Indian patents depend not on the design of a drug but on the process by which it is made, so companies have devised alternative processes to manufacture drugs still under patent internationally. These drugs sell in India for as little as one-tenth of the world price. GATT will oblige India in future to give patents for the drugs themselves, not the manufacturing process, and to extend patent life from seven years to 20. This will raise the price in India of around 10-15 per cent of drugs sold;
- GATT will force India to abandon its subsidized ration shops for grain and other basic goods.

In a country where 73 per cent of the population is rural and half is illiterate, many villagers are none the less scared that they will be hit by the impact on seed sales of new rules on intellectual property rights. Farmers' groups in north and south India have opposed the Uruguay round. Only in western India do farm groups see a net advantage in the new export opportunities provided by GATT. (Extracted from *The Economist*, 2 April 1994)

India's Plant Bank

India's National Bureau of Plant Genetic Resources (NBPGR), established in 1976, has its headquarters in New Delhi and possesses a network of subsidiary units located in other regions where plants can be tested under various different agricultural and climatic conditions. The Bureau maintains strong links with other related institutes in India, such as the International Crop Research Institute for Semi-Arid Tropics (ICRISAT) at Hyderabad, and acts as a coordinating centre for activities in the field of plant genetic resources. A computerized database at the headquarters contains up-to-date information on research in the field.

Varieties are preserved there at the bank as seed or as plant tissue, which is kept under refrigeration until needed for propagation. At present the bank contains over 180,000 varieties, but its capacity is currently being expanded to hold up to 800,000 samples. In addition to many types of wheat, rice, maize, millet, sugar-cane, potato and other familiar crops, the bank also contains numerous rarer and lesser known plants. The NBPGR also has a plantation where a wide variety of crops are cultivated in the field. To obtain its samples, the NBPGR has built up teams of dedicated and sharp-eyed plant collectors, who often have to scour remote areas in India and elsewhere.

NBPGR scientists are continually testing the plants in their collection for resistance to pests and diseases as well as for yield, nutritional value and other qualities. Over the years they have tested and selected many varieties that are now proving to be of immense value to farmers, including various strains of tomato, okra, cow pea, gooseberry, pecan and mung bean.

Many of NBPGR's activities come under the heading of technical cooperation among developing countries (TCDC). For instance, the Bureau works in close collaboration with a number of international bodies with which it continually shares its expertise and research findings. These include the International Maize and Wheat Improvement Centre in Mexico, the International Rice Research Institute in the Philippines, the International Potato Centre in Peru, and the International Centre for Agricultural Research in Dryland Areas, based in Syria.

One of the Bureau's most important TCDC activities is carrying out germplasm exchanges with over 80 other developing countries, including China, Cyprus, Indonesia, Iran, Mongolia, Nepal and the Philippines. During the year 1990-1991 the NBPGR received over 40,000 crop samples from 42 countries. Some of the most promising of these were varieties of maize from Mexico, rice from the Philippines, castor from Egypt and sweet potato from Peru. During the same period, responding to requests from 48 countries, the NBPGR exported over 2,000 germplasm samples, including wheat, rice, maize, barley, sorghum, papaya and Napier grass.

Other TCDC activities of the NBPGR include training courses for participants from developing countries on genetic resources management, and joint expeditions to identify and collect germplasm. In collaboration with the International Board for Plant Genetic Resources, scientists from NBPGR have participated in explorations in Ethiopia, Kenya, Malawi, Mali, the Maldives, the Sudan, Zambia and other countries.

The NBPGR is fully committed to continuing its work with other developing countries to make good use of our precious collective heritage of plant genetic resources. Only by a collaborative effort in this area can we hope to meet the agricultural challenges that the South is facing.

For further information, please contact: National Bureau of Plant Genetic Resources, Pusa Complex, New Delhi - 110 012, India.

Ireland

Forbairt takes over

From January 1994 BioResearch Ireland will operate within Forbairt. Forbairt is the New National Agency with responsibility for the development of Irish business enterprise and for developing the technology needs of industry.

It brings together the functions of EOLAS—the Irish Science and Technology Agency, and of the sections of the Industrial Development Authority with responsibility for indigenous industry. IDA-Ireland will continue to promote Ireland as a base for overseas industry. Forbairt is an Irish language word meaning "development".

Mr. Dan Flinter has recently been appointed Chief Executive of Forbairt. The internal organization of the new agency will be clarified over the next few months. (Source: *Irish Biotech News*, January 1994)

Republic of Korea

Government announces investment in biotechnology

The nation's ambition to join the ranks of industrialized countries recently received a boost when the Government unveiled a 14-year plan to spend 16 trillion won to help develop bioengineering technologies.

The plan, announced by an interministerial committee headed by Science and Technology Minister Kim Si-joong, aims at enhancing the nation's bioengineering technologies to the levels of advanced countries.

The project, code-named Biotech 2000, will be implemented in three phases. The South Korean Government will channel 16 trillion won over the next 14 years towards this goal, with 10.3 trillion won of the funds coming from private industry.

By the time the project is completed in 2007, bioengineering will have emerged as the major source of the nation's export revenues, according to government officials.

The project's name itself symbolizes South Korea's ambition to develop bioengineering as one of its key industries.

In the first phase of the project, which runs through 1997, the Government will concentrate on production skills. In the second phase, which extends to 2002, most of the basic research will have been done. In the final phase, from 2003 to 2007, bioengineering will have become one of the nation's key export industries.

The Government estimates that the global market for bioengineering will generate $100 billion by the year 2000. By that time, it says, the domestic market volume will have grown to 4 trillion won. (Extracted from *Korea Newsreview*, 25 December 1993)

Mexico

Research in advanced studies centre unit in Irapuato

In 1981 the Research in Advanced Studies Centre of the Polytechnic Institute of Mexico created a Unit in Irapuato to carry out research on plant biology and offer specialized training in this subject. The government of the State of Guanajuato donated 20 hectares, 9,000 m^2 of construction, a power station and a deep water well.

The Unit is divided in two departments: Biotechnology and biochemistry which includes 10 researchers, and Genetic engineering, with 20 researchers integrated in multidisciplinary fields. Biotechnology and biochemistry researchers study the identification of some defence proteins that make plants resistant to the attack of insects and fungi; use of *Bacillus thuringiensis* and other local strains of bacteria, as well as viruses, fungi and protozoa in the production of bioinsecticides; studies on the association of mycorrhiza of some plants; basic aspects on active cell wall transport of nutrients; isolation and characterization of some particular proteins and carbohydrates; identification of various plant substances (medicines, dyes, flavours, fragrances) with potential industrial use. Genetic engineering researchers study the production of new varieties of tomato, potato, tobacco, rice, amaranth, asparagus (some of the transgenic plants are being tested in the field); manipulation of genes that encode the synthesis of proteins that inhibit fungal growth; transfer of the genes that encode the synthesis of the protein of *B. thuringiensis* with insecticide properties, to the genome of different crops; studies on genes that encode proteins of high nutritional value, such as that of amaranth, and their potential use in the genetic transformation of beans, maize and other crops; also, research is being done on the possible transfer of artificially-produced micro-chromosomes. (Source: *Boletin de Biotecnologicia*, Vol. 10, No. 2, December 1993)

UNAM's biotechnology institute

The Research Centre on Genetic Engineering and Biotechnology was created in 1982 by the National Autonomous University of Mexico (UNAM). A new infrastructure including 8,500 m^2 of construction, was inaugurated in 1985 in Cuernavaca. In 1992 the name Biotechnology Institute was adopted. The Institute activities are mainly in three directions: basic and applied research in areas such as molecular and cell biology, microbiology, biochemistry, biochemical engineering, immunology, microbial ecology, etc.; development of new technologies in close collaboration with the industrial sector, to solve problems in the areas of health, agriculture, industry and the environment; and participation in the training of manpower through high-quality research.

The Institute includes four departments: Molecular biology, Biochemistry, Bioengineering and Molecular biology of plants. At present 58 researchers and 45 technicians are working full time at the Institute.

Some of the main lines of research are: molecular biology and biochemistry of bacteria, viruses and parasites; molecular biology and biotechnology of plants; genetics and molecular biology of the interaction plant-micro-organism; structure, function and manipulation of peptides and proteins; engineering and technology of fermentations; design of certain industrial equipment; retrieval and purification of certain products; engineering and technology of enzymes; prospectives in biotechnology; optimization and integration of processes and prototypes. Technological developments taken by the Institute are: the transfer of 11 technologies to Mexican enterprises; an enzymatic technology for the production for semisynthetic penicillin and cephalosporins; a process of fermentation for the production of xanthan; two fermentation processes for the production of unicellular protein from milk serum and another one from methane; a pilot plant to produce *Saccharomyces cerevisiae* for alcohol production; a process to produce sweet syrups from hydrolysis of lactose; enzymatic extraction of plant pigments. Furthermore, the Institute has signed more than 45 industrial agreements for technological developments; has produced cloned micro-organisms for the production of human interferon and insulin, and some enzymes of industrial interest. It has yielded four patents, with 22 more in the legal process. (Source: *Boletin de Biotechnologicia*, Vol. 10, No. 2, December 1993)

Russian Federation

Western companies initiate hunt for Russian microbes

An increasing number of Western biotechnology companies are awakening to the fact that many institutes in the former Soviet Union hold significant collections of micro-organisms that, for the first time, have become available for commercial exploitation. At least 30 collections are in existence in Russia and the former Soviet republics with a combined holding of more than 50,000 strains.

One of the most innovative holdings in the Russian Federation is the Collection of Marine Microorganisms (KMM) at the Russian Academy of Sciences Far Eastern Division's Pacific Ocean Institute of Bioorganic Chemistry (TIBOKh) in Vladivostok. This collection embraces more than 10,000 microbial strains that have been harvested from

seas all over the world by the institute's own 2,600-ton research vessel.

Several dozen strains in the Institute of Bioorganic Chemistry's collection have been found to produce useful compounds including antibiotics (*Bacillus pumilis, Streptomyces pluricolorescens*), uridine-specific RNAase, and restriction enzymes.

The largest collection of strains in the former Soviet Union would appear to be the All-Russian Collection of Industrial Micro-organisms (VKPM) based at the Scientific Research Institute of Genetics and Selection of Industrial Microorganisms in Moscow. It was created in 1968 with the aim of establishing a national holding centre for industrially useful microbial strains. An analogous holding of approximately 8,000 strains, the All-Russian Collection of Microorganisms, for the supply of pure cultures to the academic sector, was established in Pushchino, near Moscow. Currently, VKPM holds approximately 12,000 strains and embraces a range of general-purpose vectors, including those based on phages and plasmids. The collection also holds more than 200 strains of *Bacillus thuringiensis* that are effective against insect pests and another 200 strains selected for their oil-degrading potential. In the future, it is hoped to use VKPM as the basis for the creation of a new National Reserve Centre of Industrial Microorganisms.

Other more specialized collections also exist. For example, Vladimir Kuznetsov, working at the State Centre for Antibiotics, Moscow, established Russia's first culture collection of actinomycete strains that produce antibiotics and other physiologically active compounds. This collection has since received international status and was registered in 1972 in the *World Directory of Collections of Cultures of Microorganisms*. Actinomycete strains are also held in the Russian Academy of Medical Sciences' Institute for the Investigation of New Antibiotics' Collection of Microorganisms, Moscow. Other specialized collections are held at the Russian Academy of Medical Sciences' D.I. Ivanovski Institute of Virology (2,800 strains of viruses), the Russian Academy of Sciences' K.A. Timiryazev Institute of Plant Physiology (microalgae), the Russian Academy of Sciences' Institute of Biochemistry and Physiology of Plants and Microorganisms (strains of *Azospirillum* species isolated from grains in the Saratov region), and at least another 12 sites in the Russian Federation. Further information from Anthony Rimmington, PhD, Centre for Russian and East European Studies, School of Social Sciences, The University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom. (Source: *Microbiology Europe*, November/December 1993)

United Kingdom

European States cut red tape

Promises by various European Union Governments to cut the red tape said to be strangling the commercial development of biotechnology in Europe are beginning to be delivered. The United Kingdom Department of the Environment has published details of its fast-track authorization procedure for the field testing of genetically modified organisms (GMOs), while Germany has a new law easing the authorization of experiments in genetic engineering.

Under the new United Kingdom rules, industry and researchers planning to field test low-risk GMOs now have to wait only 30 days after submitting their applications before proceeding with the release. Previously, the procedure took 90 days and required formal consent.

The United Kingdom's fast-track programme will be watched closely by officials at the European Commission, as a similar approach to granting consent could be introduced throughout the EU. (Source: *ChemicalWeek*, 2 February 1994)

Biodiesel trials in UK cars

United Oilseeds, a United Kingdom agricultural cooperative, has launched the UK's first long-term trial of biodiesel in cars.

In a joint project with car manufacturer Rover three company vehicles will run on Novamont's *Diesel-Bi* rapeseed ester for the next 12 months. The cooperative hopes the results will help persuade the UK Government of the viability of the use of biodiesel.

United Oilseeds believes the fuel holds greatest potential in environmentally sensitive areas, particularly for use in urban transport and boats. If the Government indicated support, the cooperative believes a small biodiesel production plant could be set up in the UK.

To date the fuel has not found favour with the UK Government; a report by the Department of Trade and Industry last year concluded that a subsidy of 15 p/litre (22 cents) would be required for biodiesel to be commercially viable.

A trial last year by Reading Buses proved technically satisfactory, but costs precluded its continued use. (Source: *European Chemical News*, 7 February 1994)

BIA seeks to close biotechnology gap

Major changes have taken place at the UK's Bio-Industry Association (BIA) in an effort to give necessary support for the rapidly expanding United Kingdom's biotechnology industry.

At an extraordinary meeting held in London recently, a board of directors of the association was elected to replace the current BIA council. The new board is headed by the chief executive of British Biotechnology, Dr Keith McCullagh, as chairman and is composed of eight chief executive officers of Britain's pioneer bioscience companies.

The initiative was made to strengthen the BIA's management structure, change its constitution, and focus its objectives to achieve greater effectiveness, Dr. McCullagh said.

McCullagh said, "The investment gap between Britain and the United States is a major concern. Last year US funds invested nearly $2 billion in biotechnology companies. UK investment in bioscience was only 10 per cent of this".

With around 10 new companies going public on the London Stock Exchange in the past year and several more flotations in the offing, the growth and potential of the UK biotech industry is one of the most exciting movements in the UK's industrial sector for many years. (Source: *Manufacturing Chemist*, December 1993)

United States of America

DNA decision

The US National Institutes of Health (NIH) is to abandon its controversial 32-month pursuit of patents for human cDNA sequences—full or partial—with unknown functions because it is not in the public or scientific interest.

"I do not believe that patenting at this stage promotes technology development and it may impede research collaborations here and internationally", says Harold Varmus, NIH director. "The sequences are primarily useful as research tools rather than as commercial products", he adds.

William Waldegrave, UK Science Minister, approves of the NIH decision, believing that it will encourage further research in the area. "The Medical Research Council (MRC) and NIH patent applications were filed in order to protect the interests of the UK and US taxpayers, with least damage to the international research effort in genome mapping, which requires the free flow of information." In October 1993, the UK MRC decided not to file any further patent applications on newly-obtained cDNA sequences of unknown function unless accompanied by knowledge of the gene function.

Since 1991 all the NIH's patent applications have been rejected. Opponents argued that biomedical research would be hindered if such fundamental parts of life were subject to monopoly ownership. (Source: *Chemistry & Industry*, 21 February 1994)

Organic farms face dilemma over new gene technology

Organic farmers in the United States, who provide a small but important market for agricultural biotechnology companies, are divided over whether to accept the use of recombinant-DNA products.

The debate has intensified as the National Organic Standards Board (NOSB), the advisory panel that helps to set standards for US organic farming, prepares to discuss recommendations on how to treat recombinant plants and pesticides.

The NOSB is expected to recommend either a moratorium on the use of recombinant DNA, or a general ban that would still allow companies to apply to use individual products. But it could also prohibit recombinant DNA products entirely.

Urgency has been given to the Board's deliberations by the fact that three pesticides incorporating genetically engineered bacteria have recently arrived on the market, and several new vegetables are awaiting regulatory approval.

In the United States, organic farmers are generally suspicious of recombinant-DNA technology and its impact on the web of ecological relationships on which their farms rely. The Organic Food Production Association of North America, a trade group, has rejected the use of recombinant-DNA technology, saying that it is incompatible with organic philosophy and that there are in any case natural substitutes available.

Others, however, believe that some recombinant products could provide useful tools consistent with their philosophy. These accept that recombinant-DNA technology should be seen as a synthetic process, some of whose products can be used in organic farming provided they pass various tests.

Some researchers believe that acceptance of some biotechnology products by the organic community would be an important breakthrough. (Extracted from *Nature*, Vol. 367, 13 January 1994)

Milk hormone clears final hurdle

The publication of a favourable report by the Clinton administration on the economic and social impacts of recombinant bovine somatotropin (rBST) has helped to clear the way for the Monsanto Company to begin marketing the drug to dairy farmers when a temporary ban on its sale is lifted.

With almost all congressional avenues for derailing the product now exhausted, it will now be up to farmers and consumers to decide whether this new aid for the dairy industry—which will appear under the trade name Posilac more than nine years after the company first applied for regulatory approval—sinks or swims.

The drug was approved for commercial use in the United States by the Food and Drug Administration (FDA) last November, but Congress imposed a 90-day ban on sales of rBST following its approval, during which time the administration agreed to undertake a study of its implications for consumers, dairy farmers and the economy.

The report paints a rosy picture of the technology, and says that consumers and dairy farmers could stand to benefit from lower milk prices and an increase in milk yields per cow of 10-20 per cent.

Opponents say that the report plays down the effect that rBST will have on the dairy industry and on the cost to the federal Government for the milk price support programme, and focuses too heavily on the impact of the ban on Monsanto and the biotechnology industry as a whole. (Extracted from *Nature*, Vol. 367, 20 January 1994)

Biotechnology labelling opposed

The US Food and Drug Administration in a recent survey has found that 90 per cent of the 2,164 respondents opposed mandatory labelling of all genetically engineered foods. Most regard it as unnecessary, impractical or confusing. (Source: *Australasian Biotechnology*, Vol. 4, No. 1, February 1994)

Biomass projects are funded

The US Department of Energy, in a partnership with US industries, has picked 12 proposals for a new initiative to boost the production of energy from biomass.

The proposals for cost-shared case studies could lead to biomass-to-energy demonstration projects in almost every region of the country.

"Harvesting energy crops for electricity or ethanol and other liquid fuels means new industry, jobs and economic development for many regions of the country", says Dr. Duane Sunderman, director of DOE's national renewable energy laboratory (NREL).

NREL issued the calls for proposals in May 1993. Submitted plans had to detail the dedicated energy crop to be grown as the source of biomass—usually fast-growing trees, grasses or sugar cane—and how to convert the biomass to energy, either electricity or ethanol and other liquid fuels.

Twelve proposals were selected from a field of 24 submitted by lead companies in cooperation with a team of other interests. DOE contributed between $50,000 and $200,000 to each of the proposals.

More than 70 companies, universities and government agencies from 19 states and Puerto Rico have also committed resources to the biomass initiative.

Government and private studies estimate that energy crops could provide 5 quads (a quad is 1,000 million million BTUs of energy) of electricity by 2010 and up to three times that amount by 2030. In comparison, the US imported the equivalent of 15 quads of petroleum in 1990. (Source: *Chemical Marketing Reporter*, 28 February 1994)

Study finds reform plan hampers biotechnology

The Clinton Administration's health-care reform plan could "drive a stake through the heart of the US biotechnology industry", Senator Judd Gregg (R-N.H.) declared, citing a survey by Brandeis University's Robert M. Goldberg, which found that the prospect of price controls is already hampering the biotechnology industry's ability to raise the funding it needs for medical research.

With few products on the market, most of the 1,300 US biotechnology companies are dependent on independent capital to continue their research and development, according to Biotechnology Industry Organization, an industry trade group.

Of the 107 middle-sized biotechnology companies surveyed, 83 per cent cited price control proposals as harmful to their efforts to raise capital in 1993, and only 27 per cent said they met their funding goals last year.

Senator Gregg said he was especially concerned that nearly 90 per cent of the biotechnology companies surveyed stated they would have to seek foreign investment as one way to cope with the capital shortage and that 77 per cent of the firms also said they would have to cut basic research and delay near-term drug development.

While most of the firms surveyed said they would look to foreign partners to survive financially, Dr. Goldberg, a senior fellow at Brandeis' Gordon Public Policy Centre, said investment by foreign pharmaceutical companies "would be unable to sustain" US biotechnology at levels supported by domestic capital markets. (Extracted from *Chemical Marketing Reporter*, 14 March 1994)

C. RESEARCH

Research on human genes

Blood test could pinpoint colon cancer tumours

Researchers from an American biotechnology company believe they are near to developing a blood test to detect colon cancer, the second biggest cause of cancer-related deaths in the West. The team, from the Massachusetts-based Matritech, has identified a group of proteins found only in the cells of colon cancer tumours.

The Matritech researchers studied 18 samples of colon tumour cells, and 10 samples of healthy cells. They found that all the tumour cells contained six proteins that were not found in healthy cells, while the healthy cells contained four proteins that were absent in the tumour cells. Over the past year, three other similar groups of proteins have been discovered, specific to breast, bone and prostate cancers.

The researchers suggest that antibodies could be designed to bind to the various tumour-specific proteins as a "marker" for malignancy. These could then be used in a simple blood test to detect the marker proteins, indicating both the presence and the location of a malignant tumour. The reagents could also measure the progress of cancer treatment, the team claims.

Unlike lung cancer, the causes of colon cancer are largely unknown. It is also difficult to detect at an early stage, or to monitor, without removing and analysing tissue samples, which involves quite drastic surgery.

The proteins identified by the team are produced in the cell's nuclear matrix, the "scaffolding" of the nucleus. This matrix controls the positions—and, to a certain extent, the function—of the cell's DNA and RNA, and the proteins involved in the transcription of the DNA code. Proteins found in a cell's nuclear matrix are often specific to the cell's tissue type. (Source: *Chemistry & Industry*, 21 March 1994)

Cloning cDNAs without functional assays

The research team of Professor T. Honjo of Kyoto University (Department of Medical Chemistry, Faculty of Medicine) has developed a new signal sequence-enriching system, which allows cloning of cDNAs encoding soluble factors and transmembrane molecules carrying specific N-terminal signal sequences without specific functional assays.

Effective general methods are needed to identify and isolate complementary DNAs (cDNAs) encoding intercellular signal molecules involved in complicated regulation such as morphogenesis and hematopoiesis. It is difficult and tedious to clone cDNAs for the many different growth

factors and adhesion molecules required for transmitting specific intercellular signals by establishing a bioassay system specific to each molecule and measuring the biological activities of unknown molecules.

The signal sequence-enriching system takes advantage of the fact that most precursors for secreted factors and transmembrane molecules carry specific N-terminal signal sequences and that most of such sequences are located within 400 base pairs (bp) from the 5′ termini of the mRNA. The team constructed a vector which can direct cell surface expression of Tac (human interleukin 2 receptor α chain) fusion proteins when introns carrying signal sequences are cloned in a frame with the correct orientation. Using this vector, an expression of cDNA library was constructed containing the 5′ terminal-enriched cDNA (average size of 400 base pairs) of a mouse bone-marrow stromal cell line, ST-2, and cloned cDNAs encoding novel potential cytokine molecules, SDF-1 α and β of the intercrine/MIP superfamily.

5′ terminals of cDNAs were enriched and ligated in the proper orientation in order to reduce the likelihood of stop codons and to increase the possibility of producing fusion proteins. The method has two additional advantages; (1) the selected fragments are short enough to be sequenced without recloning, which allows selection of new genes easily by comparison with the data base; and (2) asymmetric adaptor ligation allows amplification of introns with PCR whenever necessary. (Source: *JETRO*, January 1994)

Oral cancer gene cloned

The Cancer Research Institute (CRI) in Bombay, India has identified and cloned the gene that causes oral cancer. The discovery may help in early diagnosis of oral cancer caused by chewing tobacco.

In India oral cancer ranks as number one cancer in males and number three in females.

There is evidence for the presence of the gene in tissue samples from most of the 102 oral cancer patients studied. The genetic material from the tissue samples injected into mice induced cancer in 85 per cent of these animals confirming its presence.

Several constituents of tobacco, such as nitrosoamines and polycyclic aromatic hydrocarbons are carcinogenic. These interact with oncogenes and tumour suppressor genes present in the cells of the oral cavity, inducing aberrations in the genes and causing oral cancer. (Source: *The Hindu*, 1 December 1993)

California researchers develop "superantigens"

Newborn babies, the elderly and people whose immune systems are weakened by disease are particularly vulnerable to bacteria that cause pneumonia and infections of the brain and blood. Vaccines exist, but many are limited in efficacy. For example, according to Gregg J. Silverman, assistant professor of medicine at the University of California at San Diego, pneumonia vaccines fail to work in as many as 30 per cent of elderly patients.

Now, however, Californian researchers believe that they have identified a protein, Protein A, which they have dubbed a "superantigen" and which they think could some day boost the effectiveness of such vaccines. The immune system recognizes threatening bacteria through their antigens, which are molecules—usually proteins, carbohydrates or fats—that are produced by, or are part of, the bacterium. When lymphocytes detect the antigen, they change into two different types of cells: *plasma cells*, which produce antibodies that kill the invading organisms; and *memory cells*, which live on to fight future battles against the bacteria. Vaccines give the immune system a "taste" of a bacterial infection, just enough to produce memory cells that will allow the body to respond quickly when a real infection occurs. But some people do not produce enough—or, in some cases any—of these memory cells. Superantigens are proteins produced by a common bacterium, *Staphylococcus aureus*, that most people harbour on their skin. The superantigen acts as a universal antigen that antibody-producing white cells can recognize. In early research funded by the US National Institutes of Health (NIH) and the Arthritis Foundation, Dr. Silverman is looking into the possibility of attaching such superantigens to the antigens used in vaccines. White cells, he believes, are more likely to recognize the superantigen, which would "open the door" for the attached vaccine antigen. (Source: *Biotechnology Bulletin*, Vol. 12, No. 11, December 1993)

Key cells switch found that turns on a form of leukaemia

In a discovery that could aid understanding and treatment of a range of cancers, a research team has found how an enzyme in bone marrow cells switches on the uncontrolled growth of certain leukaemias. Lead researcher of the team is Ann Marie Pendergast, assistant professor of pharmacology at the Duke University Medical Center (Durham, NC). The scientists studied the Philadelphia chromosome, on which a gene segment called BCR is positioned on to the cABL gene, which codes for protein tyrosine kinase. In the abnormal BCR/ABL protein, the ABL enzyme remains "on", adding phosphates to tyrosines in the BCR region and in the ABL portion of the BCR/ABL protein.

The scientists report finding an adaptor molecule called GRB-2 that plugs into one of the phosphorylated tyrosines of BCR. Their experiments showed that GRB-2 appears to be the main control link between BCR/ABL and cell machinery that switches on the cell growth protein Ras. The uncontrolled action of the Ras protein is central to many cancers. Using human bone marrow cells, the scientists found that by abolishing just the single tyrosine on BCR/ABL, they could eliminate the ability of GRB-2 to link with BCR and also BCR/ABL's ability to transform the bone marrow cells into proliferating leukaemic cells. (Source: *Genetic Engineering News*, 1 November 1993)

US researchers devise new tool in gene therapy

A US research team may have found a way to install a biological "switch" in human cells that could turn genes on and off as needed. The discovery may open a new way to treat human ills with gene therapy.

In existing gene therapy, a patient's cells are removed, implanted with a gene that tells cells to manufacture a protein that helps fight or resist disease and then reintroduced to the bloodstream.

Now a Harvard University chemist and a Stanford University biologist are talking about a new era of "regulated gene therapy," in which one pill switches on a protein-making gene, and then a second pill turns it off.

It may be possible, for example, for a diabetic to get an infusion of cells engineered with the gene switch and the insulin gene. Then, instead of taking several injections of insulin a day, the patient could take non-toxic pills to switch the insulin gene on and off as needed.

The US research team is designing a "fail-safe" switch that will cause the genetically engineered cells to self-destruct if they malfunction, cause unwanted side effects or have simply finished their job.

The invention hinges on the workings of cell receptors designed to grab hold and react to chemical signals drifting by in the bloodstream. Each protein receptor reacts to one particular chemical signal and no other.

When a receptor is tripped by a passing chemical, it launches a train of signals that reach into the nucleus of the cell where the genes reside. The signals tell the cell to start reading the "message" written in a particular gene: instructions to begin making a certain protein. For instance, a rising concentration of glucose in the blood trips a receptor that turns on the insulin gene in certain cells in the pancreas gland.

Drs. Schreiber and Crabtree created a synthetic receptor, derived from T-cells, that helps fight off invasions of foreign tissues. The T-cell receptor consists of several identical but separate proteins that hang side by side just below the cell surface.

The receptor lies dormant until some chemical permeates the cell and links two or more of the proteins together. This linking tells a gene in the T-cell to begin making proteins that launch an attack against, say, a transplanted kidney. (Source: *The Wall Street Journal Europe*, 27 January 1994)

HIV-killing cells used as experimental gene therapy

Targeted Genetics Corp. (TGC, Seattle, WA) announced the start of a gene therapy trial using genetically modified cells that specifically recognize and destroy HIV-infected cells. The trial will evaluate the safety and anti-viral effects of HIV-specific cytotoxic killer T-cells in participants who are HIV-positive.

The trial is a collaboration between scientists at Targeted Genetics and the Fred Hutchinson Cancer Research Center, and is being sponsored by TGC.

The treatment involved adoptive immunotherapy in which T-cells that specifically kill HIV-infected cells will be isolated and expanded in tissue culture by investigators at the Hutchinson Center. The cells will then be modified to contain a special suicide gene (HyTK) developed by scientists at TGC. The genetically modified cells will then be expanded to several billion cells and reinfused into participants to enhance their immune system's ability to fight off symptoms of HIV. (Source: *Genetic Engineering News*, 1 November 1993)

Mitsubishi Kasei visualizes protein nuclear entry

Mitsubishi Kasei Corp. has developed a new way to visualize how an extrinsic protein enters the nucleus when microinjected into a living cell.

The method involved serial microinjection of proteins into one thousand living cells. Since the proteins begin to enter the nucleus as soon as they are injected, the cells are killed at one thousand stages after injection to freeze the penetration process at a thousand steps. The technique is analogous to motion picture frames with each frame showing a specimen at one point in an ongoing process.

The specimens can be labelled with fluorescence or dyes to investigate the changes in the cell caused by protein injection and the behaviour of a protein in the cell. Key to developing the technique was ensuring successful microinjection which requires a high degree of skill. Mitsubishi Kasei devised a method to ensure virtually 100 per cent successful microinjection at a rate of 10 to 30 injections per minute. (Source: *McGraw Hill's Biotechnology Newswatch*, 7 February 1994)

Showa University develops gene detector

A research group at Showa University has developed a highly sensitive gene detection method that can be used for diagnosing hereditary diseases. The method combines capillary electrophoresis with laser fluorescence and is 100 times more sensitive in detecting neonatal hereditary diseases than ultraviolet detection methods. The researchers believe that the new technique will also prove useful for automatic analysis in final diagnosis of viral diseases. (Source: *McGraw Hill's Biotechnology Newswatch*, 7 February 1994)

Tay-Sachs gene screen yields baby and new hope

The delivery of a 5-pound, 12 ounce girl in an East Texas hospital may be the birth of hope for couples carrying the gene for Tay-Sachs and other genetically transmitted diseases.

The healthy infant was one of four fertilized ova tested as an 8-cell-old pre-embryo by a team led by Gary Hodgen of the Jones Institute for Reproductive Medicine, Norfolk, VA.

The team used a needle a fifth the width of a human hair to extract DNA from one of the eight cells of the pre-embryonic baby and the three other eggs. Then Hodgen said he used a speeded up version of PCR amplification that he developed to produce 1 million to 1.25 million copies of the DNA from the cellular matter within six to eight hours. Time was a factor because the fertilized ovum had to be implanted before it grew too large.

Of the four pre-embryos tested, three were clear of the Tay-Sachs gene, one was a carrier. Only one of the three implanted pre-embryos developed.

In the near future Hodgen hopes to expand his portfolio of diseases to include cystic fibrosis, haemophilia and perhaps a dozen other genetic ailments.

Similar tests are being worked on at four medical schools, Hodgen said. The most advanced is in Hammersmith, England, where an X-chromosome link test has been developed for pre-embryos carrying cystic fibrosis genes. Cornell, New York and Baylor, Texas, are working on other diseases. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 7 February 1994)

Structure of immune system protein determined

Six years ago, biochemists Jack L. Strominger, Don C. Wiley, and co-workers at Harvard University published the first 3-D structure of human class I MHC (major histocompatibility complex) protein, one of two classes of membrane-bound proteins that "present" antigenic peptides for immune recognition. Now, the same group has also determined the x-ray structure of the human class II MHC protein. MHC proteins display processed (partially digested) peptide fragments from foreign antigens. Processed antigenic peptides complexed to class I MHC proteins are recognized by killer T-cells, which then proliferate and destroy antigen-containing cells. Antigens displayed by class II MHC proteins are recognized by helper T-cells, which proliferate and secrete cytokines that induce production of killer T-cells and antibodies. A major difference between the two classes now appears to be that the peptide binding pocket is blocked at both ends in class I MHC proteins, whereas it is open in class II MHC proteins, enabling peptides to poke out at the ends like a foot-long hot dog in a 10-inch bun. In addition, class I MHC proteins are heterodimers, whereas class II MHC proteins crystallize as dimers of heterodimers—suggesting that dimerization of class II MHC proteins may occur as part of the mechanism by which helper T-cells become activated, the researchers say. (Reprinted with permission from *Chemical & Engineering News*, 5 July 1993, p. 19. Copyright (1993) American Chemical Society)

Antibiotic produced by catalytic antibody

Catalytic antibodies have been developed that hydrolyse a biologically inactive chloramphenicol ester to produce the antibiotic chloramphenicol, a possible step towards the use of catalytic antibodies in medicine. Ikuo Fujii and co-workers at the Protein Engineering Research Institute, Osaka, Japan, chose to work with chloramphenicol and its monoester derivatives for a number of reasons. For one, the molecules contain a *p*-nitrophenyl group, which means they are likely to be highly immunogenic. Also, the monoester and chloramphenicol have quite different conformations, which should suppress product inhibition of catalytic activity. The researchers elicited antibodies against a phosphonate transition-state analog of the hydrolysis reaction. The antibodies catalysed the hydrolysis of the chloramphenicol monoester with multiple turnovers to generate enough chloramphenicol to inhibit bacterial growth in an assay. The researchers suggest that use of catalytic antibody technology could help overcome the problem of delivering highly toxic agents exclusively to target tissues through creation of bifunctional antibodies that combine site specificity with the ability to catalyse reactions that cannot be accomplished by natural enzymes *in vivo*. (Reprinted with permission from *Chemical & Engineering News*, 7 June 1993, p. 28. Copyright (1993) American Chemical Society)

Genes turn on to a puff of gas

Nitric oxide, already one of the brightest stars in the physiological firmament, has yet another talent, US researchers have discovered.

Nitric oxide is a short-lived gas that our bodies use as a chemical signal. Despite enjoying only a few seconds of existence, it has a hand in all manner of processes. The gas, which is toxic in large amounts, also helps the immune system to ward off infections.

Now a dramatic new accomplishment has been added to nitric oxide's repertoire: altering the activity of genes. Natalia Peunova and Grigori Enikolopov of the Cold Spring Harbor Laboratory in New York made their discovery while working with cultured, neuron-like cells from the adrenal gland.

The researchers studied the activity of a pair of genes called *c-fos* and *c-jun*. The role of these genes is to control the actions of other genes. So any chemical that switches on *c-fos* and *c-jun* is ideally placed to influence the destiny of cells, perhaps opening up new avenues of growth and development. In the brain, such changes could underlie memory.

Peunova and Enikolopov wondered if nitric oxide could switch on *c-fos* and *c-jun*. Their first results were disappointing: nitric oxide on its own could not throw that all-important genetic switch. They then decided to see what would happen if they supplied nitric oxide while simultaneously supplying chemicals that increase levels of calcium ions in cells. They tried this because calcium is a ubiquitous chemical messenger that can switch on *c-fos* and *c-jun* if present in large enough amounts.

The experiment paid off. Nitric oxide and calcium together had a much greater impact on *c-fos* than calcium alone. This cooperative behaviour disappeared if the two stimuli were applied separately.

Nitric oxide, it seems, amplifies the effects of calcium—but only if it arrives in the cell at the same time as the calcium. This means that a calcium signal too weak to turn on *c-fos* might be made more potent with help from nitric oxide. Enikolopov says: "If the calcium signal coincides in time with a wave or a puff of nitric oxide—which might be produced even by a neighbouring cell—then this weak calcium signal effectively becomes a strong signal, in terms of its consequences."

Such a mechanism could turn chemical ephemera—the ebbing and flowing of calcium ions and gentle currents of nitric oxide—into changes in gene expression and finally into alterations in the "wiring" of the nervous system. That proposal is consistent with modern ideas about the workings of memory, a process in which nitric oxide seems to

play a crucial part, according to other independent evidence.

Enikolopov now wants to extend the team's findings to fully fledged neurons from a rat's brain. "What we're doing now is working with cortical neurons to see whether the same effect can be detected," he says. First indications are promising. "We can see the same thing, but on a much more complicated level," he says.

Work is also under way to unravel the biochemistry behind this most impressive process—by which a simple, fleeting puff of gas brings about profound and long-lasting changes in the behaviour of cells. (Source: *New Scientist*, 11 September 1993)

Insulin secretion from a single cell observed

Insulin secretion from individual pancreatic beta cells has been detected for the first time by assistant chemistry professor Robert T. Kennedy and colleagues at the University of Florida, Gainesville. The researchers achieve millisecond time resolution and zeptomole (10^{-21}) sensitivity in an amperometric measurement made using a carbon-fibre microelectrode modified with a polynuclear ruthenium oxide-cyanoruthenate film. To detect the secretion event, the electrode is placed 1μm away from a beta cell that is stimulated with K^+ or glucose. The detection of approximately 600 zeptomoles of insulin corresponds to the expected value for the amount of insulin contained in a single vesicle. Another approach, designed for *in vivo* measurements, is based on microdialysis sampling combined with capillary zone electrophoresis with laser-induced fluorescence detection. The researchers are exploring the use of a fluorescent-labelled antibody as a tag for insulin to increase the selectivity of tagging reactions in this scheme. (Reprinted with permission from *Chemical & Engineering News*, 12 April 1993, p. 38. Copyright (1993) American Chemical Society)

Do genes jog the body's immune memory

Researchers in Britain are gaining new clues from studies of people with acute viral infections such as glandular fever, chickenpox and the early stages of HIV infection. Their findings support growing evidence that the immune system's memory needs more "jogging" than was thought. And their work could lead to new treatments.

At the heart of the studies is a gene so important that it is conserved in most species. This gene, known as *bcl-2*, is best known in humans for what it does when it goes wrong. When it is overactive, the body makes too many white blood cells and this can cause certain leukaemias. But when it functions normally, *bcl-2* regulates the numbers of T-cells of the immune system.

Now Arne Akbar, Mike Salmon, George Janossy and colleagues at the Royal Free Hospital in London have studied *bcl-2* in people with chickenpox and Epstein-Barr virus—the cause of glandular fever. The patients' immune systems respond rapidly to these infections by activating large numbers of a particular subset of T-cells that specifically recognize the virus. These cells are "primed" to respond to the infection if it returns.

Yet within a short time, most of these cells die off. If they did not, the balance of cell numbers would be disturbed. The cells commit "suicide"—a form of programmed cell death known as apoptosis.

Scientists have already shown that *bcl-2* can prevent cell suicide in certain groups of cells. And they have found that, compared with healthy subjects, *bcl-2* is much less active in the primed T-cells of patients with viral infections. Low levels of gene expression are found in apoptosing cells. The Royal Free scientists believe there is evidence that the gene protects against apoptosis in mature T-cells.

At first sight, this looks like a paradox. The very cells that are primed to respond to the infection are also prone to suicide because they lack *bcl-2*. So how can they "remember" the infection for next time? The answer could be that "memory may be far more dynamic than we thought," say Akbar and colleagues.

Several studies have shown that small amounts of antigen from invading organisms remain in the body long after the infection has been fought off. If the cells are constantly stimulated by these antigens, they express more *bcl-2*, which in turn protects them against suicide.

In the laboratory, the Royal Free group tested blood samples from the patients. They found that primed cells from these patients could be "rescued" by adding to the culture a messenger protein or cytokine known as interleukin-2. IL-2 is produced by CD4 cells of the immune system and stimulates the production of *bcl-2* by the primed cells. Another means of rescuing cells is to add fibroblasts, a type of tissue cell that also prevents apoptosis.

The findings could help to unravel some of the abnormalities seen in the immune systems of people with HIV infection. Researchers know that in HIV-positive patients, more T-cells commit suicide than in healthy people. Because the virus persists in their bodies, their immune systems are constantly overstimulated, until T-cells become exhausted and fail to respond to new infections. Another problem is that the virus kills off a number of their CD4 cells in the lymph nodes and elsewhere. So some of their cells are dying by apoptosis and other cells that make IL-2 are directly killed by HIV. Until now, says Janossy, scientists have tried to explain these problems without studying the role of *bcl-2*, but now the Royal Free scientists have shown that cells in the lymph nodes of HIV-positive people produce less *bcl-2* than normal.

Could the immune systems of people with HIV be restored by keeping the expression of the gene at higher levels? The team is interested in the idea, but warns that there is no obvious, safe therapy yet: IL-2 could overactivate the immune system and levels of *bcl-2* protein would have to be carefully monitored because overactivity could cause leukaemias. They stress that their findings are a first step. (Source: *New Scientist*, 28 August 1993)

Alzheimer's gene "the most important ever found"

A gene linked with the most common form of Alzheimer's disease is electrifying researchers who study this degenerative neurological disease. There is now strong

evidence that people who carry a particular version, or allele, of the gene have an increased risk of developing Alzheimer's disease after the age of 65. The gene codes for apolipoprotein E (ApoE), a protein known principally for its role in ferrying cholesterol through the bloodstream. Now researchers have discovered ApoE in suspicious amounts in the plaques, deposits and neurofibrillary tangles in the brains of Alzheimer's patients.

Previously, two genes, located on chromosomes 21 and 14, had been linked to the rarer form of Alzheimer's, which strikes before 65. In 1991, Margaret Pericak-Vance, a genetic epidemiologist working in the laboratory of Allen Roses at Duke University in North Carolina, reported an association between late-onset Alzheimer's and a region on the long arm of chromosome 19.

A team from Roses' laboratory led by Warren Strittmatter and including Pericak-Vance pointed out that ApoE binds to the mysterious plaques in the brains of Alzheimer's patients, that the gene for ApoE is found in the same region of chromosome 19 which Pericak-Vance had associated with Alzheimer's, and that patients with late-onset Alzheimer's were more likely to carry one particular ApoE allele known as ApoE4. John Hardy of the University of South Florida, who led the group which found the Alzheimer's gene on chromosome 21, calls the link with the ApoE4 gene "the most important finding that's ever been made in the epidemiology of Alzheimer's disease".

In the study, the Duke team showed that in 42 families with familial late-onset Alzheimer's, both the risk of getting the disease and the age at which the disease struck varied with the number of ApoE4 alleles a person carried. Of those who did not carry the ApoE4 allele, 20 per cent got Alzheimer's, and the mean age of onset was 84 years. Of those who carried only one copy of ApoE4, 47 per cent got the disease, and the mean age of onset was 76 years. And of those who inherited ApoE4 from both their mother and their father, 91 per cent were afflicted and the mean age of onset was 68 years. So the risk of getting the disease was eight times as high in those who had the highest "gene dose" of ApoE4. "We were surprised that the effect appears to be so strong," says Pericak-Vance.

Meanwhile, the Duke team, this time led by Ann Saunders, also found the "gene dose effect" in some Alzheimer's patients who do not come from families where the disorder appears to be inherited. The link between the gene and both the familial and "sporadic" forms of late-onset Alzheimer's has already been confirmed by at least half a dozen other laboratories. Hardy and his former colleagues at St. Mary's Hospital Medical School in London, led by Martin Rossor, have confirmed the link in a series of British families.

The Duke researchers have left open the possibility that it is not the ApoE gene itself which is implicated in Alzheimer's disease, but another gene that is so close to the ApoE gene that it is inherited virtually all the time along with the ApoE gene. However, the fact that ApoE is associated with the lesions in the brains of Alzheimer's patients greatly strengthens the argument that ApoE does play a role in causing Alzheimer's. "Such a double coincidence just doesn't seem likely," says Hardy.

Although researchers see ApoE4 in the brains of Alzheimer's patients, at this point they can only guess the role that it plays in the disease. Hardy says the new findings fit "surprisingly well" with the idea that the beta amyloid plaques and deposits found in the brains of Alzheimer's patients lead to the death of brain cells and subsequent dementia. One possibility is that the ApoE4 form of the protein binds to the beta amyloid and somehow anchors the deposits in the brain.

But even before the role the protein plays in the disease is understood, clinicians could use the new genetic link to help diagnose Alzheimer's in patients by determining how many copies of the ApoE4 allele they carry. Until a prevention or cure for the disease is developed, however, the ability to test for a predisposition to Alzheimer's could be a mixed blessing for people who dread the onset of the disease. (Source: *New Scientist*, 21 August 1993)

Chemical Imbalances in Alzheimer's measured

A new technique that uses standard magnetic resonance imaging (MRI) equipment to characterize chemical imbalances in the brains of Alzheimer's disease patients has been developed by scientists at the Huntington Medical Research Institutes in Pasadena, CA. The group's work may lead to a rapid, straightforward diagnostic test for Alzheimer's disease and may be applicable to diagnosing other dementias.

Using an MRI version called magnetic resonance spectroscopy (MRS), a team led by MRS unit director Brian D. Ross studied two regions in the brains of 11 elderly Alzheimer's patients and 10 healthy age-matched control subjects. Compared with the controls, the patients showed a 22 per cent increase in *myo*-inositol—derivatives of which serve as messengers in cells—and an 11 per cent decrease in *N*-acetylaspartate, a nerve cell marker.

The MRS-based test for Alzheimer's disease takes about 30 minutes, Ross notes. By contrast, current procedures for diagnosing Alzheimer's involved lengthy memory function and neurophysiological tests that often upset patients and, in any case, do not provide definitive results. Currently, only an autopsy can confirm the presence of Alzheimer's disease.

The new findings also challenge current thinking about the mechanism of Alzheimer's, Ross says. In Alzheimer's disease, neurons that respond to the neurotransmitter acetylcholine—so-called cholinergic neurons—are lost, so researchers have speculated that the disease somehow involves disruption of acetylcholine processing in the brain. Many recently developed therapeutic agents for Alzheimer's disease focus on acetylcholine and its receptors.

Ross and his co-workers found no difference between the concentration of acetylcholine precursors in patients in the early or middle stages of Alzheimer's disease and in control subjects. This suggests acetylcholine is not involved in these stages of the disease.

Use of MRI to study Alzheimer's disease was made possible by software called Clinical Proton MRS, which was developed at the Huntington facilities. This software

enables researchers to extract spectroscopic information from MRI signals. An automated version of the software, called Proton Brain Examination (PROBE), allows a patient to be tested in only 10 minutes, Ross says.

The team used MRS to quantify four classes of brain metabolites: *N*-acetyl residues, phosphorylcholine and glycerophosphorylcholine, *myo*-inositol, and creatine. The decrease in *N*-acetyl residues observed in Alzheimer's disease patients was not unexpected, Ross says. A decrease of this metabolite is a common pathologic finding in proton magnetic resonance studies of diseases that cause nerve cell loss.

The consistent elevation of *myo*-inositol in the brains of Alzheimer's disease patients was largely unexpected. The most likely mechanism is inhibition of the enzyme or enzymes responsible for converting *myo*-inositol to phosphatidyl inositol. This points to disruption of the polyphosphoinositol second-messenger cascade as a possible cause for the pathology observed in Alzheimer's disease, Ross explains. (Abstracted with permission from *Chemical & Engineering News*, 10 May 1993, p. 6. Copyright (1993) American Chemical Society)

Cell growth acceleration by immobilized growth factor proteins

Professor Y. Imanishi and his assistant Y. Ito of Kyoto University (Division of Material Chemistry, Faculty of Engineering) have developed a method to accelerate cell growth by immobilized growth factor proteins. Biosignal molecules, such as cell growth factor proteins and cell adhesion factor proteins, were immobilized upon various matrices. These included surface-hydrolyzed-poly(methyl methacrylate), surface-hydrolyzed-poly(ethylene terephthalate) and polyurethane containing amino groups incorporated by glow-discharge, etc. The immobilized biosignals (the growth factors insulin and transferrin) were not only bioactive without being incorporated into the cell, but were also more active than free proteins. The strong biosignals were attributed to the high concentration of molecules localized on the surface, the promotion of crosslinking of the biosignal-receptors in the cell membrane, and the inhibition of biosignal down-regulation. The developed biosignal-immobilized materials can be applied to cell culture and artificial organs.

Mammalian cell culture is an important technology in the fundamental research and for the industrial production of a large quantity of biologically significant materials. Serum or serum substituents must be used to support cell growth in addition to nutrients. However, the use of serum is undesirable because of it high cost and the complications due to the serum proteins in the separation of various products. Therefore, serum-free media are being sought. The concept of an immobilized biosignal provides a completely new culture technique. The other application of biosignal-immobilized materials is in the area of hybridization of synthetic materials and organs such as artificial blood vessels. In the experiment, the artificial vessel made of a plastic tube was coated with blood endothelial cells, which was provoked by the immobilized biosignal proteins. A tube supporting both insulin and collagen was rapidly covered by endothelial cells which were stable for more than a year.

To increase the growth acceleration, two approaches were used. A spacer chain consisting of polyethylene glycol was incorporated to enhance the mobility of the immobilized protein because crosslinking of the biosignal/receptor complex was considered very important. A variety of biosignal molecules form a complex network by cross communication to maintain cellular homeostasis, so coimmobilization of different biosignal molecules was introduced. When cell adhesion factor proteins such as collagen and fibronectin or the core peptide, Arg-Gly-Asp-Ser (RGDS) with insulin were coimmobilized, both the cell adhesion and growth were remarkably accelerated.

Biosignals are classified into two types: low molecular weight types, such as steroid hormones, which permeate the cell membrane and directly interact with the nucleus; and high molecular weight types such as polypeptide growth factors which interact with receptors on the cell membrane. These are bound by their receptors on the target cell surface and the complex is internalized into the cell, dissociated and decomposed in lysosomes, and some of the liberated receptor is transported back to the cell surface. When the biosignal is immobilized or insolubilized, it is not internalized even after forming a biosignal/receptor complex and the immobilized biosignal continues to act. For more information contact: Kyoto University, Division of Material Chemistry, Faculty of Engineering, Yoshida Honmachi, Sakyo-ku, Kyoto 606. Tel: +81 75-753-5608, Fax: +81 75-753-4911. (Source: *JETRO*, January 1994)

Gene encodes nitric oxide enzyme

The first cloning and expression of the human gene for inducible nitric oxide synthase, the enzyme that produces large quantities of nitric oxide (NO) in the body, may have important therapeutic implications. The gene was discovered by David A. Geller, Timothy R. Billiar, and colleagues at the University of Pittsburgh Medical Center, and Charles J. Lowenstein and Solomon H. Snyder of Johns Hopkins University School of Medicine. Nitric oxide is currently under intense study because of its key role in nerve signal transmission, blood pressure regulation, blood clotting inhibition, and other functions. Production of inducible NO synthase (and hence NO) increases in response to sepsis, a bacterial infection that causes some 100,000 deaths per year in the US. Although increased NO has beneficial effects, such as prevention of blood clotting and organ damage, it also dramatically lowers blood pressure, causing septic shock. "By understanding this specific gene and enzyme, we could potentially enhance NO synthesis when it would be beneficial to a patient or block NO production when it would be harmful", says Billiar. (Reprinted with permission from *Chemical & Engineering News*, 26 April 1993, p. 22. Copyright (1993) American Chemical Society)

Progress in gene therapy of neurological diseases

Two gene therapy studies reported recently offer hope for treating Parkinson's disease and repairing the demye

linating nerve damage that occurs in multiple sclerosis and other neurodegenerative diseases. Jon A. Wolff and colleagues in the departments of paediatrics and medical genetics at the Waisman Center of the University of Wisconsin, Madison, report progress in transplantation of cells into the brains of Parkinson's patients to increase production of dopamine. The researchers introduced muscle cells engineered to express a dopamine-producing enzyme into the brains of parkinsonian rats. The enzyme was expressed at a high and stable level for six months, yielding functional concentrations of dopamine. Mark Noble of the Ludwig Institute for Cancer Research, London, and colleagues also report that injection of cultured neural cells into demyelinated sections of rat spinal cords causes extensive remyelination of the injured nerve fibres. (Reprinted with permission from *Chemical & Engineering News*, 5 April 1994, p. 26. Copyright (1993) American Chemical Society)

Enzyme clue to cause of degenerative disease

Until now there has been no cure for amyotrophic lateral sclerosis (ALS). But researchers led by Robert Brown of Massachusetts General Hospital have opened the door to possible new treatments. They have found a gene on chromosome 21 which they believe is responsible for many cases of the disease. The discovery could also shed light on other degenerative nerve diseases such as Parkinson's and Huntington's diseases.

The gene is responsible for the production of an enzyme called superoxide dismutase. This neutralizes the highly reactive oxygen compounds that appear to damage motor nerves. The researchers report they found mutations in the superoxide dismutase genes of 13 families with an inherited form of ALS. About 10 per cent of cases are inherited: the rest seem to arise spontaneously.

Brown believes that about half of the inherited cases of ALS may be the result of mutations in the gene, and he suspects that some of the spontaneous cases may also be caused by defects in this gene. There are two other genes, on different chromosomes, that code for different forms of the enzyme, and the team is now investigating whether mutations in these genes might be responsible for the other cases of ALS.

Researchers began the search for the ALS gene in 1984. It proved particularly difficult to trace the inheritance of the defective gene through families because many people were already dead: most die within five years of the symptoms appearing.

Brown cautions that the presence of the defective gene will need to be confirmed in many more ALS patients. And the group is also trying to confirm its discovery by transferring the defective gene into a mouse to see if this will cause the disease.

If it turns out that oxygen "free radicals" do kill motor neurons, this would suggest a number of possible drug treatments, including giving patients the enzyme itself, or drugs that scavenge the free radicals. (Source: *New Scientist*, 6 March 1993)

UCLA researchers discover mechanisms of anti-ageing gene

Scientists at the UCLA School of Medicine have found the mechanisms by which a proto-oncogene (BCL-2) can prevent the death of brain cells. A research team led by Dr. Dale Bredesen found that BCL-2 decreases brain cells' production of reactive oxidants. "The exciting thing about this finding is that BCL-2 prevents cell death from conditions that are analogous to Alzheimer's disease and other degenerative diseases", said Dr. Bredesen, at the UCLA Center on Aging. "In addition, we now understand for the first time how BCL-2's protective influence works."

The study has important implications for planning future clinical interventions to treat neurodegenerative diseases. "One possibility is gene therapy to replace BCL-2 in brain cells", Dr. Bredesen said. "But we may be able to increase anti-oxidant levels in the brain in other, simpler ways. At least now we know where to focus our efforts."

The researchers removed a key antioxidant (glutathione) from neural cells in culture. Some of the cells contained BCL-2 and some did not. In those cells without BCL-2, production of free radicals increased 23 times. The same type of cells with BCL-2 experienced only a small rise in production of free radicals.

In addition, 100 per cent of the cells without BCL-2 were killed by the sudden influx of free radicals, whereas none of the cells with BCL-2 died. "This proves that BCL-2 prevents cell death by decreasing the cells' production of reactive oxygen species," noted Dr. Bredesen. (Source: *Genetic Engineering News*, 1 January 1994)

New substance found to increase brain nerve growth factor

Mitsubishi Gas Chemical announced the discovery of a substance that accelerates production of a protein triggering nerve growth in the brain. Results have been confirmed at the stage of animal experiments, and possibilities exist for future development as a therapeutic drug for Alzheimer's dementia. The company plans joint development with a pharmaceutical firm and is searching for a partner.

Mitsubishi Gas Chemical produced the substance held promising as a therapeutic drug for dementia by partially altering the structure of pyrroloquinoline quinone (PQQ), a vitamin-like substance present in the body. Mitsubishi and the Sagami Central Chemical Research Institute are continuing joint research on the substance, known as oxazopyrroloquinoline (OPQ).

A protein present in the brain known as nerve growth factor, which brings about the growth of cerebral nerves, and the fact that OPQ stimulates production of nerve growth factor was reportedly learned in experiments with rats. According to the company, nerve growth factor in the cerebrum of rats doubled when 1 mg OPQ per 1 kg body weight was administered four times. In addition, the amount of nerve growth factor produced changed in accordance with dosage when different dosages were given.

Mitsubishi Gas Chemical surmises that OPQ in the brain is converted to PQQ, and PQQ accelerates the

production of nerve growth factor. Future plans are to bring about the conversion chemically. (Source: *Nikkei Sangyo Shimbun*, 11 June 1993)

Research on animal genes

Arresting the ravages of time

Men and women have sought eternal youth throughout the ages. Today, the ageing process remains hotly debated as scientists strive to understand and control it. But now US scientists report convincing evidence to support one particular ageing theory.

A popular hypothesis—but one that has never been proven—puts ageing down to reactive oxygen species (ROS), such as oxygen free radicals and hydroperoxides, which escape the body's antioxidant defences. Nerves and muscles deteriorate as ROS inflict molecular damage, some of which is irreparable and accumulates with age.

ROS are initially produced when dioxygen is reduced to generate superoxide anion radical and hydrogen peroxide. If hydrogen peroxide is not eliminated by the body, it goes on to produce the highly reactive hydroxl free radical which is widely believed to be the main culprit in oxidative damage.

William Orr and Rajindar Sohal at the Southern Methodist University in Dallas worked on the assumption that if ROS were linked to ageing, then enhancing defences against them would extend life-span. The two generated transgenic fruit flies that contained two extra copies of both Cu-Zn superoxide dismutase (SOD) and catalase genes. These enzymes act in tandem to provide the primary route of antioxidant defence: the first enzyme converts superoxide anion radical into hydrogen peroxide and the second breaks it down into water and oxygen.

The team found that the flies lived a third longer than usual. Their physical "fitness" lasted longer and they suffered less protein damage. The key seems to be the co-overexpression of the CuZn SOD and catalase genes, says Orr; only the enzymes together have this effect.

Long-lived flies may not be popular with most people but, as the biochemistry of flies and mammals is almost equivalent, it looks like there is a good chance of a similar strategy working in mammals, explains Orr. (Source: *Chemistry & Industry*, 7 March 1994)

The spiteful gene

People inherit diseases. This presents biology with an intriguing question. Why have the genes that cause them not been eliminated by natural selection? The usual explanation is either that such genes are recent mutations awaiting their turn for the Darwinian reaper to call, or that they cause diseases of old age that affect only those whose reproductive days are behind them.

The persistence of some genetic diseases can be explained neatly by natural selection. For instance, one copy of the gene that causes sickle-cell anaemia confers immunity to malaria; two copies (one from each parent) kill the carrier. So an uneasy compromise ensues: the sickling gene cannot take over, but nor is it eliminated. Other genetic diseases appear to confer no benefit. The only thing that severe combined anaemia and thrombocytopenia (SCAT) does for a mouse is to kill it. And yet Laurence Hurst of the University of Cambridge believes that SCAT, too, is maintained by natural selection.

The genetics of SCAT were worked out by Luanne Peters and Jane Barker of the Jackson Laboratory in Bar Harbor, Maine. Two rival genes, SCAT+ and SCAT-, compete with each other for a single site on mouse chromosome eight. What is odd about SCAT inheritance is that although it is SCAT+ that seems to cause the condition, it does so indirectly. A mouse will get the disease only if (a) it lacks a SCAT+ gene and (b) its mother has one.

Dr. Hurst's suggestion is that the SCAT+ gene is not merely selfish but spiteful—attacking its rivals while they are still in the womb, thus promoting its own chances of survival and propagation at the expense of its rival, SCAT-. His hypothesis is that the presence of SCAT+ in a mother causes her to produce a toxin that harms only those foetuses that have no SCAT+ in at least one of their chromosomes. This way the SCAT+ eliminates individuals carrying its competitor before or shortly after they are born, and so increases its own relative reproductive success.

Although his proposal is still theoretical, a gene with an action identical to that proposed by Dr. Hurst has already been shown to operate in a species of beetle. There is also a possible candidate for the toxin—an antibody to the blood's clot-forming platelets.

To some biologists this story of a mother producing an antibody to her own offspring sounds rather familiar. A rhesus-negative woman, too, will produce antibodies that may kill her own foetus if that foetus is rhesus-positive. Genetically inherited diseases may not, therefore, always be the result of genetic mistakes. Instead, such diseases could be the consequences of spiteful behaviour that is favoured by natural selection. (Source: *The Economist*, 22 January 1994)

Tufts researchers seek DNA markers to grow plumper prawns

Using DNA fingerprinting, Tufts researchers are hoping to boost American production of shrimp.

Acacia Alcivar-Warren, assistant professor of comparative medicine at Tufts School of Veterinary Medicine, in North Grafton, MA, has found genetic markers that can be used to identify high- and low-growth shrimp families.

Professor Alcivar-Warren is studying differences in mitochondrial DNA patterns and mRNA expression as potential predictors of growth. Her "subjects" are wild shrimp from Mexico, Panama and Ecuador, and samples of three specific pathogen-free (SPF) *penaeus vannamei* shrimp populations grown at the Oceanic Institute in Hawaii.

The researchers took the mDNA and mRNA from small samples of gills, allowing the specimens to remain alive for further study. Her study has revealed markers of polymorphism that can distinguish among the different populations of the pathogen-free and wild populations. The

polymorphisms of mitochondrial DNA and nuclear DNA "can be used as biomarkers to correlate with desirable growth and reproductive performances of the SPF *p. vannamei* stocks for use in selective breeding programmes", Prof. Alcivar-Warren stated. "mtDNA markers may also be useful for identifying the presence of non-indigenous species, for establishing the origin of packaged shrimp, and for identifying illegally imported shrimp." (Source: *McGraw Hill's Biotechnology Newswatch*, 7 February 1994)

Gene injections for cancer

Mice have been cured of colon cancer and a type of muscle cancer after being injected with "packages" of DNA. This method is much simpler and potentially quicker than most other forms of gene therapy. Using gene therapy to treat cancer usually involves taking immune-system cells out of the patient, priming them genetically against the cancer, and then returning them. With the DNA injection none of this is needed.

The work on mice is in the recent issue of *Proceedings of the National Academy of Sciences*. The injected DNA contains a gene from another type of mouse which manufactures a protein that marks foreign or defective cells. The protein, called H-2K^5, acts as a "siren", summoning the body's killer T-cells to come and destroy the defective cell.

The cancerous mice that received the injections did not themselves have the gene for making H-2K^5. The idea was to see whether the extra gene would help them to fight off colon cancer and a form of muscular cancer called fibrosarcoma. Before injecting the gene, it was "packaged" either in a retrovirus—a type of virus capable of inserting its own DNA into that of its host—or in microscopic "envelopes" of fatty compounds known as liposomes.

The DNA packages were injected directly into tumours. Twenty per cent of the mice receiving the treatment were cured completely, while tumours shrank markedly in 70 per cent. Untreated mice all died.

The injected DNA did not affect only the cells it was injected into, but appeared to trigger the immune system to destroy distant tumours elsewhere, including secondary growths. When tumours grow, they can avoid detection by the immune system. The injected DNA is like a "wake-up" call for the immune system, and a localized response somehow becomes a generalized response.

Moreover, it was found that while some traces of DNA reached other organs, it appeared to trigger no damage or side-effects. (Source: *New Scientist*, 22 May 1993)

Making mice a little more human

Mice genetically engineered to produce human antibodies for treating diseases such as cancer and rheumatoid arthritis could soon become a reality. Several teams around the world have now reprogrammed mice to produce fragments of human antibodies, and most are confident that mice can ultimately produce entire human antibodies, which could then be extracted and used to treat patients.

Marianne Brüggemann and her colleagues at the Agricultural and Food Research Council's Babraham Institute in Cambridge have developed mice that produce important fragments of human antibodies, called "human light chains". These carry the parts of an antibody that cling to and neutralize specific infectious agents.

The new findings build on results from 1989 when Brüggemann and Michael Neuberger of the nearby Laboratory for Molecular Biology developed mice that produce human antibody "heavy chains", the other major components of antibodies. Biotechnology companies such as GenPharm of Mountain View in California are also bidding to make mice that produce entire antibodies. The key will be to produce both heavy and light chains together—something no one has achieved yet.

Antibodies are made by the immune system to fight infections. Traditionally, pharmaceuticals companies trying to combat a human disease make antibodies that might be therapeutic by first infecting mice with it. The animals produce their own antibodies, and researchers isolate them from samples of body fluid.

Unfortunately, some patients treated with mouse antibodies develop serious allergies because their immune systems recognize surface proteins on the mouse antibodies as "foreign" and destroy them before they can be of benefit.

Some biotechnology companies have tried to overcome this by modifying mouse antibodies to include parts of human antibodies. But some, including the Cambridge team, are taking a different approach: getting the mice to produce entirely human antibodies. The mice are first given genes that humans use to make antibodies, and then the mice's genes for making mouse antibodies are deactivated.

Until recently, genetic engineers could not transplant pieces of DNA as large as those containing the instructions for making human antibodies. In humans, it consists of a piece about 2 or 3 million nucleotide bases long, but earlier methods could not transplant stretches longer than about 50,000 bases.

But now it is theoretically possible to transplant chunks of DNA millions of bases long—using yeast. This acts as a carrier for stretches of DNA so long that they have been dubbed "yeast artificial chromosomes", or YACs.

The Cambridge team, and researchers at the Washington University School of Medicine in St. Louis, mixed a broth of human DNA from blood cells with yeast cells to form millions of different YACs and used chemical probes like molecular "tweezers" to pick out yeast cells that had taken up the gene sequence for making "light chains"—a DNA segment more than 300,000 bases long.

Brüggemann's team then fused these yeast cells with "stem" cells, taken from mouse embryos a few hours old, when the cells are still undifferentiated and can become any part of the body. These fused cells bearing the YAC were then implanted into mouse embryos at the "blastocyst" stage, a few days old, and transferred into the uteri of foster mice.

The researchers found that at least three of the seven mice produced human antibody fragments in body fluids, confirming that they had assimilated the genetic instructions for making human light chains. But Neuberger was

disappointed with the amounts of fragments, which were dwarfed by those of mouse antibody. To improve on that, the researchers are crossbreeding the mice containing the YACs with mice whose immune systems have been "knocked out" by gene manipulation. (Source: *New Scientist*, 21 August 1993)

Research on plant genes

Safety assessment of introduced genes

Researchers at Monsanto's Missouri laboratories report a detailed safety assessment of the gene encoding neomycin phosphotransferase II (NPTII), which is used routinely as a selectable marker in genetically engineered crops. The safety assessment was achieved by introducing the same coding sequence into the bacteria *E. coli* and in this way produced gram quantities of the NPTII protein. Having established the equivalence of the bacterial protein to the plant protein, the researchers, headed by Roy L. Fuchs, showed in a series of experiments the complete safety of NPTII.

These results, they claim, support the view that ingestion of genetically engineered plants expressing the NPTII protein pose no safety concern. (Source: *Australasian Biotechnology*, Vol. 4, No. 1, February 1994)

New pathway to inhibit spread of viral plant disease

A team of researchers led by Roger Beachy, Ph.D., head of the division of plant biology at The Scripps Research Institute (La Jolla, CA), has determined that the spread of a prevalent plant virus can be effectively blocked by the use of genetic engineering techniques. The research shows that the Tobacco Mosaic Virus (TMV), which attacks numerous crops, including potatoes, tomatoes, eggplant, bell peppers and orchids, can be substantially slowed by manipulating a key protein—the movement protein—that enables the virus to spread from plant cell to plant cell.

In this study, Dr. Beachy's research team introduced a mutant TMV movement protein—created by deleting three amino acids—into transgenic tobacco plants. By so doing, they were able to reduce the spread of TMV from the site of infection to adjacent cells and to upper leaves presumably by preventing the gates of the plasmodesmata from opening as wide as is necessary to allow virus passage. While the experimental results prove that a mutant movement protein can confer a degree of inhibition of viral spread, the precise nature of the interference is unknown. (Source: *Genetic Engineering News*, 1 January 1994)

New protocol speeds up transgenic wheat

Researchers at Monsanto have developed what they claim is an improved protocol for the rapid and efficient production of transgenic wheat.

Using a technique first developed to modify rice and maize, Indra Vasil and colleagues have demonstrated the direct delivery of DNA into immature wheat embryos. The method permits the recovery of flowering transgenic wheat plants seven to nine months after culture.

Until now, wheat had been genetically modified using a special type of long-term regenerable callus for the introduction of foreign genes. This so-called type C callus, however, is difficult to identify and maintain.

Furthermore, it takes 12-15 months from excision and culture of the immature embryos to callus formation, DNA delivery, selection of transformed cells and the production of the first flowering generation. Such limitations have hindered the modification of wheat.

Vasil's team delivered three plasmids, each containing the selectable bar gene for resistance to the herbicide *Basta* and the beta glucuronidase reporter gene, via particle bombardment, directly into immature embryos of two spring and one winter cultivar of wheat. "The procedures used by us to obtain high frequency transformation of three winter and spring wheat cultivars should be applicable to other varieties of wheat."

The decision plant biotechnologists now have to make is which genes should they introduce into wheat. "It is likely that all the genes that are currently available, such as those for resistance to viruses, insects and other herbicides, and for starch synthesis, seed proteins, male sterility/fertility, etc., will be successfully introduced into wheat within the next two to three years," he notes. (Source: *European Chemical News*, 20/27 December 1993)

Research on viral genes

Hepatitis D responds to high doses of alpha interferon, study finds

Hepatitis D, a severe form of liver disease common in southern Europe, appears to be responsive to high doses of alpha interferon (IFN), according to a recent study.

The randomized study was conducted in Sardinia, Italy, where the disease is endemic. It evaluated 42 patients with chronic hepatitis D, a rapidly progressive form of liver disease related to dual infection with hepatitis B virus.

There is no proven therapy for hepatitis D. However, alpha interferon is widely used for the treatment of hepatitis C and hepatitis B.

In the new study, patients received either 9 million or 3 million units of IFN alpha-2a three times a week for 48 weeks or no treatment at all.

By the end of the 48-week treatment period, half of the 14 patients treated with the highest doses of IFN had a complete response, defined as a return to normal levels of serum alanine aminotransferase, a liver enzyme, and no detectable serum hepatitis D virus, the study said. In contrast, only three of 14 patients treated with the lower doses of interferon had a complete response. No one in the control group that received no drug showed a response.

Treatment with the highest doses was associated with a marked improvement in the condition of the patient's liver tissues, according to the study. Patients were followed for up to four years after stopping the therapy.

Despite the response of some patients to the IFN, relapse was common after the treatment had been stopped, according to the study led by Patrizia Farci, a researcher at the National Institute of Allergy and Infectious Diseases at the National Institutes of Health.

However, in two patients treated with the highest doses of the drug, their condition changed from chronic active hepatitis to persistent or lobular hepatitis, a less severe form of the disease. That finding, the study said, suggests IFN could prevent disease progression. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 7 February 1994)

Dyes mediate photochemical neutralization of viruses

A class of yellow, fluorescent dyes is able to enter viral membranes, absorb blue light, and undergo a chemical transformation that converts them into potent antiviral agents that can neutralize a number of viruses, including human immunodeficiency virus (HIV), according to chemists at South Dakota State University, Brookings. Associate chemistry professor David E. Lewis and co-workers have synthesized and investigated the anti-viral activity of 3-halo-4-(alkylamino)-*N*-alkyl-1,8- naphthalimides. In contrast to known photodynamic agents, the compounds do not require oxygen as a mediator of biological activity. Lewis says the research suggests that the compounds inactivate viruses by a mechanism that involves three steps: formation of a pi complex between the dye and aromatic side chains of transmembrane proteins, photochemical isomerization of the aminonaphthalene to the imino tautomer, and single electron transfer from the protein side chain to the imino tautomer resulting in covalent modification of the protein. A dimeric naphthalimide effectively neutralizes HIV *in vitro*, Lewis says, and could find use in inactivating HIV for production of vaccines or killing HIV in blood and blood products. (Reprinted with permission from *Chemical & Engineering News*, 12 April 1994. Copyright (1994) American Chemical Society)

Immune system's blind spot helps HIV

New ideas are emerging on why HIV can wreak so much havoc on the body's immune system, when for long periods it infects very few cells. Our immune system, some researchers propose, may have a deadly blind spot.

Throughout the course of HIV infection, numbers of a key immune cell—the CD4 T-cell—slowly decline. The infected person's immune system becomes less and less efficient, and eventually AIDS may develop.

Yet today's sensitive probes for the virus suggest that for much of that time, the vast majority of CD4 T-cells circulating in the body are not infected. Since the virus cannot be killing uninfected cells directly, scientists are considering other, less direct mechanisms for the depletion of the cells.

Leonard Adleman, a computer scientist at the University of Southern California, has proposed a new mechanism. The theory, simply stated, is that when the body loses T-cells, it tries to compensate by bringing the overall T-cell count up to normal. But it fails to distinguish between two types of T-cell—CD4 and CD8—and makes copies of both.

Under normal circumstances that lead to cell loss—such as bleeding—this is no problem, because both types of T-cells are lost in equal proportions. But HIV is different, because it infects and kills CD4 cells, yet leaves CD8 cells intact. If the body then normalizes the T-cell count by making both types of T-cell, the result will be a skewed ratio: too many CD8s and too few CD4s. Keep killing the CD4 cells—just one in 1,000 cells a day, Adleman has calculated—and the body's replacement mechanism could wipe out all its CD4 cells at a similar rate to the progressive loss seen in early HIV infection.

Two recent reports, both published in the *Journal of Acquired Immune Deficiency Syndromes* (Vol. 6, p. 144 and p. 153), provide evidence supporting this theory. In the first, Adleman and David Wofsy, an immunologist at the University of California, San Francisco, used antibodies to kill CD4 cells in mice. In the months following antibody injection, the overall level of T-cells in the mice returned to normal. But—just as predicted—there were too many CD8 cells and too few CD4s.

A second strand of evidence comes from a study of 321 men who were tracked for years before and after they became infected with HIV. Joseph Margolick and colleagues with the Multicentre AIDS Cohort Study noted that people infected with HIV suffered from a progressive loss of CD4 cells and a concurrent rise in CD8 cells. Yet overall T-cell counts remained normal—again, just as expected from the model, which Margolick derived independently.

The theory could not account for the whole disease, since at later stages more types of cells die.

The authors of the two studies say they would like to see the theory—and a possible therapy—tested in a monkey model for AIDS. The theory predicts that removing CD8 cells from the CD4-deficient monkeys should turn the CD4:CD8 ratio back in favour of CD4 cells once more. But since CD8 cells are vital for killing cells infected with HIV, it might be safer to identify, purify and administer blood factors that replace CD4 cells without altering the numbers of CD8 cells.

Separate studies have already shown that large amounts of HIV are hidden away and replicating in the lymph nodes even when the virus is barely detectable in circulating cells. T-cells are constantly passing in and out of the lymph nodes and come into direct contact with the virus there. This may powerfully add to the depletion of cells. (Source: *New Scientist*, 27 March 1993)

Pasteur team finds HIV opening

Researchers at the Pasteur Institute are claiming they have identified the gateway through which HIV enters and infects human cells, a discovery which could help in vaccine development. Ara Hovanessian, who heads the Pasteur team, believes the doorway is a receptor molecule called CD26. AIDS researchers have known for several years that HIV links up with the CD4 receptor but did not know how the virus entered the cell.

Presenting the Pasteur group's findings at an AIDS conference in October 1993, Hovanessian said: "The AIDS

virus has always managed to have the key to open the CD4 receptor-lock. We hope to be able to develop drugs capable of jamming the CD26 lock". And because every HIV strain uses CD26 to infect cells, he hopes to be able to develop a universal vaccine.

Hovanessian's announcement was given a mixed reception by the scientific community. While leading AIDS researcher Robert Gallo of the US National Institutes of Health described the findings as very exciting, Marc Girard, head of vaccine development at the Pasteur Institute, cautioned that the reported results are at an early stage.

Similarly, other researchers noted it is possible that HIV could infect cells using other receptors. (Source: *European Chemical News*, 1 November 1993)

Virus transports "foreign" gene into rat's brain

Prospects for two new forms of gene therapy have improved with findings announced by separate teams of French scientists. One group has transferred a gene into the brain cells of rats, using a weakened form of adenovirus, a common respiratory virus. The aim is to develop treatments for neurological disorders such as Parkinson's disease. The second team has brought therapy for muscular dystrophy a step closer by inserting an altered adenovirus into the muscle cells of mice and making it produce dystrophin, a protein that sufferers lack.

A team at the national research agencies CNRS and INSERM tested the ability of adenovirus to enter brain cells by inserting into its genetic material a "marker" gene, which produces the protein enzyme betagalactosidase. Copies of the virus were transferred into cultures of rat neurons, and virtually all the cells expressed the gene—that is, they made detectable quantities of the protein it encodes—without any obvious toxic effects. The protein has no therapeutic value, but the experiment shows the procedure works.

Next, the scientists introduced the altered virus directly into various different parts of the brains of adult rats. After 24 hours, the brain cells began to express the marker gene strongly, and they continued to do so for two months. Although very high concentrations of the virus killed nerve cells at the injection site, the concentration that would be needed for gene therapy was not toxic, says the team.

Until now, no one has succeeded in making adenovirus infect brain cells. Naturally, the virus targets the cells lining the airways. The adenovirus infection remained localized to cells around the point of injection. The virus had been disabled so that it was incapable of replicating. Jacques Mallet of the CNRS says this suggests that any future treatments using this technique would be very subtle and specific, replacing cruder experimental techniques such as grafts of foetal tissue. Other scientists have attempted to target brain cells for gene therapy. Retroviruses, the most widely used carriers of genes to be tested so far, are not suitable because they express genes only in cells that are dividing. Healthy brain cells rarely divide after birth. Another approach to gene therapy for neurological diseases is to inject skin cells infected with an altered virus that carries a gene for a nerve-nourishing protein, NGF. The skin cells should then secrete the NGF close to the nerve cells.

In the second experiment, a team led by Thierry Ragot at the Gustave Roussy Institute in Paris injected an altered adenovirus carrying a "mini" version of the dystrophin gene, which is faulty in people with Duchenne muscular dystrophy, into mouse muscles. To everyone's surprise, the gene expressed the protein in up to half the muscle fibres of the injected animals.

DMD is a common and crippling disorder which affects one in 3,500 newborn boys. Attempts at gene therapies for the disease have so far been disappointing, partly because it is difficult to make the gene express the dystrophin protein efficiently in muscle cells. By contrast, the Paris team has produced encouraging results. They injected 10 "mdx" mice—a special strain of mouse with a gene defect comparable to human DMD—with adenovirus carrying the minidystrophin gene. Between 5 per cent and 50 per cent of the muscle fibres injected expressed the protein. The team warns that these findings are only the beginning and that more tests will be needed to see whether the virus can be made to infect all muscles in the body. So far, they have attempted only to inject one muscle. Ragot says it is too early to predict whether trials of the therapy in people might be possible. (Source: *New Scientist*, 20 February 1993)

The expression of hybrid somatostatin-hepatitis B surface antigen particles with recombinant vaccinia virus

Research carried out by Xu Wenzhong and Du Nianxing of the Department of Veterinary Medicine, Nanjing Agricultural University, and Li Guangdi, Zhu Nongliao, and Wang Yuan of Shanghai Institute of Biochemistry, Academia Sinica, report that the synthesized somatostatin (ss, 14 aa) gene was fused with hepatitis B surface antigen gene (HBs gene) at the 3′ end corresponding to amino acid residue 223. The fusion gene ss/HBs was then cloned into the transfer vector pGJP-5 under the control of P7.5 promoter. CV-1 cells were contransfected with pGJP-ss/HBs and vaccinia virus (Tian Tan strain). TK⁻ phenotype recombinant viruses were selected by plaque technique and identified by Southern blot and hybridization. The expression of ss and HBsAg was detected by dot-ELISA and RIA. The secreted ss/HBsAg hybrid particles at about 22 nm in size were seen under electron-microscope. It was suggested that the ss antigens were exposed on the surface of the hybrid particles. (Source: *Acta Biochimica et Biophysica Sinica*, Vol. 25, No. 2, March 1993)

Isolation of epidemic haemorrhagic fever virus from a premature brain infected in utero

Shang Shouli, Ma Lixian, et al. of the Department of Infectious Diseases, Shandong Medical University, Jian, report that a strain of virus was isolated by cell culture and epidemic haemorrhagic fever (EHF) viral antigen was identified by immuno-histochemical staining from brain

tissue of a 7-month dead foetus aborted from a pregnant woman, who was suffering from EHF at febrile phase. After a series of specific serological tests and animal inoculation study, the virus was determined to be Hantaan strain of EHF virus, and the possibility of reovirus contamination was ruled out. This virus could be steadily passed on Vero E6 cell line, producing typical cytopathic effect and with strong antigenicity. (Source: *Chinese Journal of Infectious Diseases*, Vol. 11, No. 2, May 1993)

Virus lies in wait for plant diseases

Crop plants could one day be protected against several viral diseases at once by viral "sentinels" that live harmlessly within the plants but are specially primed to help combat invading viral pests.

John Antoniw and Ray White of the Institute of Arable Crops Research at Rothamsted in Hertfordshire are working with genetically altered plant viruses, called gemini viruses, which would lie dormant in plant cells except when "enemy" viruses enter the cell. The gemini viruses are primed to latch onto the enemy virus, marking it so that an enzyme called RNase H can then destroy it. The enzyme would be produced by a foreign gene specially transplanted into the DNA of the plant cell.

This double-barrelled approach of gemini virus and enzyme could tackle numerous viral diseases, saving crops worth millions of dollars. In addition, farmers would no longer need to buy expensive and environmentally damaging pesticides to block the spread of viral diseases.

Antoniw and White have already taken a gene that makes RNase H from the common bacterium *Escherichia coli* and transplanted it successfully into tobacco plants.

Antoniw and White plan to alter the gemini virus, replacing the gene which codes for the protein coat with synthetic DNA that is specially designed to bind with the RNA of viruses harmful to crop plants.

Different sections of the DNA could be programmed to bind to the RNA of different viruses, so that a single cassette of DNA sequences slotted into the gemini virus could bind to several types of invading virus.

To protect a plant, Antoniw and White would genetically alter the plant's own DNA to include the gene that codes for RNase H, and infect the whole plant with the altered gemini viruses.

White points out that the method should be safe because, without their protein coats, gemini viruses cannot be spread to other plants by the insect that normally transmits these viruses. (Source: *New Scientist*, 27 March 1993)

Research on bacterial genes

Production of chitin decomposition enzyme with marine microbes

Osaka National Research Institute of the Agency of Industrial Science and Technology (AIST) has discovered that a chitin decomposition enzyme can be mass produced using a marine microbe belonging to the Biblio family.

Today, chitin is decomposed with high concentration of mineral acid. This new enzyme, in addition to increasing the production yield depending on the substrate characteristics, allows decomposition under much less severe conditions, so is useful for application to industrial processing of food or medical drugs processing.

Chitin occurs in the outer shells of planktons and crabs, and is an enormous biomass resource estimated to be produced naturally at a rate of about 100 billion tons per year. In contrast to land environment, marine environments have poor nutrition, so chitin circulates in the marine ecological system as a vital source of carbon and nitrogen.

Various long-chain compounds such as oligosaccharides and glucoacids obtained through chitin hydrolysis are widely utilized as flocculation agents, ion exchange substances, as an ingredient in cosmetics, medical drugs, and foods. The low molecular weight oligosaccharides, in particular, are attracting attention as a substance displaying biological activities such as antibacterial effects and immunity promotion functions.

Chitin is a polysaccharide that includes N-acetyl D-glucosamine (GlcNAc) residues. The marine microbe enzymes which decompose chitin are chitinase, N-acetyl B-glucosaminidase, and chitin diacetylase that generates chitosan by deacetylation.

In experiments, 20 different Biblio family bacteria were cultured in a bed containing chitin powder, and the bacterium displaying the highest decomposition function (IFO15429) was selected through galactic halo experiments. The enzyme generated by the bacterium was studied in depth, showing that a large quantity of decomposition enzyme chitinase is present outside the bacterium, and that a large quantity of N-acetyl glucosaminidase exists inside the bacterium. In addition, while chitinase decomposes the aqueous solution derivative glucol chitin, the chitinase obtained from this bacteria strain has been confirmed to decompose solid chitin.

The Biblio family bacteria have a short generation cycle of about 15 min. and achieve an extremely rapid proliferation, so are suitable for the mass production of chitin decomposition enzymes. Research to analyse the mechanism of chitin decomposition is being advanced with the aim of developing Production Technology for Useful Chemicals/Utilization Technology for Useful Bio-Functions of Marine Organisms, as a part of the Industrial Science and Technology Frontier (ISTF) Programme. Further information is available from: Osaka National Research Institute, AIST, 1-8-31, Midorigaoka, Ikeda-city, Osaka 563. Tel: +81-727-51-9606, Fax: +81-727-51-9621. (Source: *JETRO*, January 1994)

Bacteria neutralizes acidified soil

A joint research team from the Kanagawa Environmental Research Centre and Shizuoka University have discovered a bacteria that neutralizes soils by absorbing aluminium acidified by acid rain.

The bacteria is a type of soil-dwelling flavobacterium and was discovered in the soil of one of the tea plantations

that abound in Shizuoka prefecture. When the bacteria was added at 0.1 per cent by volume to a one-litre aqueous solution with 100 ppm aluminium and a pH level of 3.3, the concentration of aluminium was reduced by half within ten days and acidity was lowered to pH 4.1. The research team reports that enzymes from the newly discovered organism would improve the effectiveness of lime for neutralizing soils. (Source: *McGraw Hill's Biotechnology Newswatch*, 21 February 1994)

Scientists find that tuberculosis can strike same AIDS patients twice

A group of scientists reports that tuberculosis can strike AIDS patients more than once. The finding contradicts medical dogma that a TB attack provides immunity to future bouts. Peter Small, M.D., of Stanford University (California) Medical School led a research team that included Dr. Gary Schoolnik, also at Stanford, and Dr. Philip Hopewell of the University of California at San Francisco, and others. Moreover, while the group has evidence of reinfection in AIDS patients only, the report raises the possibility that all people can repeatedly catch TB, according to Dr. Small.

The scientists looked at TB bacteria cultured repeatedly from 17 patients at Kings County Hospital in Brooklyn, NY. They used restriction fragment length polymorphism (RFLP) analysis to study the bacterial DNA. On comparing the fragments obtained from consecutive cultures taken from the same patient, they found radically different fragment patterns in some cases. The new patterns reflected reinfection by new drug-resistant strains of TB in patients who had recovered from their first infection, Dr. Small said. The researchers found that people can become resistant to TB medications in two ways: as a result of a mutation in the original disease-causing strain, or through a new infection by a drug-resistant strain.

The finding that TB can reinfect AIDS patients, and perhaps others, comes at a time when the disease is on the rise in the US. In 1991, the Centers for Disease Control and Prevention (Atlanta, GA) received reports of 26,283 active TB cases in the US alone, an increase of 18 per cent since 1985. (Source: *Genetic Engineering News*, 15 May 1993)

How bacteria avoid the immune system

Biotechnologists at the Pasteur Institute have moved close to understanding how bacteria avoid the immune system. Researchers at the Paris-based institute told how *Listeria monocytogenes* and *Shigella flexneri* both avoid exposure to the extracellular immune system by moving from cell to cell through the epithelium via adjacent membranes.

Listeria monocytogenes, responsible for severe food-borne infections, is able to invade a wide variety of cell types, by inducing its own phagocytosis. Within 30 minutes of entry, the bacteria replicate and begin their colonization using "a spectacular mode of locomotion which involved the polymerization of host cell actin", the Pasteur Institute's Pascale Cossart noted. The genes involved in the invasion and colonization processes have now been identified and are potential targets for effective therapies.

Similarly, *Shigella flexneri*, which causes enteric diseases such as bacillary dysentery by invading the human colonic mucosa, uses a similar method to subvert the immune system. The bacterium is able to produce proteins that aid the breaking of and entry into the target host cells; proteins that can cut through the membrane-bound phagocytic vacuole, allowing the bacteria to escape into the host cell cytoplasm; and an actin-promoted movement from one cell to adjacent ones.

Interestingly, while the processes of *Listeria* and *Shigella* are similar, the genes responsible for them show very little similarity. Nevertheless, researchers believe that knowing the genetic basis of the invasion processes of these potentially lethal bacteria will help yield new therapeutics. The researchers have already demonstrated that use of a monoclonal antibody in animals slowed down both the invasion and spread of *Shigella*. (Source: *Chemistry & Industry*, 6 September 1993)

Studies on expression of E. coli β-galactosidase fusion gene under the control of Autographa californica NPV p10 promoter

Long Qingxin, Lin Guangyun, et al. of the Institute of Entomology, Zhongshan University and National Laboratory of Biological Control, Guangzhou report that a transfer vector plasmid pQP10/gal containing β-galactosidase gene of *Escherichia coli* in phase with the coding sequence of the *Autographa californica* nuclear polyhedrosis virus (AcNPV) p10 gene was constructed. The fusion gene was then inserted into the AcNPV genome by contransfection of the transfer plasmid and wild-type AcNPV DNA. Infection of *Spodoptera frugiperda* cells by the resulting recombinant virus AcNPV-p10Z-9 showed high level expression of the p10-gal fusion gene, but no synthesis of p10 protein. (Source: *Acta Biochimica et Biophysica Sinica*, Vol. 25, No. 2, March 1993)

Research Instrumentation

Antigen-enzyme labelled immunoelectrophoresis and its application for quantitation of components in snake venoms

Liao Gongshang, Lin Baixi, and Huang Xiangping of the Snake Venom Research Institute, Guangxi Medical University report a novel immunoassay named Antigen-Enzyme Labelled Immuno-electrophoresis (AELIE) with characteristics of high specificity and sensitivity was developed. A homologous antigen was labelled with horseradish peroxidase, a trace amount of this labelled antigen was mixed with the sample and electrophoresis was performed on an immunoplate containing polyspecific antiserum. Rocket-shaped immunoprecipitates containing polyspecific antiserum were visualized by incubation with enzyme substrate. Positive correlation ($r=+0.98$) was obtained between rocket heights and concentrations of antigen. In this study the method was applied for quantitation of cardiotoxin and L-amino acid oxidase in snake

venoms. The sensitivity was a 30 fold increase as compared with protein stain technique and a 20 fold increase as compared with enzyme assay while monitoring chromatography. By distinguishing specific antigens in snake venoms, this method may provide authentic evidence for diagnosis of snakebite and replace bioassay of various components in snake venoms. (Source: *Shezhi* (Snake Journal), Vol. 5, No. 2, June 1993)

AIST Bioscience Institute develops fat-splitting bioreactor

The Agency of Industrial Science and Technology's National Institute of Bioscience and Human Technology has developed a bioreactor for breaking down fats and oils. It can continuously recover high concentrations of fatty acids and glycerin for more than a month. The bioreactor was created by combining lipases affixed to an ion exchange resin with a reactor that was developed in-house. It is very difficult to separate water and oil inside a bioreactor, and this problem has remained an obstacle to the full-scale utilization of enzymes to degrade fats and oils, but this new bioreactor makes oil/water separation easy. This bioreactor is still in the experimental stage, but we can expect these results to clear a path for full-scale commercialization of oil and fat degradation with enzymes.

The developers of this bioreactor are a research group led by Keiji Kosugi, Director of the Enzyme Development Laboratory in the Biological Reaction Engineering Department at the National Institute of Bioscience and Human Technology.

The lipases affixed to the ion exchange resin are enzymes extracted from a type of *Pseudomonas* bacteria discovered in 1990 by Mr. Kosugi and Rakuto Chemical Industries.

With better than 90 per cent efficiency the reactor can break down lipids such as sardine and linseed oil, castor oil, and lard into fatty acids and glycerin. The group successfully increased the degradation capability by affixing the lipases to the ion exchange resin.

The bioreactor itself consists of a tank in which the lipase reaction occurs and an oil/water separation tank connected in a loop. A pump feeds the liquid from the oil/water interface in the oil/water separation tank into the tank containing the lipases. There the lipases break down the oil and water into fatty acids and glycerin, and then the reaction mixture is fed back into the water part of the oil/water separation tank.

When this cycle is repeated, the fatty acids accumulate in the oil part of the oil/water separation tank and the glycerin accumulates in the water part. When these are recovered, they yield high concentrations of fatty acids and glycerin. The glycerin does not get mixed in with the oil, and the fatty acids do not get mixed in with the water, which was the case with previous reactors.

When researchers used this reactor in an experiment to break down rice bran oil, over a one-month period they were able to recover fatty acids in concentrations higher than 80 per cent and glycerin in concentrations higher than 40 per cent. The research group believes that this level of recovery will hold up on a commercial scale, and they say that they obtain the same results no matter what kind of oil or fat is used. (Source: *Nihon Kogyo Shimbun*, 12 May 1993)

More powerful algorithm speeds search of DNA databases

An algorithm borrowed from the field of computer vision technology may help biochemists and geneticists search DNA databases more rapidly. The method was developed by IBM researchers Andrea Califano and Isidore Rigoutsos at the company's Thomas J. Watson Research Center in Yorktown Heights, NY. Described earlier at a conference on Intelligent Systems for Molecular Biology in Bethesda, MD, the algorithm could help researchers involved in the human genome project cope with the ever-increasing rate at which new DNA sequences are found and deciphered. It also could aid the study of the evolutionary relatedness of living organisms, as well as research on inherited and other types of diseases. Whereas the fastest available conventional scanning methods take about five minutes to process 100 megabytes of DNA sequences, the new algorithm, called FLASH (Fast-Lookup Algorithm for Sequence Homology), can find 99 per cent of all sequence similarities within a few seconds, the researchers say. FLASH is part of a general class of algorithms pioneered at IBM that can be used to search very large databases containing diverse information, including such retrieval capabilities as finding molecules of similar shape or structure for drug design. The algorithm is available free to genome scientists around the world through the computer network Internet. (Source: *Chemical & Engineering News*, 19 July 1993)

Molecular recognition

Scientists at the Naval Research Laboratory (NRL) in Washington believe they are the first to measure and study directly a single molecular recognition interaction. The technique, which uses an atomic force microscope (AFM), has potential for use as a chemical/biological sensor or as a cell mapping device.

Molecular recognition is the basis for assembly and regulation in living organisms. But characterizing discrete interactions can be difficult because of the very small forces and distances involved. However, it is in this area that the AFM shines. As Richard Colton of the NRL explains, the AFM is sensitive to forces of 10^{-14} N and to displacements of 0.01 nm; can control contact areas as small as 10 nm^2; and can work on living systems as well as on synthetic ones.

The NRL team, including Gil Lee and David Kidwell, measured the adhesive forces between the receptor streptavidin and its ligand, biotin. By attaching biotin to the surface of a sphere at the end of a cantilever beam, and attaching streptavidin to another surface, the interaction force between the two species can be measured by approaching, and then retracting, the two surfaces. Using this method, the team say they have measured adhesive forces three to eight times greater than normal "back-

ground" forces. These forces, they believe, result from the rupture of one biotin-streptavidin bond.

As the biotin and streptavidin molecules are constrained sterically, and the location of the binding site is buried deep within the streptavidin molecule, the number of possible interactions is greatly reduced. This, and the magnitude and distribution of the observed forces, implies that the rupture force of a single molecular recognition event has been measured, they claim.

Colton hopes to have a laboratory prototype of a chemical sensor within two years. As well as applications in medical diagnostics, it may also have environmental use—detecting pesticide residues, for example. It could also be used to map the surface of a cellular membrane so that binding sites can be pinpointed and studied one at a time. (Source: *Chemistry & Industry*, 4 October 1993)

New Alpha columns for affinity and hydrophobic interaction chromatography

Affinity Chromatography Ltd. (Freeport, Ballasalla, Isle of Man) has now made their unique range of MIMETIC™ and HIC adsorbents for protein separations available as prepacked Alpha Columns. With fixed 10 ml bed volume and operational flow rates to 20 ml/min, the Alpha columns offer linear scale-up direct from ACL's PIKSI™ and PIKSI-H adsorbent screening kits, and are supplied fully compatible with most biochromatographic systems. Sanitization and CIP are simple with molar sodium hydroxide, and all MIMETIC and HIC adsorbents are available in larger individual packs for lab scale separations and in bulk for process applications. (Source: *Press Release*, 1993)

New non-radioactive DNA labelling and detection system

The ELITE range of non-radioactive DNA labelling and detection kits made by Cambridge Research Biochemicals of Northwick, UK is said to offer a real alternative to ^{32}P.

Optimized to allow the detection of less than 0.1 pg of target DNA, the system has also been developed to ensure low backgrounds, highly reproducible yields of labelled DNA and reliable stripping and reprobing performance.

The DNA is labelled by the incorporation of a hapten using a random priming reaction. Subsequent detection is with a monoclonal antibody-alkaline phosphatase conjugate. The signal is visualized with either chemiluminescent or colour substrates. (Source: *Press Release*, 8 June 1993)

Sensor observes cell metabolism in tissue culture in real time

A newly-developed electrical sensor will continuously monitor how cells behave without taking them out of the incubator, without touching them, and without requiring long hours bent over a microscope.

The sensor will tell researchers when minute disturbances in cells indicate potential trouble in a biomolecule production process.

Charles R. Keese, formerly senior research scientist at Rensselaer Polytechnic Institute, and Ivar Giaever, Professor of Physics at RPI, a 1974 Nobel Prize-winner in Physics, showed an American Association for Advancement of Science conference in Boston earlier this month how their ECIS (electric cell-substrate impedance sensor) can also track changes in the cell when biological or chemical substances are added. The essential component of the sensor is a tiny gold electrode in a tissue culture dish. A very low (one microamp) alternating current is passed through the culture medium.

The medium carries the current, while the electrode on which the living cells are cultured act as insulators. Changes in cell morphology, however slight, produce changes in the electrodes' impedance.

The sensor's computer continuously observes and records the impedance changes in real time. Only about 100 cells can populate the small electrode, but the activity of even a single cell can be detected. ECIS can observe the metabolism of almost all types of cells so long as they can anchor to surfaces in culture—a property of most animal cells, the inventors declared.

A prototype ECIS is now in a feasibility test at the Johns Hopkins Cancer Research Center, where studies had confirmed a close correlation between cellular metabolism and metastases. (Source: *McGraw Hill's Biotechnology Newswatch*, 16 August 1993)

800 base/sample automated DNA sequencer

Sequence read lengths up to 800 bases or more are typical with LI-COR's Model 4000L Automated DNA Sequencer. The Model 4000L utilizes infrared fluorescence sequencing technology and a 66 cm gel to yield single base resolution at base 800. For shorter DNA fragments, other gel sizes have run-times as short as one hour. Samples can be prepared using Sanger dideoxy protocols with labelled primers or infrared dye-labelled dATP's. Cycle sequencing protocols are also available. DNA fragments labelled with an infrared fluorophore are excited with a solid-state laser diode and the IR emission detected with a solid-state, silicon avalanche photodiode. Solid-state IR technology increases reliability and throughput, while reducing the initial purchase price and operating costs. Electrophoresis results are presented in an autoradiogram-like image format. LI-COR's Base ImagIR™ software provides automatic base calling with typical accuracy for ss DNA of 99 per cent to 800 bases. Multitasking software allows two additional sequencers to be operated by the same computer for economical future expansion. Further information available from Ron Wall, Marketing Communications Manager, LI-COR, Inc., 4421 Superior Street, Lincoln, Nebraska 68504. Tel.: 1-800-645-4267 or (402) 467-3576, Fax: (402) 467-2819. (Source: *News Release*, 11 October 1993)

Alcohol oxidase-based biosensor developed

A biosensor that in one to two minutes can measure ethanol concentrations in fermentation broths or clear filtered liquors has been developed by Yellow Springs Instrument Co., Yellow Springs, Ohio. Yellow Springs senior scientist John R. Woodward says the instrument uses

immobilized alcohol oxidase to generate hydrogen peroxide from oxygen and ethanol. The hydrogen peroxide that is produced is measured at an electrode and provides an accurate measure of ethanol concentration. Woodward points out that, although gas chromatography and distillation can provide very accurate measurements of alcohol concentration, the former is relatively expensive and the latter is time consuming and requires a skilled technician. The Yellow Springs instrument is completely automated and each analysis costs between 10 and 20 cents, Woodward says. The system also can measure methanol concentrations, and this feature has been employed in a device produced to measure concentrations of the sweetener aspartame at levels found in diet soft drinks and other commercial products. This device uses chymotrypsin to cleave methanol from one of the three amino acids that make up aspartame. The alcohol oxidase generates hydrogen peroxide from the methanol and the electrode detects the generated compound. (Reprinted with permission from *Chemical & Engineering News*, 12 April 1994. Copyright (1994) American Chemical Society)

Solid detection

Biotechnologists at the Cranfield Institute of Technology believe they have developed the first biosensor based on a solid, rather than a solvent, that can detect specific gases. They hope to have a working, commercial device within four to five years.

Anthony Turner, the head of Cranfield's biotechnology centre, believes that the sensor, which works independently of its environment and can operate in air, would make a good personal alarm or fixed monitor. At present, it can be tailored to detect methane, sulphur dioxide or phenol using polyphenol oxidase, sulphite oxidase and methane-oxidizing bacteria respectively.

In Turner's device, two gold electrodes are held within an electrolytic gel. They need to be small, so Turner uses lithography to achieve dimensions down to 7 microns. He hopes to go even smaller: "The smaller the better and the closer together the better because it cuts down the resistance of the gel which is only poorly conductive".

According to Turner, the new biosensor which has a patent pending, will have greater selectivity than present inorganic sensors—it will not be set off accidentally by a perfume—but may not be as stable. (Source: *Chemistry & Industry*, 7 June 1993)

Bio-compatible biosensor developed

In cooperation with Nippon Suisan, Professor Isao Karube of the Research Centre for Advanced Science and Technology, University of Tokyo, has developed a biocompatible biosensor that can measure glucose concentrations, etc., continuously within the body for more than one month. It is made by affixing the enzymes used for the assay in chitin, which is harmless to the human body and gradually decomposes when placed inside the body. This device has potential as an implantable sensor to monitor blood glucose for use in combination with an artificial pancreas.

After the researchers ground up cuttlefish cartilage and dissolved it in water to form a jelly, they added 5 per cent glucose oxidase for measuring the glucose concentration. They then spread out this chitin/enzyme mixture to a thickness of 0.05 mm, as if forming a sheet of paper, and let it dry and harden at room temperature.

By giving the chitin a special pretreatment, it is possible to freely adjust the time it takes to dissolve inside the body from one week to three months. To extract the results of the sugar-enzyme reaction (for glucose concentration) in the form of an electric signal, the group deposited a thin layer of gold on one side of this film and attached wires to it. Gold causes almost no damage at all when placed in the body in very small amounts.

The group created and tested a sensor 1cm long by 1.5 mm wide. When they placed the sensor with wires attached in a solution of glucose, they could measure the concentration within 30 seconds. In the future the group will study performance and safety in animal experiments, and proceed with research on methods for extracting the measurement data from the body with the goal of improving the device for practical application.

In the past, miniature biosensors that could be placed in blood vessels have been developed, but more than half have been made of materials such as silicone. As a result, placing them in the body caused inflammation, etc., and long-term continuous measurement was impossible. There has been great demand for biosensors that are safe when implanted in the body. (Source: *Nikkei Sangyo Shimbun*, 9 April 1993)

Bioreactor design mimics bone marrow

A new bioreactor design that more closely resembles the natural bone marrow environment shows an improvement in blood cell differentiation over conventional tissue culture techniques. Chemical engineering professor J.H. David Wu and co-worker T.Y. Wang of the University of Rochester uses a polycarbonate plastic shell packed with porous microspheres to mimic the natural three-dimensional matrix in human bone marrow. The structure provides a scaffolding to anchor the cells and to provide the kind of 3-D interactions between them that apparently are necessary for complete differentiation of blood cells. Conventional flask culture supports only two-dimensional cell growth and produces only two kinds of cells, whereas Wu's reactor produces almost all of the stages and subtypes of blood cells in natural marrow. (Source: *Chemical & Engineering News*, 12 April 1993)

Prediction of intron and exon sequence in eukaryotic gene by neural network approach

Cai Yudong of the Shanghai Institute of Metallurgy, Academia Sinica and Chen Changqing of the Shanghai Research Centre of Biotechnology, Academia Sinica report in a paper that a neural network method was applied to predict the splice site locations in a eukaryotic gene. Ninety human glycoprotein genes were selected as the training set to construct a network model and 27 human glycoprotein genes were used as the samples for prediction. Generally,

the predicted splice sites were more than the true splice sites and only a very few nonconsensus splice sites could not be predicted. When the position of the start codon (ATG) and total amount of amino acids were known, the unique sequence of introns and exons could be obtained by computer from numerous possible combinations of predicted splice sites. (Source: *Acta Biochimica et Biophysica Sinica*, Vol. 25, No. 2, March 1993)

Kobe Steel develops production technology for high purity useful protein without using cells

Kobe Steel has developed a technology for producing highly purified useful protein for pharmaceuticals without using cells. Kobe Steel recreated an artificial system in a tank for protein synthesis in cells and made it work for many hours. So far the production of pharmaceuticals using cultured cells has a major disadvantage.

During the process, some impure proteins are also synthesized, thereby contaminating the products. Using Kobe Steel's new method, substances that the micro-organism cannot synthesize may be produced.

Since high purity protein can be produced by this new method, the time for production can be shortened by eliminating the purification process.

In the new production method, plasmid combined with a gene for specified protein synthesis will be added to the solution of crushed *Escherichia coli* cells. Since the solution has enriched contents required to synthesize protein, specified protein synthesis will be done by the gene's command.

The research team has succeeded in continuous protein synthesis for 20 hours. This was achieved by continuously supplying nutrients and other ingredients of energy sources for protein synthesis and removing synthesized proteins and waste by-products using an ultrafiltration membrane filter.

In the test tube where there is no flow of the culture solution, the protein synthesis will stop in about an hour. In drug research using biotechnology, research is under way for the design and synthesis of materials of special functions and molecular structure, which have not naturally existed before.

It is still unknown whether cells or micro-organisms will be able to synthesize artificially designed proteins. The new method developed by Kobe Steel will open the door to the production of new materials.

The confirmation of gene analysis can be done by synthesizing protein. The new method is also useful for analysis of human gene decoding. This new method is distinctive because of the controlled synthetic reaction of a specific purified protein production by manipulating enzymes required for the synthetic reaction.

Ordinarily in the course of genetic recombination, different genes are recombined simultaneously as a label to confirm the introduction of a new gene. Therefore, impure proteins of labelled genes were also synthesized. In the newly developed method, only pure protein will be synthesized, thus eliminating the purification process.

Kobe Steel has been emphasizing research in electronic materials, high polymer materials and information and communications technology. In 1989, Kobe Steel established a biology research laboratory for biotechnology research in Tsukuba. This new technology was developed in the laboratory. (Source: *Nikkei Sangyo Shimbun*, 13 April 1993)

General

Mummy's day

Studies of DNA fragments from a 1,000-year-old Peruvian woman indicating that she suffered from tuberculosis (TB) provide the most conclusive evidence possible to support the controversial argument that TB existed in the New World before Columbus landed there over 500 years ago. What is more, it is the first successful attempt to determine the existence of an infectious disease in antiquity using molecular biology.

"Reconstructing evolutionary patterns of infectious diseases such as TB, malaria, AIDS and others carries an enormous potential for understanding the nature of our present encounters with these conditions as well as guidance to rational policy decisions for their control", believes Arthur Aufderheide of the University of Minnesota, who led the research team of bioscientists and anthropologists.

The team analysed DNA fragments from a lymph node and a lung lesion taken from a 40-45-year-old woman, who lived in southern Peru some time around AD 1000-1300. Using PCR techniques, they were able to "fish out" a segment of the extracted DNA that was unique to *Mycobacterium tuberculosis*.

The team found that their ancient DNA sequence was identical to contemporary *M. tuberculosis*; it had not changed over the past 1,000 years. Taken together with characteristic, but not definitive, signs of disease in the woman's lungs, Aufderheide thinks he has an excellent case for claiming TB pre-dated Columbus' arrival. This work should help "refine our appreciation of the 'Columbian exchange' of diseases." (Source: *Chemistry & Industry*, 21 March 1994)

Gene therapy: who is being treated?

On 15 December 1993, France's Centre d'Etude du Polymorphisme Humain (CEPH) unveiled the first comprehensive "map" of the genes found in every human cell. The map is expected to guide researchers towards the genetic causes of thousands of diseases, ranging from asthma and diabetes through to rare forms of cancer. In the process, the work—which is still far from complete—is likely to provide a massive stimulus to the emerging field of gene therapy.

A recent BioIndustry Association brief on gene therapy noted that at present only 2 per cent of human genes have been mapped to specific locations—and, so far, only a few of the approximately 4,000 genetic diseases have been traced to their malfunctioning genes. Whilst the first physical map of the human genome was published in 1992, this only gives scientists information about the chromosomal location of genes and their relative position, not the

exact location of all genes. Now, as scientists race ahead to map more and more genes, questions arise about the dilemmas posed by the possibility of cures for genetic diseases.

Gene therapy, which involves the deliberate repair or replacement of damaged genes, is likely to prove particularly rich in such dilemmas. Currently, gene therapy is advancing along a very narrow front—and it is restricted to somatic or body cells, rather than sex or germ cells. But the front is likely to open out rapidly as the technology evolves.

The BIA brief outlined four approaches currently being tested in the UK. The first study, at Oxford and Cambridge, involves cystic fibrosis. The idea here is to insert copies of a gene called CFTR into the lungs. Enclosed in liposomes (fat globules), the genes then adhere to—and pass through—the cells and correct the disorder.

The second approach involves inserting normal genes into white blood cells taken from patients with leucocyte adhesion deficiency, a rare disorder that leaves victims exposed to recurrent life-threatening infections. The idea is to replace the defective population with new cells.

The third approach is being undertaken in the USA and involves using cancer patients' own white blood cells in conjunction with interleukin-2 (IL-2). This aims to enhance the tumour-destroying capacity of white blood cells.

And the fourth approach, being pioneered in the UK at Great Ormond Street Hospital and in the USA, targets Severe Combined Immunodeficiency (SCID). This rare disorder affects some 40 children each year world-wide. Here, defective bone marrow cells are extracted and missing genetic material inserted, before replacement.

Recently, too, reports have reached the west from China of a gene therapy trial aimed at replacing a defective gene involved in haemophilia. The pressure on Chinese parents to limit their families to one child has meant that there has been a particular interest there in the potential of gene therapy for ensuring that any children they do have enjoy good health. (Source: *Biotechnology Bulletin*, January 1994)

Curious coils

Up to now, the spontaneous self-assembly of organo-metallic complexes has depended on strongly bonding transition metals. But now American chemists have shown that even humble sodium ions can control the self-assembly of elaborate double-helical supramolecules, which may prove useful as nanoscale electronic or ionic devices.

Thomas Bell and Hélène Jousselin from the State University of New York used a class of large pyridine ligands which twist around themselves to form a spiral shape. When they added sodium salts to a solution of these "molecular coils", they found that the coils wrapped themselves around the sodium ions to form a double helix. Depending on the salt used, one of two complexes formed: two coils slot together like the threads of a nut and bolt, with a single sodium ion at the centre; or two coils wind around two sodium ions in opposite directions, to form a structure like a DNA helix.

As the interaction between the metal and the ligand is so weak, Bell and Jousselin think that the ligands may interchange between their free, monomeric forms and the two-molecule double helices in metal-free solution. Longer coils, they add, may even be able to form double helices without metal complexation, forming a molecule similar to a type of antibiotic currently being tested for its ability to form ion channels in lipid membranes. (Source: *Chemistry & Industry*, 21 February 1994)

DNA goes missing in Polynesian triangle

Several thousand years ago, in the greatest human migration in history, the Polynesians swept across the Pacific and settled in the "Polynesian triangle": Hawaii in the north, New Zealand in the south-west and Easter Island in the east. But where did the Polynesians come from? An answer is being provided by fragments of human DNA taken from ancient bones and amplified by the polymerase chain reaction (PCR).

Linguistic and archaeological evidence suggests that the proto-Polynesians came from the "Lapita" culture of the south-west Pacific, somewhere between New Britain (which lies near New Guinea) and Fiji (which lies farther south-east). The culture, which flourished between 3,600 and 2,500 years ago, was characterized by navigational skills and pottery. The Lapita settlers are, in turn, believed to have come from the islands of South-East Asia.

This migration pattern fits a genetic observation: Polynesians lack a sequence of nine base pairs in the non-coding fifth region of their mitochondrial DNA. The "deletion" is also common in the people of South-East Asia, but not in Caucasians. However, a comparison of skeletal features suggests that the Lapita people came from Melanesia to the south-west.

Now Erika Hagelberg and John Clegg of the Institute of Molecular Medicine in Oxford have analysed the mitochondrial DNA from human bones found in several sites, ranging from New Britain in the west to Tonga in the east. The bones are between 1,700 and 2,700 years old and were found with artefacts from the Lapita culture. The researchers have discovered that the bones do not have the deletion which is characteristic of today's Polynesians. The mitochondrial DNA findings dent the idea that the Lapita people were essentially Polynesians on the fast train to Polynesia.

Instead, it seems likely that the Lapita people were a mix of Melanesians and people of South-East Asian origin. However, it will be difficult to settle the issue until a genetic marker for Melanesians, assuming there is one, is discovered.

If the Lapita people were indeed a mixed group, then it seems that the mitochondrial DNA lineages of the Melanesians died out. The early Polynesians endured hazardous long voyages, and it seems only those with the nine-base-pair deletion, brought from South-East Asia, tended to survive. (Source: *New Scientist*, 10 July 1993)

Temperature-controlled DDS material developed

Professor Tadao Fujie and instructor Yoshiko Yokoyama of Kyoritsu College of Pharmacy have

developed a vitamin B-fatty acid complex in which drug release can be controlled by temperature. They have confirmed that when crystals of the complex are dispersed in solutions with a hydrogen ion concentration (pH) ranging from the strongly acidic juices of the stomach to the nearly neutral fluids of the intestine, they release vitamin B when heated and stop releasing it when cooled. This substance differs from the gels that have been studied in the past as drug delivery systems (DDS) because, thanks to the uniform structure of the crystals, it should be easy to set the rate and amount of release as desired.

This complex contains a 21 carbon fatty acid and nicotinamide, the vitamin B complex, bound in a one-to-one ratio. It is obtained in the form of small crystals after both substances are dissolved in heated dichloroethane and cooled to 40° C. The researchers added the complex to an aqueous solution with the combined hydrogen ion concentrations of stomach (pH 1.2) and intestinal (pH 6.8) fluids, and found that while the structure of the fatty acid remains unchanged, the nicotinamide is released into the solution at temperatures above 37° C, and at lower temperatures the release stops. This process can be repeated by raising or lowering the temperature. Fatty acids inherently exhibit a characteristic called association in which the molecules come together and behave as one unit, and at 70° C their crystalline structure undergoes a change (transition). Dr. Fujie and co-workers suspect that the nicotinamide is held within a crystalline structure of several fatty acid molecules, and when the crystalline structure changes due to the temperature, the nicotinamide is squeezed out. Polymer gels have been viewed as good candidates for DDS material and it is difficult to make the mesh and the granules of a gel uniform. Cyclodextrin has also attracted attention, but it can only form complexes with hydrophobic compounds. In this case, the researchers have succeeded in forming a complex with a hydrophilic compound, and they believe that the on-off temperature can be raised by increasing the number of carbons in the fatty acid. They have also found that they can form complexes with compounds that have several aromatic rings. This substance is sure to be closely watched as a new DDS material. (Source: *Nikkei Kogyo Shimbun*, 23 March 1993)

Fermentation peptide found effective in lowering blood pressure

Professor Mitsumi Kajiwara of Kobe Women's College and a group including researchers from Nitta Gelatin, a leading gelatin manufacturer, have confirmed that a fermentation peptide made from collagen, the main component of animal skin, is effective in controlling increases in blood pressure in laboratory experiments with rats. This was announced at the general meeting of the Japan Nutrition and Food Society that was held in Tokyo in May 1993. The group also confirmed that the peptide is effective in preventing ulcers in the esophagus. It is expected that the peptide will become widely used as an ingredient in health foods and drinks.

The group from Kobe Women's College, Nitta Gelatin and Kono Food Laboratory (Osaka, Tomomi Kono president) used SHR rats, which inherently develop high blood pressure, in the experiments. Immediately after being weaned the rats were given standard food. In the 20th week, when they had reached adulthood, the experimental rats were given food containing the fermentation peptide. Although the control rats that were continued on a diet of standard food developed and sustained high blood pressure, the experimental rats that had eaten the fermentation peptide showed a 20 per cent drop in blood pressure after one week.

A peptide originating in soybeans also is effective in controlling rising blood pressure, but the group reports that the fermentation peptide has a greater effect than the one obtained from soybeans. In previous *in vitro* experiments, the fermentation peptide was less effective than the soybean peptide in inhibiting angiotensin-converting enzyme, the enzyme responsible for increased blood pressure, and scientists had expected that it would also be less effective in controlling high blood pressure *in vivo*.

The fermentation peptide is made by lysing collagen with pineapple juice that contains proteolytic enzymes and then fermenting the lysate with yeast. Collagen it a substance that can be extracted from skin, bones, etc., by boiling them in water and then letting the liquid harden to form gelatin. In the experiments, liquid fermentation peptide was formed into a solid and fed to the rats. The fermentation peptide is manufactured and sold by Nitta Gelatin as an ingredient of health food. (Source: *Nikkei Sangyo Shimbun*, 18 May 1993)

Pesticides linked to breast cancer

Chemicals in the environment that act like human hormones could be the cause of "an unexplained increase in breast cancer", says Devra Lee Davis, a toxicologist and senior adviser to the US Assistant Secretary for Health. Chemicals should be screened for their ability to mimic the hormones oestrogen before they are released into the environment, she says.

Oestrogen has long been linked to breast cancer though epidemiological data, which relates a woman's risk to her estimated exposure to the hormone, and through the finding that oestrogen stimulates cells in the breast to multiply rapidly. Now some scientists are claiming that extra doses of oestrogen-like compounds in the environment may increase the quantities of hormone some women receive to dangerous levels.

Data show that deaths from breast cancer in the US have been rising since the 1940s at about 1 per cent a year. Davis and her colleagues claim that established risk factors for breast cancer, such as early menstruation, late childbearing, late menopause and a family history of the disease, can account for only 30 per cent of these cases.

Scores of industrial chemicals—including organochlorine pesticides such as DDT as well as polychlorinated biphenyls (PCBs)—are now known to act as weak oestrogens. Some of these chemicals have a long half-life and can "bioaccumulate", that is build up in fat stores and in the food chain.

"The environmental hypothesis is extremely interesting and scientifically important, and we are going to pursue it",

says Samuel Broder, director of the National Cancer Institute in the US. "This is an area that is certainly high priority."

Early in 1993, the institute's journal published a startling paper by Mary Wolff of Mount Sinai School of Medicine in New York. Wolff analysed frozen blood samples from women who later went on to develop breast cancer, and found that they contained much higher levels of DDE, a breakdown product of DDT, than women who did not go on to develop breast cancer.

Another researcher, Leon Bradlow at Cornell University, New York, believes he has found a biochemical mechanism that can explain this finding. He has shown that organochlorines enhance the metabolic pathway that converts oestradiol, the body's most potent oestrogen, into 16-alpha-hydroxy-oestrone, which stimulates breast cells to divide and so promotes tumours. But not all oestrogen is "bad" in this way, says Davis: she points out that the oestrogens in oral contraceptives or in hormone replacement therapy (HRT) might not have this metabolic effect. A link between HRT or oral contraceptive use and breast cancer is not proven.

But not all authorities in the field are convinced by Davis' argument. Julian Peto of the Institute of Cancer Research in London says he is deeply sceptical of Davis' work, and points to established findings that link breast cancer with affluence. (Source: *New Scientist*, 25 September 1993)

D. APPLICATIONS

Pharmaceutical and medical applications

Biodegradable surgical bandage

Nycomed Pharma (Oslo) has launched what it describes as a "revolutionary" new product to arrest internal bleeding during surgery. The product, called Tachocomb, has been successfully launched in Austria and has won marketing approval in most European countries, as well as Saudi Arabia and China.

The product, which biodegrades in three to four weeks, is applied directly to bleeding organs or tissue and coagulates into a tight, though flexible, bandage within three to five minutes, halting the bleeding process. It is made up of a sheet of collagen covered with a layer of "fibrin glue", which is made up of fibrinogen, thrombin, and aprotinin. When this layer comes in contact with blood, the components dissolve, forming fibrin.

Clinical trials for the product involved 1,400 surgery patients. It produced "effective" coagulation in 95 per cent of patients, "satisfactory" coagulation in 3 per cent of patients, and "insufficient" coagulation in 2 per cent of patients. The product "offers surgeons a new tool to treat areas of diffuse bleeding, which, with orthodox methods, are difficult to treat, since conventional compressing agents have a propensity to float away after being applied". (Extracted from *Bio/Technology*, Vol. 12, February 1994)

Good news for diabetics

The first tests on humans of a novel diabetes therapy appear to show that it can overcome the disease. Two patients given special capsules of insulin-producing cells, which mimic a healthy pancreas, no longer needed their daily insulin injections. Doctors hope the treatment will be routine in four years' time.

The key to the treatment is the capsule, which protects the insulin-producing cells from rejection by the immune system, explains Patrick Soon-Shiong of the St. Vincent Medical Center in Los Angeles. "Identifying a biocompatible immunoprotective membrane to prevent graft rejection has eluded investigators for years." Unprotected cells need to be administered with immunosuppressants, which can sometimes poison the cells.

Soon-Shiong encapsulates insulin-producing cells (islets of Langerhans), usually taken from pancreatic tissue in human corpses, in a polysaccharide membrane, extracted from alginate, a seaweed protein. The capsules are semi-permeable, allowing insulin out but nothing in, and each holds two or three pinpoint-sized islets.

With the patient under local anaesthetic, Soon-Shiong makes a small incision and "pours" the capsules into the abdominal cavity. "Once implanted, the islets produce insulin like a normal pancreas, responding to changes in blood sugar and effectively curing the disease for the cell's lifetime", he says. The islets should normally last about three years.

Significantly, the islet-produced insulin is absorbed into the bloodstream but eventually comes to rest, as normal, in the liver. Insulin injections can cause excessive insulin levels in the blood, which have been linked to heart disease.

Both patients treated by the St. Vincent team had type 1 diabetes and had received kidney transplants. The first, a 38-year-old man, needed only 5 per cent of his usual insulin injections after two treatments. In fact, when Soon-Shiong withdrew all extra insulin, the man was completely insulin-independent. A month later, however, Soon-Shiong decided to restart supplements to prevent the islets from becoming over-stressed. Nevertheless, he expects that with the right dose, supplements will be unnecessary.

The man's glucose levels appear to have been tightly under control, he experienced no side-effects, his pain stopped, he could walk unaided and work for the first time in seven years. These results will appear soon in *The Lancet*.

Two months ago, Soon-Shiong reported, a 36-year-old woman also became insulin-independent a week after her first dose. Soon-Shiong is now planning to study 20 diabetics in phase II clinical trials. He is also exploring pig pancreatic cells as an alternative source and seeking ways to proliferate human pancreatic cells. (Source: *Chemistry & Industry*, 4 April 1994)

Revolution in infant formula brewing in Herman's calves, rDNA algae

Herman, GenPharm's transgenic dairy bull, had sired his first transgenic offspring, the chief executive told

investors at the Hambrecht & Quist Life Sciences Conference.

Of 18 births, eight transgenic calves carried the gene for human lactoferrin, a protein that helps protect infants against infection. However, GenPharm must wait until the calves mature to learn whether they produce lactoferrin in their milk. If they do, the company aims to develop a commercial herd numbering 200.

Martek Biosciences Corp. Inc. reported it also has an additive for milk, but it has tapped the production system of microalgae instead of land-based creatures. The algae produce pure forms of two fatty acids found in human milk that appear to be building blocks for mental and visual development, according to Pete Linsert, chairman and chief executive of the public company.

Martek, a Maryland company, was spun out from Martin Marietta to exploit a huge collection of micro-algae.

Martek expects infant formula sales to begin this year in Europe, with US sales following by about six months. Several studies commissioned by the infant formula makers looking at the impact of the two fatty acids on mental ability and IQ should be appearing in paediatric journals sometime after, Linsert said.

The marketing agreements should generate $50 million a year for Martek, he estimated. Linsert said the company also envisions fatty acid baby foods, medical foods and adult supplements that would lower cholesterol in humans and counter the development of Alzheimer's and other neurodegenerative diseases. These products would likely also be sold without specific medical claims, he said. The Food and Drug Administration was unavailable to comment whether claims made at investment conferences must also be approved. (Source: *McGraw Hill's Biotechnology Newswatch*, 17 January 1994)

Drug helps rats recall where chips are hidden, could improve human memory

A drug that allowed rats to remember where chocolate chips were hidden in a maze has potential to be a human memory booster.

BDP, a member of a family of compounds called Ampakines, halves an individual's learning curve and doubles retention—but only in rats so far, said Gary Lynch, professor of psychobiology at the Centre for the Neurobiology of Learning and Memory at the University of California, Irvine (UCI). Results were good, and the apparent side-effects few.

Cortex Pharmaceuticals, Inc., in Irvine, has taken over BDP's patenting and development. Tests will focus on two very specific areas where disease has impaired memory.

The first will be in early- to mid-stage Alzheimer's disease patients, for whom it is hoped the drug will improve their quality of life. It cannot, however, halt the progression of the disease, and will eventually become ineffective. The other patient group will be people who suffer from multi-infarct dementia, memory loss caused by tiny infarcts in the brain. After that the company may look into other forms of age-associated memory impairment. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 17 January 1994)

Organic synthesis of taxol

Chemists from Florida State University have completed the first total synthesis of taxol. The 40-step synthesis, which starts from readily-available camphor and takes two weeks, may lead to the development of a whole new class of anti-cancer drugs.

The 20-strong team, led by Robert Holton, finally completed the synthesis early last December.

Taxol, which is used to treat stubborn ovarian and breast cancers, occurs in the bark of the slow-growing Pacific yew. A 40-foot tree only contains about 0.3 g of the chemical, and the tree has to be chopped down to extract the taxol. Moreover, the Pacific yew is now protected in the United States because it provides a roost for the rare northern spotted owl.

Taxol is a convoluted tangle centred around four fused rings, with 11 chiral centres and innumerable functional groups. This unique structure has attracted almost as much attention among organic chemists as its pharmaceutical properties.

The total synthesis of taxol has been Holton's ambition for almost ten years.

Another group, led by Kyriacou Nicolaou, working at Scripps Research Institute at La Jolla, California submitted its synthesis in late January. According to John Mann, an organic synthesis expert at Reading University, there are around 30 groups working on taxol, all at a similar stage, and any one of them could have been first. Nicolaou's scheme is different from Holton's, says Mann, and involves more steps, as it depends on the synthesis of a chiral intermediate.

Samuel Border, director of the US National Cancer Institute, believes taxol is the most important new cancer drug for 15 years. (Source: *Chemistry & Industry*, 21 February 1994)

Biocompatibles aims to transform contact lenses

Within a year, a new material for making contact lenses will be on offer from Biocompatibles International plc. According to Biocompatibles, the material will radically improve comfort for the wearer. By identifying and mimicking the key compatibility factor in human cell membranes, the company has produced a contact lens which clinical trials indicate significantly reduces irritation to the eye—and may also cut the need for lens care solution. (Source: *Biotechnology Bulletin*, January 1994)

Biochemical pharmacology—the study of pharmacological properties of drugs with biochemical methods

Like other research and development industries, the pharmaceutical industry is highly competitive and the success of a company is often determined by the innovativeness of the new drug and the drug's position in the market-place. Thus, Captapril and Melvacor, two highly successful, first-in-their-class of drugs to treat hypertension and high cholesterol, propelled Squibb and Merck into successful world class pharmaceutical companies. With the average cost of bringing a new drug to market estimated to

be $240 million, success in the future will go to those companies which can most efficiently discover and patent an efficacious new chemical entity (NCE) and develop it into a marketable drug.

Up until 10-15 years ago, NCEs were discovered by random testing (or primary screening) of a large number of chemicals synthesized by chemists. The "hit" rate was about one active chemical in 20,000 chemicals tested. Of these selected chemicals, about 80 per cent of them are lost due to lack of efficacy, lack of selectivity, and appearance of undesirable side-effects. Furthermore, these primary screens were both time-consuming and expensive, using tissues or even whole animals which required chemicals in large quantities. In fact, over half of the $240 million spent on drug research goes into discovering and characterizing NCEs. Any means which streamline or rationalize the process of compound identification and characterization can reduce cost and increase productivity. This is where biochemical pharmacology plays a critical role.

Biochemical pharmacology is the primary step in a mechanism-based strategy to streamline drug discovery. This strategy utilizes rational drug design for specific molecular targets, such as a receptor or an enzyme thought to be directly involved in a given disease. By understanding the structure, shape and chemical make-up of the target, compounds can be synthesized rationally to fit that target, and tested for activities in appropriate biological models. This approach has proven to be cost- and time-effective, improving the "hit" rate to one in 2,000 or better. The cost savings from this strategy over the traditional broad-based screening is obvious. With advances in automation technologies, targeted rational drug design is now combined with broad-based screening of chemicals to further improve the probability of discovering active NCEs.

Over the past decade, receptor-ligand binding assays have become the mainstay of the biochemical tools used for drug discovery. It provides a rapid and effective means to study the interactions of chemicals with the targeted receptors. The methodology is simple, and is amenable for high-volume primary screening. It involves the use of a membrane receptor, a radio-labelled ligand, and the chemicals in question. With the advent of molecular biology, receptors are now cloned, expressed, and are available in quantities for screening. Typically, the assay can be completed within a day and the data can be generated the same day or the following day. The data are then reviewed and fed back to the chemists to guide them in their next designed synthesis. In the case of broad-based screening of a chemical library (typically consisting of over 30,000 compounds), as many as 1,000 compounds can be tested per week with a fully automated test system. Any active "hits" will then be re-tested to determine their pharmacological potencies and activities. If these active "hits" are known to possess other adverse biological activities, then the chemical structures of these "hits" can be modified and new compounds can be synthesized in an attempt to eliminate them, leaving only the desired biological activity.

Although receptor-ligand binding data provide valuable information on the interaction of the chemicals with the targeted receptor, it does not provide information on whether active chemicals can actually elicit a biological response. Therefore, functional tests are also set up to test the active "hits" for their intrinsic biological activity. These functional tests can be in the form of enzyme activity inhibition, cell activation, or tissue contraction/relaxation. The information from these functional tests determines whether the chemical of interest possesses significant biological activity to warrant further pharmacological testing in whole animals.

The two essential functions described above, i.e., primary screening of compound-target interactions and functional testings, are usually performed by the biochemical pharmacology team. Typically the team is comprised of biochemists and pharmacologists who, using biochemical techniques and tools, study the pharmacological properties of chemicals. Their prime responsibility is to identify active chemicals by playing a key role in the discovery process, generating accurate data and information on a large number of chemicals in a timely manner. The ability to utilize biochemical pharmacology to identify and characterize NCEs correctly has greatly increased the productivity of drug discovery while reducing time, material and labour costs.

Over the last two years, Allelix of Allelix Biopharmaceuticals Inc., Mississauga, Ontario, Canada, has built and strengthened the three essential groups required for drug discovery, including medicinal chemistry, molecular biology and biochemical pharmacology. The biochemical pharmacology group consists of cell biologists, biochemists, and biochemical pharmacologists. This group participates fully in the discovery process, capable of carrying out both primary and functional testing of compounds from chemistry. Allelix is now beginning to implement automation for selected tests so that broad-based screening can be performed. (Source: *Spotlight*, January 1994)

Innovative RNA process promises new therapies for diseases

A new biological strategy developed at the University of Colorado in Boulder now allows scientists to "address" therapeutic RNA molecules with chemical signals and send them on cellular journeys to destroy harmful viruses. Professor Thomas Cech and post-doctoral researcher Bruce Sullenger, of the chemistry and biochemistry departments, said the process involves coding catalytic RNA molecules (ribozymes) to travel to locations in cells containing viral RNA. The ribozymes then locate and snip the viral RNA, rendering it harmless.

The new therapeutic approach has potential for medical treatment that runs from attacking viruses and halting infections and cancers, to alleviating symptoms of genetic disorders. A long-term goal of the therapy is to destroy the AIDS virus, said Dr. Cech, who received the 1989 Nobel prize for chemistry along with Yale's Dr. Sidney Altman for their independent RNA research.

In their experiments, Sullenger and Cech used a mouse leukaemia virus with a specific chemical sequence responsible for "packaging" the viral RNA. Since viral RNA relies on that chemical signal to guide it to particular cell locations for assembly into a viral particle, the researchers

designed a ribozyme containing the same chemical address, anticipating the ribozymes would be directed to that same pathway. The experiments showed that tracking signals used by the leukaemia virus to navigate within cells also directed the therapeutic ribozymes to the same destination, resulting in destruction of about 90 per cent of viral RNA being packaged, while leaving untargeted RNA virtually intact.

Since cells infected with the mouse leukaemia virus contain viral RNA in two distinct cellular locations, the researchers were able to test their hypothesis, said Dr. Cech. The therapeutic ribozyme "knocked out" about 90 per cent of the viral RNA being packaged into infectious particles—the RNA with which it was localized—while leaving the RNA with which it was not localized virtually intact. (Source: *Genetic Engineering News*, 1 January 1994)

First direct gene transfer in human patients

Researchers from the University of Michigan Medical Centre (Ann Arbor) have performed the first gene therapy using direct transfer of modified human genetic material. They successfully demonstrated gene expression, lack of toxicity and therapeutic potential in malignant melanoma patients.

The scientists injected a gene directly into malignant tumours of five skin cancer patients. The gene for a transplantation antigen, HLA-B7, was carried by the liposomes to the tumour cells. The immune system responded by recognizing cells into which HLA-B7 had been introduced as foreign. No complications were noted, and in each patient an immune response was triggered. Transfer of genetic material was verified by analysis of the tumour tissue. No antibodies to the DNA were detected in any patient.

The study was designed to prove the feasibility and safety of direct gene transfer for therapy in humans. The scientists say this was demonstrated in all five patients. Additionally, actual tumour regression was observed on two occasions in one patient who received DNA treatment. (Source: *Genetic Engineering News*, 1 January 1994)

Novel human antibody CDP 671 selectively targets ovarian cancer

Initial results of the first clinical study with Celltech's novel human antibody CDP 671 were reported at the Ninth Annual Meeting of IRIST (International Research Group on Immunoscintigraphy and Immunotherapy) in Velden, Austria. Investigators at Nottingham and Amsterdam Universities have shown in a phase I study that the antibody specifically targeted the tumours in eight patients with confirmed ovarian cancer.

On average, 6.6 times more antibody was bound to tumour tissue than to a range of normal tissues in these patients. CDP 671 also successfully imaged the tumour mass in six of the eight patients. The study is continuing and the antibody has so far been administered to five further patients at a higher dose, in order to extend the potential of the antibody to target cytotoxic drugs.

The results support the planned use of CDP 671 for delivering a novel cytotoxic agent, calicheamicin, for treating ovarian cancer, which has an incidence of 60,000 new cases each year world-wide. Celltech is also exploring the potential of this antibody to treat lung cancer.

The antibody was administered to 13 patients suspected of having primary or recurrent ovarian malignancy, at two centres in Amsterdam and Nottingham. Eight of them were subsequently found upon surgery to have ovarian cancer. The antibody, labelled with a radioisotope, was shown to selectively target the cancer both by comparing the extent of binding of the antibody to malignant and normal tissues in these patients and by direct imaging of the tumour.

CDP 671 is a recombinant human antibody that recognizes a protein antigen which is over expressed on the surfaces of cells of cancers of epithelial origin. This protein is termed polymorphic epithelial mucin (PEM). For this study the antibody was labelled with the isotope indium-111.

Each patient received 0.1 mg/kg of labelled CDP 671, administered intravenously. Imaging studies were carried out on the patients up to 120 hours after administration of the antibody. Specific tumour imaging was achieved in six of the eight patients. At surgery, six days after dosing with the antibody, samples were taken from tumour and some normal tissues in order to determine the specificity of antibody binding to the tumour. It was found that the level of antibody binding to the cancer compared to a range of normal tissues was, on average, 6.6 times higher in the eight patients, clearly demonstrating the high specificity of targeting achieved by the antibody. No adverse effects were observed.

Approximately 60,000 new cases of ovarian cancer are diagnosed world-wide each year. In early stage ovarian cancer, surgical and chemotherapy treatment can lead to greater than 75 per cent five-year survival. In later stage ovarian cancer, however, patients have only 25 to 30 per cent five-year survival. (Source: *News Release*, 15 April 1994)

Hangover cure

A Californian company recently announced it is developing a drug which claims can sober people up within minutes.

The human metabolism normally takes about eight hours to break down eight units of alcohol (four pints of beer or eight glasses of wine). A large dose of the new drug, called *Detoxahol*, can clear all alcohol from the bloodstream within a few minutes, claims Bob Stuckerman, the chairman of CompuMed, the company that is developing the drug. However, so far *Detoxahol* has only been tested on animals, although CompuMed hopes to begin human clinical trials next year.

The drug, which contains a combination of liver enzymes, induces a "secondary liver function" in the small intestine, increasing the body's ability to metabolize alcohol in the blood, and, as all its breakdown products already occur naturally in the body, it should have no side-effects, Stuckerman believes.

The company is developing *Detoxahol* initially for use in ambulances and hospital casualty departments where it estimates that up to a fifth of the United States' 90 million annual visits are alcohol-related. Eventually, CompuMed

hopes that an over-the-counter version of the drug will be available in bars and supermarkets. (Source: *Chemistry and Industry*, 3 January 1994)

Revolutionary 'flu drug

A revolutionary Australian 'flu inhibitor will be tested in the United States. If the drug is successful, it would have world-wide social implications, as the first cure developed for any virus.

The drug—developed by Biota Holdings and manufactured by Glaxo Australia Pty Ltd.—will be tested on humans for the first time in the United States in 1994 after receiving approval from the United States Food and Drug Administration. Trials in Australia are expected to follow. The success of this drug would be a breakthrough as significant as penicillin was in the treatment of bacterial disease. (Extracted from *Australasian Biotechnology*, Vol. 4, February 1994)

Scientists aim to free diabetics from injections with islet-saving pills, MAbs

Replacing needles with easy-to-swallow pills is just one strategy scientists are exploring to improve treatment of juvenile diabetes.

Fusion toxins, monoclonal antibodies and oral tolerance therapy are among several high-tech methods under development to help the body process food when its own metabolic system goes awry.

In the United States, it is estimated that there are about 14 million people with either Type-I or Type-II diabetes, and the National Institutes of Health figures that about one half of those are undiagnosed. If left untreated, it can cause blindness, kidney disease, amputations and death.

The majority of patients have Type-II or non-insulin-dependent diabetes, in which there is still some insulin produced, but the patient's body cannot use it. This can be brought under control through diet, exercise, drugs and, sometimes, insulin.

Only about 500,000 of the total patient population are Type-I or insulin-dependent diabetics (IDD). This form of the disease is a sudden onset autoimmune condition in which the body's defences attack the cells of the pancreas. The standard treatment for IDD is daily insulin injections to replace what a patient's body can no longer produce.

IDD most often strikes the young, and any parent can appreciate the challenge of giving a child daily injections. And, even if a patient sticks with the regimen and takes systemic immunosuppressive drugs the destruction of pancreatic cells is progressive. If a therapy can halt the destruction of the pancreas, diabetics may be able to live without daily insulin injections.

Automatic Inc. now has four clinical trials under way, the most recent of which is a study of a drug for diabetes, called AI-401, a recombinant insulin that will be administered orally. AutoImmune's approach is to use the process of oral tolerization, which allows food to pass through the body without sparking an immune response. Once the gastrointestinal tract accepts the protein, the whole body becomes tolerant.

AutoImmune has trials under way in multiple sclerosis, rheumatoid arthritis and a retinal disease called uveitis, which causes blindness. In diabetes, there is a chance to eliminate the need for insulin injections with a single pill, taken at breakfast like a vitamin.

Seragen (Hopkinton, Mass.) has its fusion toxins in clinical trials aimed at reducing the insulin requirements in Type-I diabetes. The company said that it has finished the Phase I/II trial on one version of the drug, and another trial has just started, using an improved shortened version of the toxin.

The Seragen drug links a diphtheria toxin to an IL-2 ligand that homes to a receptor on activated T-cells that have targeted the pancreas. By preventing the destruction of the islet cells, there is the potential that the body will re-regulate itself, and cut out the need for insulin injections. In the company's clinical trials they have seen patients who need no insulin or just a limited amount after treatment.

In the experiment, they treated diabetic mice with anti-CD3 monoclonal antibodies, and observed both inhibition of an accelerated form of the disease induced by cyclophosphamide and complete remission of overt disease in some animals. They wrote that the study results, if confirmed in humans "will open a new era in the immunotherapy of autoimmune diabetes", because it eliminates the need for continuous long-term immunosuppression.

Another very different approach is the development of a bio-artificial pancreas, an implant that regulates glucose levels. Neocrin Co., in Irvine, California, is in the process of conducting animal studies with such a device, consisting of porcine islets in an immunoprotective membrane.

The Pharmaceutical Manufacturers Association in Washington, D.C. has published a listing of more than 20 new medicines in development, designed to control both forms of diabetes and complications of the disease. (Extracted from *McGraw Hill's Biotechnology Newswatch*, 7 February 1994)

AZT boost

A clinical trial has shown that Wellcome's AIDS drug, AZT (Retrovir), can cut the risk of HIV transmission from pregnant women to their babies by more than two-thirds. Currently, around a quarter of HIV-positive mothers pass the virus on to their children.

The trial involved 477 HIV-positive women, who were given AZT or a placebo from between the 14th and 34th week of pregnancy. According to Wellcome, only 8.3 per cent of the women given AZT passed the virus on to their babies, as opposed to a 26 per cent cross-infection rate for those given the placebo. "These data are both exciting and encouraging", says Sandra Nusinoff Lehrman, Wellcome's head of infectious disease and immunology research in the US. "They demonstrate that we may be able to modify the course of this epidemic."

The trial, which began in 1991, was sponsored by the US National Institute of Allergy and Infectious Diseases, along with the National Institute of Child Health and Human Development and the French Institut National de la Santé et de la Récherche Medicale. The investigators have now halted the trial and have offered AZT treatment to the women from the placebo group.

The only side-effect of the treatment is reversible mild anaemia in some of the babies, says Wellcome. The

company has already submitted data to the US Food and Drug Administration, and plans to alert regulatory authorities in other countries.

According to Wellcome, 7,000 HIV-positive women give birth to children each year in the US alone—around 0.2 per cent of all births. In some parts of Asia and Africa, where almost a third of pregnant women have the virus, the figure is much higher. (Source: *Chemistry & Industry*, 7 March 1994)

New vaccine against cancer

Scientists at the Pittsburgh Cancer Institute (PCI)—University of Pittsburgh Medical Centre (UPMC) are using a new vaccine to immunize patients against their own cancers (breast, colon and pancreatic).

The vaccine is developed from an abnormal form of mucin, a complex of protein and sugars found on the surface of cells of the breast, colon and pancreas.

"This is the first synthetic peptide cancer vaccine in clinical use", says Olivera Finn, Ph.D., director of PCI's immunology programme, associate professor in the department of molecular genetics and biochemistry and in the department of surgery at the UPMC, and principal investigator for the study.

Unlike other currently available cancer vaccines, the mucin peptide-based vaccine specifically evokes the activity of killer T-cells.

Normally mucin molecules branch from the surface of healthy breast, colon and pancreatic cells, with the protein limb of mucin completely cloaked by sugar molecules. Mucin molecules lie only on the surface of cells that line the ducts found within these three tissues.

Mucin is dramatically different in cancerous cells of the breast, colon and pancreas. Some of the sugars do not form, revealing portions of the inner protein limb, which is normally hidden. These abnormal mucins appear on the surface of all tumour cells, wherever they grow in these tissues.

Although the exposed mucin proteins could trigger a natural immune response against the tumour cells bearing them, the efficiency of this process is low.

"PCI's vaccine combines a localized, concentrated amount of a mucin peptide and a substance called an adjuvant that attracts immune cells, thus greatly increasing both the odds that the right immune cells will encounter the mucin protein and the efficiency of the whole process", explains Dr. Finn. "These encounters result in the proliferation of killer T-cells that could attack and kill tumour cells anywhere in the body."

She adds that the researchers have seen "excellent killer T-cell immune responses to the mucin peptide-based vaccine in laboratory animals and other preclinical research." (Source: *Genetic Engineering News*, 15 January 1994)

Gene therapy likely to target cancer patients on large scale

Cancer patients probably will be the first large group to benefit from gene therapy, says Kenneth Culver, M.D., executive director of the Human Gene Therapy Research Institute (Des Moines, IA).

According to biotechnology firms at the recent Second International Conference on Gene Therapy of Cancer, sponsored by the San Diego Regional Cancer Centre, viral and liposomal-based vaccines have shown high anti-tumour activity. These vaccines are also promising carriers to target such diseases as 'flu, hepatitis and AIDS.

Vical Inc. (San Diego, CA), for example, is working to restimulate the body's immune response against cancer using lipid carriers (cytofectins).

Rather than treat the tumours with a variety of therapeutic cocktails, Vical, in cooperation with Dr. Gary Nabel at the University of Michigan (Ann Arbor), has developed a therapy that causes an immune response on the surface of the tumour. Effector cells are recruited to work on the tumour, thus "kick-starting" the immune system.

To do that, Vical uses an antigen (HLA-B7) encoded on DNA that is inserted on a plasmid, which is then formulated with a lipid carrier to form what the company calls cytofectin-DNA complexes, which are injected into the tumour directly.

Less than 5 per cent of the fragment remains in the cell nucleus, floating freely. The remaining 95 per cent "... is quickly cleared", which allows the gene therapy to be administered like a drug, without the possibility of permanently altering a patient's genetics. But it also suggests that frequent reinoculation may be necessary.

The question of injection frequency has not yet been answered. That is part of the Phase I trial plan submitted to the FDA. Those trials are expected to begin sometime during the first quarter of 1994 and will be conducted at several sites, including the University of Michigan and the Mayo Clinic in Rochester, MN. (Extracted from *Genetic Engineering News*, 15 January 1994)

Cortex designs new drug that appears to improve memory

Researchers working in collaboration with Cortex Pharmaceuticals, Inc. (Irvine, CA) has designed a new synthetic drug (BDP) (1-[1,3-benzodioxol-5-ylcarbonyl]-piperidine) that enhances memory in a highly specific way in animal models. The drug may hold promise for the treatment of Alzheimer's disease, mild dementias and other conditions that result in memory loss.

Rats treated with BDP performed significantly better than did controls in three different behavioural tests of memory. The scientist involved included Dr. Gary Lynch, of the University of California at Irvine, Dr. Gary Rogers, of UC-Santa Barbara, and Dr. Ursula Staubli, of New York University.

The research team cited a number of desirable characteristics of this drug. First, it can be given orally. It is a small molecule that is easily synthesized and readily passes through the blood-brain barrier. It moves from the bloodstream to the brain in under three minutes, and it has exhibited no side-effects in animal studies when administered in therapeutic doses.

BDP belongs to a recently identified class of molecules called Ampakines™ that enhance the activity of the excitatory AMPA receptors in the brain. When an Ampakine binds to an AMPA receptor, it causes the receptor to keep the ion pore open a little longer than usual in response to

glutamate. It is believed that Ampakines may thus enhance memory by reducing the amount of stimulation needed to achieve maximal long-term potentiation (LTP). Dr. Lynch's group demonstrated that AMPA receptors with bound BDP keep pores open for 1/1,000 of a second longer than normal when exposed to glutamate and reduce by half the amount of stimulation required to produce maximal LTP.

In conditions like Alzheimer's, for example, there are fewer connections and, ultimately, fewer neurons available to produce a stimulus, but if the pores of receiving neurons were kept open longer, a higher level of stimulation might be achieved—and memory function might be improved. It is possible that BDP might have these effects.

BDP was one of a long series of modified versions of the drug aniracetam that were synthesized and tested by the researchers. Aniracetam is known to enhance the activity of AMPA receptors *in vitro*. But aniracetam is not very potent in this regard, and it is rapidly metabolized in peripheral tissue. Presumably because of these factors, it was not found to facilitate synaptic communication in the brain after peripheral administration. BDP, on the other hand, does facilitate synaptic communication after peripheral administration, and has the additional salutary pharmacological properties already mentioned.

According to Dr. Lynch, this research marks the first time that any drug has been shown to enhance the activity of excitatory receptors, as opposed to inhibitory receptors, in the brain.

In addition to its unique effect on excitatory receptors, BDP further differs from previous memory-enhancing drugs in its exquisite specificity and in the existence of a strong underlying rationale for its effectiveness.

The development of many other memory drugs has been serendipitous, with no pre-existing precise rationale for the mechanism of action.

Other drugs have been designed to address functions that are generally, but not directly, related to memory.

The behavioural evidence for the effectiveness of BDP in animals was provided by experiments conducted by Dr. Staubli. Three different behavioural models were used.

- Rats were given BDP before learning which of two odours led to a reward. This problem normally takes animals ten trials to learn. When given only four trials, BDP-treated animals, but not controls, remembered which odour was correct when the two groups were tested 96 hours after the learning experience.
- Rats swimming in a water maze were able to remember the location of a submerged platform and swim to it significantly faster than did control rats after learning visual cues for its location 24 hours earlier, under the influence of the drug.
- Rats were tested for short-term memory in an eight-arm maze that held rewards of chocolate chips at the ends of spokelike runways. After they retrieved the rewards on four of eight arms, the animals were removed. Eight hours later they were placed back in the maze to test their ability to recall which of the arms held the chocolate chips. On days when they were given BDP before first running the maze, rats made half the number of errors they did on days they did not receive the drug.

According to the scientists, these results indicate that facilitation of glutamate-mediated transmission by administration of BDP causes a general improvement in memory encoding.

Acute and long-term toxicology studies of Ampakines more potent than BDP are currently under way, and Cortex hopes to initiate Phase I clinical trials soon. The company plans to file an IND for its lead compound by the end of the second quarter of 1994. (Extracted from *Genetic Engineering News*, 1 February 1994)

Firm moves DNA probe towards more applications

At the recent "Beyond DNA Probes" conference, sponsored by the American Association for Clinical Chemistry in San Diego, scientists from a number of biotech firms discussed new developments in probe-based diagnostics, therapeutics, forensics and manufacturing.

The cycling probe technology (CPT) developed by ID Biomedical Corp., in Vancouver, Canada, provides the platform for super-fast DNA-probe-based diagnostics. When used for tuberculosis testing, results are available 30 minutes after the samples are prepared—compared with the several weeks traditionally required for growth of bacterial cultures.

Cycling probe reaction technology (CPR) is actually a linear amplification system that uses a chimeric DNA-RNA-DNA probe to hybridize with a target DNA molecule at a constant temperature, thus eliminating the need for temperature cycling and auxiliary equipment. The target molecule is identified by the sequence and length of the probe, which binds to the target. When the enzyme RNase H is added, the probe fragments at the RNA segment and falls away. Another intact probe segment then binds to the target and repeats the cycle.

Because the probe cannot bind to the target's DNA after cleavage, it falls away from the reaction and an intact probe segment binds to the same portion of the target, cycling indefinitely. Through this process of combining, cleaving and falling away, the concentration of probe fragments increases hundreds of thousands of times very quickly. Because only the probe fragments are amplified, contamination is impossible and the test is completely specific and accurate. Detection of these fragments, using fluorescence, chemiluminescence or luminescence, indicates that the test is positive.

The first application of this technology, the Tuberculosis Rapid Diagnostic Test, is expected to be commercialized by ID in late 1995 in the United States and in 1994 in Canada. This test runs at a constant 65° C and requires no new equipment for laboratories. The result is that with this method, TB testing for the first time can be conducted in hospital and clinical laboratories rather than sent to reference labs, which will dramatically expand its potential market. Cost for the TB test is expected to be about $20 to $25 in the US.

In the future, ID Biomedical will adapt CPT to a range of infectious disease applications, concentrating on respiratory ailments itself and licensing CPT to other firms for a broader range of applications. (Extracted from *Genetic Engineering News*, 1 January 1994)

Chicken collagen gives startling results

Rheumatoid arthritis is a particularly cruel disease. The body's immune system turns against itself, attacking and destroying healthy bone and tissue around the joints—and nobody knows why. An effective treatment for this crippling disease may now be a step closer, however: immunologists at Harvard University believe that they have suppressed the immune system's assault, using one of the very proteins it attacks.

The immunologists, led by David Trentham, exploited the property of oral tolerization, a trick that the body uses to stop the immune system from rejecting food as a hostile foreign body. If foreign proteins are introduced via the digestive system, the body automatically suppresses immune responses to these proteins rather than triggering them.

Trentham's experiment, a double-blind trial, involved 60 rheumatoid arthritis sufferers. Of these, 28 were given oral doses of chicken-derived type II collagen, which is the most abundant protein found in joint cartilage and is believed to be one of the immune system's targets in the disease. The results were startling: at the end of the 90-day trial period, swelling and pain in the collagen group had been reduced by 25-30 per cent; the other group, who had been given a placebo, had worsened slightly. Four of the patients in the collagen group appeared to be free of arthritis altogether.

Trentham suggests two possible mechanisms for these effects. The collagen may activate suppressor cells that migrate to joints and stop other cells from attacking the collagen there; it may also directly deactivate the cells that attack the collagen. The treatment appears to be free of side-effects, unlike current rheumatoid arthritis drugs.

The next phase of the research will be a six-month clinical trial involving around 150 US patients. This trial, run by AutoImmune, a Massachusetts-based biotechnology firm which specializes in oral tolerization treatments, will involve varying doses of collagen, and will include a one-month "washout" period before the trial. This period, when the patients will receive no treatment for their condition, will allow the effects of collagen to be measured from a "no-treatment baseline". (Source: *Chemistry & Industry*, 4 October 1993)

"Tagging out" toxic cells

Doctors one day may be able to use a process comparable to photosynthesis for ridding the body of infectious agents, including cancer cells. Scientists at Armstrong Laboratory at Brooks AFB in San Antonio have developed a compound that mimics the photosynthesis process, whereby light is absorbed and stored as chemical energy. In this process, called "slow luminescence", certain bacteria and other cells can create the chemical within themselves. When these organisms are engineered to respond to specific toxins, they search and find the toxins and "tag" them with the light-emitting chemical. The toxins can then be quickly destroyed with the light-emitting chemical, which is a microwave-activated antibiotic. Progress has been made in placing these engineered genes in animal leukaemia cells, which is the first step towards targeting this process to kill cancer cells and viruses. (Source: *BioBytes, San Antonio Biotechnology News & Information*, December 1993)

Preventing hair loss during chemotherapy

To many cancer patients, the loss of hair due to chemotherapy can be a source of embarrassment and added stress. Known as alopecia, hair loss occurs because cancer drugs generally attack not only the tumour but also healthy cells, such as hair and skin. A drug with the potential to reduce or eliminate hair loss from chemotherapy could be closer to FDA approval because of new clinical trials being conducted in San Antonio. Scientists at the Cancer Therapy & Research Centre will be testing a cream made from a vitamin D compound known as calcitriol, which will put hair cells "to sleep" just prior to chemotherapy. Patients rub the cream, called Topitriol, into their hair twice daily for seven days prior to starting chemotherapy. Preliminary tests have shown that the cream prevents the hair follicles from being affected by cancer therapy. (Source: *BioBytes, San Antonio Biotechnology News & Information*, December 1993)

Testing for predisposition to addiction

Doctors may one day be able to administer a test at birth to determine predisposition to alcoholism, drug addiction and other compulsive disorders. Studies by scientists from the University of Texas Health Science Center at San Antonio and the University of California at Los Angeles have identified a gene that appears to play an important role in severe alcoholism and compulsive or behavioural disorders in general. The researchers were using this gene discovery as the basis for developing the test, which was recently patented. Although issues regarding labelling and privacy must be addressed, they believe the test will be able to help health-care professionals recognize individuals vulnerable to such illness and help them before a disorder manifests itself later in life. (Source: *BioBytes, San Antonio Biotechnology News & Information*, December 1993)

New test detects viruses linked to cervical cancer

A new test that detects the viruses that can cause cervical cancer has been developed by researchers at the University of Texas Medical Branch at Galveston. The test can potentially identify every type or subtype of human papilloma virus (HPV)—even previously unknown varieties—in less than a week. It enables physicians to tell whether a patient has any of the cancer-causing types of HPV, some of which are missed by current tests.

The system is a combination of polymerase chain reaction and direct sequencing. By computer analysis, the researchers compare the genetic codes of patients' HPVs with those of 70 known types of the virus. (Source: *Genetic Engineering News*, 15 November 1993)

Researchers discover cause and preventive therapy for diabetes in animal model

Researchers at the UCLA School of Medicine (Los Angeles, CA) and the UCLA College of Letters and Science have identified the cause and a preventive therapy

for insulin-dependent diabetes mellitus in laboratory mice. Working with a strain of mice that is genetically prone to developing diabetes and serves as a research model for human diabetes, the team, headed by Dr. Daniel Kaufman, identified the protein first targeted by the immune system as it attacks and destroys the beta cells that manufacture insulin in the pancreas.

The protein, glutamate decarboxylase (GAD), plays an important role in cellular communication in the brain and the pancreas. The T-cell attack on GAD triggers a progressive autoimmune response that leads to diabetes. After identifying the cause of diabetes' onset, the researchers were able to prevent the destruction of beta cells in mice by turning off, or "tolerizing", the immune cells that could attack GAD. This therapy prevented the autoimmune process from forming, thereby protecting the mice from developing diabetes.

Related findings were reported by Roland Tisch and Dr. Hugh McDevitt at the department of microbiology and immunology at Stanford Medical Centre in California. (Source: *Genetic Engineering News*, 15 November 1993)

Bulk separation of insulin-producing cells

Prof. T. Akaike and his research team of the Faculty of Engineering, Tokyo Institute of Technology, have jointly developed with A. Kobayashi of the Kanagawa Science and Technology Academy and H. Ogawara of the Diabetes Centre of the Tokyo Women's Medical University, a simple method for the efficient bulk separation of pig pancreas cells which produce insulin, which is the drug for treating diabetes. These cells can be microcapsulized for application to hybrid endocrine pancreas.

Pancreas and insula pancreatica transplants are sometimes necessary to prevent complications; however, these involve many problems arising from the social background and side-effects caused by immunity control agents.

An insula pancreatica transplant technique requiring no use of immunity control agent has been developed by applying culture technology and macromolecular engineering technology, which have undergone remarkable progress due to recent advances in biotechnology. The hybrid endocrine pancreas, or bio-artificial pancreas, is an artificial pancreas that seals pancreas cells in a translucent capsule for transplanting in the same or a different type of animal. The microencapsulated islet is a type of hybrid endocrine pancreas.

Pig pancreas is presently the main source of the cells necessary for the bioartificial pancreas, but the pancreas secretes various kinds of digestive fluids other than insulin, and the number of cells producing digestive fluids is overwhelmingly larger. Therefore, it is necessary to remove the cells secreting digestive fluids and to selectively separate only the islet of Langerhans beta-cells which secrete insulin. A method of separating beta cells by adding an enzyme was previously used, but the enzyme damages the cells, so the mass separation of cells was impossible. In addition, the insulin productivity of these separated cells deteriorates and are unsuitable for use in bio-artificial pancreas.

The new technology uses no enzyme. Pig pancreas cut finely into segments measuring about 1 mm x 1 mm is immersed in a culture fluid, and the islet of Langerhans beta-cells extracted by several centrifugal separations are cultured at a temperature of about 37° C. The yield is 2.5 times that of the conventional method of using an enzyme. In addition, when the cells obtained by this new method were encapsuled and implanted into mice and the insulin secretion volume investigated, mice with a high blood sugar level of 16.5 millimol of sugar per litre of blood, secreted insulin at a rate of about 180 microunits per litre of blood (1 unit = 24 milligrams), which is effective for medical treatment. Further information is available from Tokyo Institute of Technology, Faculty of Bioscience & Biotechnology, 4259 Nagatsudacho, Midori-ku, Yokohama City, Kanagawa Pref. 227. Tel.: +81-45-922-111; Fax: +81-45-922-2432. (Source: *JETRO*, December 1993)

Growth hormone approval

Genentech (South San Francisco) has received approval from the Food and Drug Administration to market its recombinant human growth hormone for treating growth failure caused by a type of kidney disorder in children. The disorder affects some 3,000 children in the United States. Genentech already sells another biotechnology drug for treating growth hormone inadequacy. (Source: *ChemicalWeek*, 1 December 1993)

Drugs from frogs

Drugs derived from the secretions of frogs will soon be commonplace, according to Michael Tyler, a herpetologist from the University of Adelaide. He said compounds extracted from glands on frogs' skin showed promise in treating a vast range of health problems, from schizophrenia to bacterial infections.

He said 29 of Australia's 204 species of frog are in danger.

Tyler stressed that the medicinal value of frogs has been known in many cultures for thousands of years, but Western scientists have only recently appreciated the potential of the secretions.

Tyler has developed an electrical stimulation technique based on acupuncture, which relaxes the frogs and encourages secretion. The frogs are not killed.

Tyler and his group has filed patents on a new class of peptides discovered in the skin of *Litoria caerulea*, the common green tree frog. The compounds, named caerins and caeridins, have been shown to act as antibiotics. According to Tyler, one appears to act against *Staphylococcus aureus*, a bacterium that can cause serious infection, including septicaemia.

But Australia is not the only country exploiting frogs for medicinal purposes. Japanese researchers have recently injected caerulein, another compound derived from the Australian tree frog, into chronic schizophrenics. For a month afterwards, the patients were symptom-free. The same compound has also been used in Germany to treat atonic gut, a condition in which the muscles of the gut collapse.

In the United States, Magainins Pharmaceuticals, a company in Philadelphia, had found antimicrobial activity in a peptide from the skin of *Zenopus laevis*, the African clawed frog, said Tyler. John Daly, a researcher at the

National Institutes of Health in Maryland, has found an alkaloid in a South American frog that carries a painkiller 200 times as powerful as morphine, but the alkaloid is not a narcotic and it is not a drug of addiction.

A burrowing desert frog produces a natural glue that could replace stitches after surgery, said Tyler. "It is not toxic and it is very strong. Hydrofluoric acid is the only way it could be removed in the laboratory." But scientists have recently been alarmed at a sudden drop in the numbers of frogs world-wide.

But he warned that the substances amphibians offer are not always health-giving. A medical student in Sydney recently ate the ovaries of a cane toad. The student spent six weeks in intensive care and had three heart attacks. (Source: *The Hindu*, 1 December 1993)

First successful production of monoclonal antibodies in milk reported

Genzyme Transgenics Corporation (Framingham, Massachusetts) has reported the successful expression of monoclonal antibodies in the milk of transgenic animals at what are believed to be the highest concentrations ever achieved in any commercial system. The company said that it had achieved levels of four grams of protein per litre of milk, compared to expression levels that are usually in the tenths of grams per litre for similar proteins in cell culture, and that the antibody had been shown to be active and functional.

The company said that it had achieved expression through the simultaneous co-injection into one-cell mouse embryos of the light and heavy chains of the gene coding for an anti-cancer monoclonal antibody behind a casein promoter. It said that it had identified at least three separate lines of mice that expressed the transgene. The company said it had also expressed a second monoclonal antibody in milk, and expects to present details of the programme at a forthcoming conference.

Genzyme Transgenics produced the antibody under contract with a leading undisclosed pharmaceutical company. The companies have now begun a programme to produce the protein in the milk of dairy goats, with a product expected to be available from an induced lactation in about twelve months. Genzyme Transgenics is pursuing broad patent protection on the transgenic expression of monoclonal antibodies. (Source: *News Release*, 15 December 1993)

Artificial bone

A novel material that binds to bone may reduce the risk of implant and prosthesis rejection and save health-care costs The material, an innovative combination of drugs, proteins and ceramics, may be more efficient and reliable when repairing damage to the human skeleton--whether caused by accidents, disease or congenital defects—than other materials in use today.

Currently, artificial implants are coated with a ceramic called hydroxyapatite, a calcium phosphate-containing constituent of teeth and bones, to help with bonding in the body. But the chance of the implant "taking" can be low because the apatite crystals used in the coating are far larger than those in bones and teeth.

Samuel Stupp of the University of Illinois designed the new material—called organoapatite—by trapping organic materials inside hydroxyapatite. He got the idea from natural bones and teeth, where hydroxyapatite crystals are glued together, or embedded, by organics such as collagen.

The innovative part of Stupp's design is what he manages to stuff inside the hydroxyapatite spheres. In a sophisticated synthesis, he inserts an anti-inflammatory drug, indomethacin, to reduce the risk of implant rejection. Then he adds a protein extracted from sea mussels, amino acid tyrosine, which they use to stick to rocks under the sea—conditions which are not too different from those in the body, and finally he throws in a monomer used to create the biocompatible polymers in soft contact lenses, polyHEMA (hydroxyethylmethacrylate), which provides a strong, flexible coating. But there is no reason why other drugs, such as antibiotics or chemotherapeutic agents, could not be used instead, he points out.

"The challenge was to connect the three bits with covalent bonds while keeping their individual chemical identities intact", Stupp explains. The organic material formed from these components is interesting in its own right, he comments; it could be used to repair soft tissues like nerves or skin. "The entire molecule is FDA-friendly", he adds.

Stupp then grows apatite nanocrystals in the solution of organics. Depending on the organic components in the solution, he can produce different types of mineral crystals. The composite is so versatile, he claims, he can make formed implants, soft pastes that harden, or coatings on metal surfaces.

Tests on animals show organoapatites induce natural bone to regenerate and then intermesh with the artificial bone, reports Stupp. Because the molecules of organo-apatites are similar in size to those in bone, they are absorbed more readily, he explains.

Stupp, who has applied for a patent to cover his process, believes the costs of production on a large scale are feasible. In the long run, he thinks that organoapatites will save money by reducing rejections and the need for secondary surgery. (Source: *Chemistry & Industry*, 20 December 1993)

Cambio's antibody to HD gene

Cambio has also developed an antibody to the recently discovered gene associated with Huntington's Chorea. The antibody is already in use and is proving to be an excellent aid to further research into the disease. Hereditary, or Huntington's Chorea occurs in a well-defined genetic pattern, striking people between the ages of 35 and 50 and belongs to the same group of disease as St. Vitus' Dance. The antibody is a first for Cambio—and involved the use of a technique whereby the company made a polyclonal antibody using the nucleic acid sequence without first isolating the protein. (Source: *Biotechnology Bulletin*, Vol. 12, No. 11, December 1993)

Livestock applications

Recombinant rabies vaccine

Rhône Merieux, Inc., a French chemical company, has applied to the US Department of Agriculture (USDA) for a licence under the Virus-Serum-Toxin Act (VSTA) to sell a recombinant vaccine to control wild-life rabies. An approval would be the first in the USA of a recombinant virus for use as a wildlife vaccine. Ultimately, licensing could mean the distribution of millions of baits containing the vaccine in areas harbouring large populations of raccoons.

To deliver the product to raccoons, vaccine-laden baits are distributed in raccoon habitats by aircraft or other means. Since the vaccine can be taken orally, many raccoons that eat the bait will develop some level of immunity to the disease. The hope is that a large enough portion of the population becomes immune to eliminate rabies in wild raccoons.

Somewhat surprisingly, the three field trials done with the vaccine to date indicate that the vaccine is unlikely to work. Data from the tests in Virginia, Pennsylvania, and New Jersey demonstrate that fewer than half the wild raccoons develop antibodies to rabies in areas where vaccine-laden baits were distributed. The Virginia test showed a 45 per cent rate; the Pennsylvania test 20 per cent. Preliminary results from the test under way in New Jersey show that fewer than 40 per cent of the raccoons in the baiting area produced antibodies.

Scientists doubt that vaccination rates this low can control the disease in wild raccoons. A University of Pennsylvania model of rabies spread in raccoon populations suggests that a 99 per cent immunization rate must be achieved to eradicate the disease. (Source: *The Gene Exchange*, February 1994)

Agricultural applications

Herbicide resistant cotton

The US Department of Agriculture (USDA) has given Calgene Inc. the go-ahead for a new strain of cotton. As a result of an approval from USDA's plant health inspection service, already field-tested varieties of the new BXN cotton seed can now be grown and shipped throughout the US, like regular cotton. BXN cotton seeds are genetically engineered by Calgene to incorporate a patented gene that allows the resulting cotton crop to be treated with the herbicide bromoxynil without the reduction in crop yield associated with such effective herbicides. Bromoxynil, marketed by Rhône-Poulenc Ag Company as Buctril, can be sprayed over post-emergent BXN cotton without any crop injury, Calgene says.

The USDA approval of the BXN varieties is the first under its regulations for genetically engineered organisms and products, which were finalized on 31 March 1993.

In addition to giving cotton growers better economic benefit, the BXN system is good for the environment, Calgene says.

When fully adopted by US growers, the new method could cut herbicide use by as much as 9 million pounds per year. Since the system has two components—seeds and herbicide—the approval process has two steps, Calgene says. Thanks to the USDA approval, the first step has been completed. The next step, Environmental Protection Agency approval of Buctril for use with the BXN seeds, is pending. Calgene expects full registration for the system in 1995. (Source: *Chemical Marketing Reporter*, 21 February 1994)

Simple detection of pathogenic fungi using mabs

The Institute of Physical and Chemical Research (RIKEN) has developed a rapid, simple, and cheap method for detecting pathogenic fungi in crop seedlings and soils using monoclonal antibodies.

Preventing soilborne diseases of plants is vital in the production of farm produce or food plants. However, the conventional methods of detecting pathogenic fungi involve much time and difficulty, making it economically unsuitable for adoption by farmers. For example, there is a limit to the cost for detection of pathogenic bacteria causing diseases of Chinese cabbage which is shipped at a price of ¥20 apiece by farmers, sold at ¥50 on the market and retailed at ¥200 by greengrocers.

This problem has been solved by applying immunological methods. Monoclonal antibodies are used for detecting specific pathological viruses of plants.

Pathologenic fungi living in soil infect plant roots, pass through stalk tracheae and spread throughout the plant. The existence of pathological fungi in seedlings is detected in the stalk. The plant stalk is cut into fine sections and adhered to a nitrocellulose film. A contaminated plant results in fungi adhering to the sheet surface in about 15 minutes; while sugar discharged by the bacteria remains. The sugar is bonded with the monoclonal antibody to show the existence of the fungi.

Whether the sugar and monoclonal antibody are bonded well is judged by immersing the sheet in an aqueous solution containing hydrogen peroxide and chloronaphtol. If the sugar and antibody bind together, only the part with adhered fungi changes into a blue colour. When experiments were conducted on the *Fusarium oxysporun* in tomato, a clear colour change reaction was confirmed.

Cultivating agricultural products requires investigation of whether there are infectious pathological fungi in the soil prior to planting. However, diverse microbes exist in the soil other than pathological fungi, and substances consist of diverse compositions, so no practical detection method has been available. In addition, since diverse soil compositions act to obstruct the antigen antibody reaction, the application of an immunological detection method was difficult. The institute has now established its GP-IBA method that enables detection of pathological fungi in soil.

A gel layer is prepared on a membrane, and the soil to be examined is spread out on the layer. Incubation for about 20 hours causes the soil components to remain intact on the gel, but the fungi existing in the soil proliferate, pass through the gel and reach the membrane. They are detected by a colour reaction, in the same manner as in stalk bacteria detection. Further information is available from The Institute of Physical and Chemical Research (RIKEN), 2-1 Hirosawa, Wako City, Saitama Pref. 351-01.

Tel.: +81-48-462-1111; Fax: +81-48-462-4715. (Source: *JETRO*, December 1993)

Firms move on nematode technology

Plant biotechnology companies Ecogen (Langhorne, PA) and Biosys (Palo Alto, CA) have separately announced agreements to increase promotion of nematode-based insecticides technology. Ecogen says it has signed a deal with Australia's CSIRO to gain rights to a formulation for stabilizing nematodes. The biotechnological firm already markets nematode-based bioinsecticides, but says the CSIRO technology could increase the shelf life of certain nematodes. Meanwhile, Biosys has acquired licences to develop two species of nematodes, including one discovered by Rutgers University and another isolated by the US Department of Agriculture. Biosys says it expects to have a new produce to control grubs based on the Rutgers nematode in 1994. Further research will be done next year on the US Department of Agriculture's nematode, which is aimed at various pests, including cotton bollworm, according to Biosys. (Source: *ChemicalWeek*, 1 December 1993)

Tomato catch-up

A new technique devised at Purdue and Cornell Universities has allowed researchers to transfer genes conferring disease resistance from one tomato variety to another, meaning that growers would need to use less pesticide.

The researchers, led by Purdue's Greg Martin and Cornell's Steven Tanksley, chose the tomato as a subject because its genome is relatively short and well-researched; several parts (or loci) of the genome have already been identified as conferring resistance to diseases; and extensive gene libraries are available.

The researchers used a technique called map-based cloning or chromosome walking, originally developed by workers on the Human Genome Project to locate single-gene mutations, to isolate the gene conferring resistance to bacterial speck. The technique works by cloning successively shorter sections of the gene's locus until the smallest section that interacts with the bacterium's disease-causing gene is found. Chromosome walking has never before been used to isolate a gene in a growing plant.

The team transferred the isolated gene to susceptible tomato varieties, and inoculated seedlings with the pathogen bacteria. The transgenic plants, which had inherited the gene did not develop the bacterial speck. The technique need not be confined to the tomato, says Martin. Resistance could also be induced in many other crops.

According to Martin, the gene—coded *Pto*—is similar to mammalian kinase genes which are part of an alarm system warning cells about changes in their environment. He thinks that *Pto* might act in a similar way, alerting vulnerable cells about pathogen attacks. (Source: *Chemistry & Industry*, 6 December 1993)

Cassava hornworm control

Farmers in Brazil have begun controlling the cassava hornworm, with a new, environmentally friendly pesticide they can whip up in a kitchen blender at no cost. Scientists at the International Centre for Tropical Agriculture (CIAT) in Cali, Colombia, who developed the spray, said it can rid cassava fields of 60 to 100 per cent of the pest without doing any ecological damage. "This is significant because farmers use more chemical pesticides for controlling the cassava hornworm than for any other cassava pest", Anthony Bellotti, CIAT's cassava entomologist, said. The new pesticide contains a granulosis virus disease that infects only the hornworm. Bellotti said farmers can make the pesticide from caterpillars that have died from the virus. They are easy to spot in the field because they are balloon-shaped and send out a white, smelly liquid when they burst. Twelve large caterpillars liquefied in a blender and mixed with water make enough spray to protect one hectare of cassava. For further information, contact: Dr. Anthony Bellotti, Cassava Programme. CIAT, A.A. 6713, Cali, Colombia. Tel.: 57-23-675050. Fax: 57-23-647243. (Source: *Ceres*, January/February 1994)

Zeneca reveals plant cell technology

Zeneca Seeds has detailed a new method of plant cell transformation based on the use of silicon carbide crystals, which it claims will allow development of new varieties of crop plants more quickly and efficiently. The method offers an alternative to particle bombardment.

Termed "whiskers", the new method involves simply mixing a suspension of plant cells with the DNA containing the gene to be inserted and a quantity of needle-shaped silicon carbide single crystals (about 10-20 micron length, 1 micron diameter). The needle crystals collide with the cells, opening up passages in the cell walls, through which the genetic material can enter the cells.

The transformation can be performed using standard test tubes and a laboratory mixer. Additionally, it allows replicate experiments to be carried out at the same time.

Zeneca has already used the method to transform a number of plants including maize, one of the most difficult crops to transform and the company's principal target. Fully fertile genetically modified plants have been produced at Zeneca's seeds research centre near Slater, Iowa. The company believes the "whiskers" concept can be fine tuned to be applicable for any plant cell transformation.

Zeneca has been issued a notice of allowance on its patent application by the US patent and trademark office and expects a grant to follow shortly. Parallel patent protection is being sought in other countries. The company expects to license the technique on a case-by-case basis. (Source: *European Chemical News*, 7 February 1994)

Cloned pyrethrum

High prices and supply shortages may be a thing of the past for the insecticide pyrethrum, now that AgriDyne Technologies Inc. has discovered a way to ensure availability.

Pyrethrum, which combats fleas and ticks on livestock and companion animals, and in greenhouses and the home, is now derived from chrysanthemums and like flowers, but scientists for AgriDyne have cloned a gene that produces

the intermediate chrysanthemol, enabling the production of pyrethrum molecules and bringing the company a step closer to actual pyrethrum production.

The company says its research could provide a stable supply of the insecticide, and eliminate the supply problems associated with pyrethrum. (Source: *Chemical Marketing Reporter*, 28 February 1994)

Food and food processing

Japan tests recombinant chymosin

The Ministry of Health and Welfare has decided to review two applications for a food additive created by a US and a European firm that is based on recombinant DNA technology. The companies have applied to the Ministry to verify the safety of the product. The food additive is chymosin, a milk-clotting enzyme for producing cheese, that has already been approved for use in food in the US and in Europe. Reportedly, the Japanese Ministry considers biotechnology-derived chymosin to be substantially equivalent to natural chymosin. Approval may be forthcoming as early as the latter half of this year and imports may begin before the year is out. (Source: *McGraw Hill's Biotechnology Newswatch*, 7 February 1994)

New biotechnologies set to impact industrial food preservative market

The food industry is currently responding to consumer demand for foods that are perceived as fresh and natural. As a result, there is a move to replace a number of synthetic additives—such as nitrites, nitrates, sulphur compounds and the hindered phenolics—BHA, BHT, TBHQ and gallates—with more acceptable biological compounds. This trend will provide areas of growth for new additives or other methods of preservation.

However, production of these more-natural preservatives remains in its infancy, with most of the more promising candidates still in development. Many companies and universities around the world are pioneering the development of innovative products and processes for this sector (see table 1).

Food additives can be produced commercially via three principal methods: extraction from natural sources, chemical synthesis or fermentation.

Natural sources usually contain only small amounts of extractable preservatives. For example, tocopherols (vitamin E) are extracted from vapours during the manufacture of vegetable oils containing only 3-10 per cent of a mixture of vitamin E compounds, which must be purified.

By contrast, synthetic additives offer competitive advantages in the potential scale of production but are also limited by economic factors, including the cost of oil or natural gas and process efficiency. However, synthesizing a natural product may not always succeed. For example synthetic vitamin E consists of a mixture of eight different homologues that are not all structurally identical to the natural form and thus have diminished potency as preservatives. Therefore, 36-50 per cent more synthetic vitamin E by weight is required to give the same antioxidant potency as the natural source.

The third approach, fermentation, can help to create inexpensive, dependable sources of natural additives. Moreover, using the techniques of biotechnology, manufacturers can create novel variations that have improved performance profiles with respect to such properties as pH, temperature, stability and activity. Several unique features of fermentation processes make them particularly attractive—they work under conditions of mild temperature, pH and pressure, conditions amiable to the organisms involved. Synthetic chemical processes, on the other hand, operate at high temperatures and pressures, increasing capital investment and energy costs.

The strategic implications are dramatic. Sophisticated classical synthetic producers will integrate biotechnology into their processes, often joining other groups because of their strong know-how in strain selection, modification and fermentation. Other traditional manufacturers will probably have to establish in-house genetic engineering capabilities, particularly in the development of second-generation products, in order to survive.

The following factors affect the selection of a preservative and its level of use: the composition of the food (e.g., moisture, pH); the presence of minute amounts of certain heavy metal oxidation catalysts (e.g., copper, iron); contamination level; storage conditions (e.g., temperature, humidity, light); and the ability to maintain natural properties of the food (e.g., taste, texture, colour) for the duration of the desired shelf-life.

The shortcomings of these compounds, which restrict some industrial applications, include their availability, nonspecificity, lack of potency and cost.

In addition to the classic markets that will inevitably benefit from the use of biopreservatives, several new growth areas for additive technology are emerging. Novel nonthermal sterilization and ultracentrifuge techniques will compete with these new biopreservatives.

Packaging

Besides modified atmosphere packaging (MAP), vacuum skin packaging and high barrier plastics, active packaging and biodegradable coatings have been developed.

Many of the high-techology freshness enhancers do offer extended shelf-life but have yet to be approved for use on foods, with the exception of Mitsubishi Gas & Chemical's Ageless line, which uses a mixture of iron and calcium hydroxide powder oxygen scavengers for foods such as nuts, potato chips, pizza and cakes.

Natural preservatives

Oxidation of such food constituents as lipids, flavour molecules, vitamins and colour compounds has become a major problem in the packaging of minimally processed health foods. At a time when the use of chemical additives is coming under increasing consumer scrutiny, the intake of both polyunsaturated and monounsaturated fats—which need to be protected from peroxidation—is rising. Even foods with reduced fat levels are susceptible to oxidative rancidity, which is dependent on the reactivity of, rather than the amount of fat in the product.

Table 1

Examples of food preservatives in Development

New Food Application/System	Institute/Company
Recombinant cecropin, an antimicrobial peptide active against both gram-positive and gram-negative bacteria	Xoma (US)
Recombinant antifreeze proteins to extend shelf-life of frozen dairy and fruit products	DNAP (US)
Trehalose sugar and genes to protect dried and frozen food	Osmotica Foods (a joint venture of Calgene in the US and Quadrant Holdings in the UK)
Cell membrane particles/antioxidant enzymes as processing aid or in active packaging	Oxyrase (US)
Propionic acid, an antifungal using improved propionibacteria	Iowa State University (US)
Fermented whey rich in propionic, acetic and lactic acids as fungicide for cheese	Nutrinov (France)
Rosmarinic acid produced from plant cell cultures of rosemary as antioxidant	Office de la Recherche Scientific et Technique (France)
Natural yeast *Pichia guilliermondi* and *Sporobolomyces roseos* to protect fruits against fungal rot	Appalachian Fruit Research Station (US)
Lysozyme, a gram-positive natural antimicrobial expressed in *E. coli* and yeast	National Institute of Bioscience and Human Technology (Japan)
New Processes	
Two-step process to synthesize vitamin C	Lubrizol/Genencor (US)
Production of recombinant trehalose using a bacterial host system	Ajinomoto (Japan)
Production of antioxidants such as vitamins C and E or SOD using photosynthetic organisms	Commissariat a L'Energie Atomique (France)
Microbial conversion of glucose into sorbitol using two coupled enzymes	Denki Kagaku (Japan)

(Source: *George Gilliand/GEN*)

Consumers are willing to pay a premium for natural products, which they view as safer than chemically based synthetics. The variety of natural ingredients that can be used in minimally processed foods underscores the opportunities available to natural biopreservative manufacturers to compete in the limited-life foods market. Generally, the applications of natural biopreservatives developed over the next decade could be significant. (Extracted from *Genetic Engineering News*, December 1993)

Novel effluent treatment method for food processors

One of the major problems in effluent from food-processing plants is its high biochemical oxygen demand (BOD). This can reduce the oxygen content of the water to the point where fish can suffocate. Other troublesome components of the effluent are suspended solids, oil and grease.

The Alberta Research Council and Epsilon Chemicals Ltd. (E-CHEM), both in Edmonton, Alberta, Canada, have developed a new effluent treatment technology specifically for the food-processing industry. The process, EnviroFloc™, which treats waste water and produces a recyclable sludge, will be marketed by E-CHEM.

The company says that EnviroFloc has proved effective at treating all these components. In two pilot plant runs at a fish-processing plant in Vancouver, the BOD in the waste water was reduced by 60-80 per cent. There was also 95 per cent reduction in the suspended solids and the oil and grease. The entire process took approximately

30 minutes. The process will also work in poultry- and meat-processing plants. EnviroFloc also produces a re-usable sludge. The process uses a naturally occurring, biological polymer that is biodegradable and can be re-cycled and rendered to produce a protein source for use in making fish or animal meal. (Source: *Genetic Engineering News*, December 1993)

Chemical applications

Gene engineering could boost commercialization of biopolymers

Genetic engineering is probably the leading technical development of recent years to enhance "the commercial prospects of biologically derived polymers", according to a new study from the US Congress' Office of Technology Assessment (OTA).

"The advent of recombinant DNA technology has allowed researchers to exercise unprecedented control over the purity of specific properties of polymers", states the OTA in "Biopolymers: Making Materials Nature's Way". The report noted that "Advances in genetic engineering have also enabled scientists to study how biological systems produce complex polymers", which, unlike man-made materials, pose few environmental problems. This suggests that the research, in addition to producing stronger materials, "could also lead to the development of new environmentally sensitive manufacturing methods".

The OTA study is aimed at encouraging more federal Government involvement in the development of biopolymers, defined as a new class of polymer potentially biodegradable, biocompatible and renewable—created by harnessing the enzymes found in nature or by transforming agricultural or marine feedstocks.

Most plastic materials are not biodegradable and are derived from non-renewable resources. "The very properties of durability and strength that make these materials so useful also ensure their persistence in the environment and complicate disposal", said the OTA study.

Recombinant DNA techniques offer great potential, especially with protein-based materials. For example, protein polymer silk that is produced commercially by silkworms can now be made in recombinant micro-organisms, states OTA.

In addition, the chemical synthesis of DNA allows scientists to construct entirely new genes that encode unique protein polymers, the report continued.

For biopolymers other than proteins, such as poly-saccharides and polyhydroxyalkanoates, the situation is more complicated. In these cases, genetic manipulation permits control of the production of enzymes, which are responsible for the production and polymerization of the building blocks that comprise the final polymer products. (Source: *McGraw Hill's Biotechnology Newswatch*, 6 December 1993)

New synthetic resin

South Korea's Samsung General Chemicals claims to have developed a new environmentally friendly synthetic resin that can decay far more quickly than current degradable resins. The resin decomposes within 60 to 80 days of being discarded and buried. Developed by Samsung's research institute in Taejon, the "bio-cum-photodegradable" resin is a mixture of PE resin, starch and other fillers. The company has started pilot commercial production. Depending on market response, next year it could consider establishing a full-scale production plant to produce 20,000 tons/year. (Source: *European Chemical News*, 31 January 1994)

Industrial microbiology

New molecular receptor

Chemists from the CNRS Lyon Stereochemicals and Molecular Interactions Laboratory claim to have developed a molecular receptor capable of selectively capturing volatile molecules such as the hydrocarbons methane, ethane and propane and CFCs. The "imprisoned state" of the molecules within the receptor cavity is similar to a gas supercompressed at a pressure above 600 atm. The researchers believe the receptors hold potential in a variety of applications including biomimetic catalysts, dosing devices and elimination of chlorinated hydrocarbons from aqueous effluents. (Source: *European Chemical News*, 31 January 1994)

New biodegradable polymers

Novon Products Group, a division of Warner-Lambert (Morris Plains, NJ), has introduced three new starch-based biodegradable polymers and is hoping to position them as environmentally-sound alternatives to plastics in some applications. According to the company, all three products are derived from food starches, biodegrade as easily as paper, and are more water resistant than the first generation starch-based polymers introduced by Novon in 1990. The new products may be used as material for compost bags, a biodegradable alternative to plastic in the manufacture of disposable cutlery and as material for making bottles for the specialty vitamin, health food, and pharmaceutical markets. (Extracted from *ChemicalWeek*, 18 August 1993)

New biodegradable polyurethanes

Japan's National Institute of Materials and Chemical Research, based in Tsukuba, claims to have succeeded in developing new biodegradable polyurethanes derived from various kinds of plant materials such as lignin and molasses. Equally, coffee grounds after extraction of coffee and sugar-cane scraps can be used as raw materials. The physical properties of the polyurethanes are very similar to those of conventional polyurethanes, the researchers claim. (Source: *European Chemical News*, 16 August 1993)

E. PATENTS AND INTELLECTUAL PROPERTY RIGHTS

The patenting of human genetic material

In the 1980s US court decisions set international precedents for the patenting of human genetic material. As a result, exclusive monopolies over human genetic materials are becoming commonplace in the industrialized

world, without discussion of the social, ethical and political implications. In the absence of public awareness and debate, issues of equity and ethics have been eclipsed by the interests of the biotechnology industry. Most recently, the US Government has laid claim to "immortalized" human cell lines extracted from citizens of Panama, New Guinea and the Solomon Islands.

Private ownership of human biological materials raises many profound social, ethical and political issues. Industrialized nations are lobbying vigorously for "harmonization" of intellectual property laws world-wide with the ultimate goal of imposing life patenting laws world-wide. In the South, issues of development and national sovereignty are at stake. Fundamental human rights are jeopardized everywhere.

The US Government's recent patent applications on the cell lines of indigenous peoples highlight the need for international debate on the patenting of human genetic material, particularly in the context of multilateral trade agreements (GATT) and the Convention on Biological Diversity, which both cover biotechnology and intellectual property standards. National Governments and intergovernmental organizations must address the issue of life patenting on the basis of ethics and equity. The US Government should drop all claims to the human cell lines of foreign nationals and repatriate the materials to the indigenous communities or national Governments involved. International protocols must be developed by the appropriate United Nations bodies for protecting the rights of human subjects from patent claims and unjust commercial exploitation.

In the industrialized world new biotechnologies are being developed at a rate far faster than responsible social policies can be devised to guide them, or legal systems can evolve to adequately address them. In the 1980s, the US and other industrialized nations took giant steps to accommodate the biotechnology industry's desire to patent life, with public debate lagging far behind.

In the mid-1990s the biotechnology industry is lobbying vigorously to see minimum standards of intellectual property enforced world-wide. Will the US precedent for commodification of human biological materials be imposed on developing nations? Both national Governments and intergovernmental organizations must now address the issue of life patenting on the basis of ethics and equity, with the full and informed participation of civil society.

The General Agreement of Tariffs and Trade (GATT), and the Convention on Biological Diversity came to a head in the closing weeks of 1993. These multilateral agreements offer two important arenas for action and debate on the patenting of human genetic materials.

The GATT Trade-Related Intellectual Property Agreement (TRIPS) requires that signatory States adopt intellectual property laws covering both microbial materials and plant varieties. Human genetic material is not specifically excluded from the deal.

Meanwhile, the Biodiversity Convention obliges signatory States to recognize the ownership of genetic materials by countries or companies. Germplasm collected in one country prior to the Convention coming into force must be regarded as the property of the country that now stores the material. Thus, the human cell lines of people in Panama, Papua New Guinea, and the Solomon Islands stored in the United States and under patent claim by the US Government are their legal property and, according to corporate interpretations of the Convention, the people and countries involved will have to pay for access to their donated human materials and any medical products derived from them. Specific actions and decisions include:

- GATT's 118 participating States (the majority from the developing world) must determine whether or not human genetic materials are included in its definition of microbial materials.
- Similarly, contracting parties to the Biodiversity Convention must come to a clear decision on the role of intellectual property with respect to biological materials and especially whether or not human genetic materials are part of the Convention.
- The Biodiversity Convention should respond to the request of indigenous peoples for protection from patent claims.
- The US Government should drop all claims to the human cell lines of foreign nationals and repatriate the materials to the indigenous communities or national Governments involved.
- International protocols should be developed by the appropriate United Nations bodies for protecting and broadening the rights of human subjects from commercial exploitation and patent claims. The International Bioethics Committee of the United Nations Educational, Scientific and Cultural Organization (UNESCO) is one such body.

(Extracted from *RAFI Communique*, January/February 1994)

Pesticide patent angers farmers

Protestors rallied in London recently to accuse a large American chemicals company of "intellectual piracy" in obtaining patents for a natural pesticide extracted by generations of Indian farmers from the seeds of the neem tree. The protestors, who claim they are backed by leading Indian scientists, say that new international trade laws being negotiated under the General Agreement on Tariffs and Trade (GATT) could mean Indian farmers may soon have to pay a royalty before using the pesticide, known as azadirachtin.

Seeds, leaves, bark and oil of the neem tree have dozens of traditional uses in India—as a spermicide, to make antiseptic toothpicks and as a treatment for leprosy, for example. Neither traditional methods of extraction nor modern processes developed by Indian industrial chemists are protected by national patent law.

Chemicals companies in the US have taken out a series of patents of recipes for making stable neem-based emulsions and solutions. The most important commercially is likely to be the patent, owned by the Florida-based chemicals company W.R. Grace, for extracting from neem seeds a form of azadirachtin, which it markets under the brand name Margosan-O.

The company is building a factory in India to manufacture the product for export to the US. Last year, a report

from the US National Research Council predicted that the product could have a large market there as chemical pesticides are phased out in favour of "biopesticides".

Indian farmers extract azadirachtin by smashing the seeds, soaking them in water and scooping the emulsion off the top. This they pour over crops. It repels common pests, including locusts, mosquito larvae, Colorado beetles and boll weevils.

Grace's version of the chemical is stable, so it can be stored and packaged for marketing. The company says Indian farmers will not have to pay royalties because of its patent, or because of GATT. "Although traditional knowledge inspired the research and development that led to these patented compositions and processes, they are considered sufficiently novel and different from the original product of nature, and the traditional method of use, to be patentable", says the company.

Farmers fear that the network of seed suppliers being developed by Grace for its factory could leave farmers short of supplies and increasingly dependent on Grace's product. Grace estimates that it will use only 2 per cent of the seeds collected in India. (Source: *The Hindu*, 1 December 1993)

Tomato dispute settled

Calgene (Davis, CA), Zeneca, and Campbell Soup have announced an agreement aimed at settling patent fights over the marketing of genetically engineered tomatoes. The deal—covering tomatoes modified with the polygalacturonase (PG) gene—gives Calgene exclusive world-wide rights to sell fresh PG tomatoes; Zeneca and Campbell get world-wide rights to sell commercially processed PG tomato products. The agreement also calls for cross-licensing to settle outstanding PG patent disputes between Calgene and Zeneca. Calgene says the deal will "clear up current and potential disputes between the three leading tomato companies". Calgene is awaiting Food and Drug Administration marketing approval for its biotech fresh tomatoes. (Source: *ChemicalWeek*, 2 March 1994)

Researchers drop bid to patent DNA

The National Institutes of Health (NIH, Bethesda, MD) and the United Kingdom's Medical Research Council (MRC, London) will stop trying to obtain patents on thousands of pieces of human DNA they have been mapping. Two years ago, the move by NIH and MRC to file for patents on DNA fragments provoked widespread concern, particularly among pharmaceutical and emerging biotech companies. NIH has effectively given up its bid; it is not appealing the US Patent and Trademark Office's latest rejection of its patent applications. (Source: *ChemicalWeek*, 2 March 1994)

US "Federal Research Product Commercialization Act"

A cooperative research and development agreement between the Scripps Clinic and Research Foundation and the Swiss company, Sandoz Corporation, prompted a bill introduced into the US Congress by Representative Ron Wyden. The text of this Bill, introduced into the US House of Representatives on 11 March 1993, has been circulated by the Biotechnology Industry Organization. The Bill is described as being designed "to establish a process to provide for reasonable prices for drugs, devices and other tangible products made available to the public as a consequence of funding by the National Institutes of Health and for other purposes". It requires that research entities entering into agreements with commercial parties will ensure that the commercial parties will make the product available to the public at a reasonable price, and will pay to the National Institutes of Health royalties which are reasonably related to the amounts expended by the Institutes in relation to the product. In order to do so, the research entity must conduct a competitive process of bidding in order to select a commercial partner, and prospective commercial partners must specify a formula for determining the price at which the product will be made available to the public. If there are enough qualified applicants for partnerships, the research entity must approve enough applications to ensure that commercial parties compete in making the product available.

In his speech introducing the legislation, Representative Wyden criticized agreements in which drug companies had obtained exclusive access to publicly-funded research, claiming that the companies were getting a "free ride" at taxpayer expense. (Source: *Australasian Biotechnology*, Vol. 3, No. 6, December 1993)

Fee increases and examination changes in Japan

The Japanese Patent Office has increased its fees by approximately 50 per cent in respect of filing of applications, requests for examination, and granting fees. The legislation restricts the scope of amendments during prosecution.

In addition, new examination standards have been issued, including a chapter relating specifically to biotechnology applications. Since 1964, the Japanese Patent Office had examined applications in this field according to the old standard in relation to "applied microbial industry" and "new plant variety". The standards largely confirm existing practice in the Japanese Patent Office, particularly in relation to deposits made under the Budapest Treaty where the invention involves or uses a living organism. Deposit is required unless the organism is commercially available, has been deposited at a reliable depositary and is readily available to the public before the filing of the application, or is reproducible by the methods described in the specification. Otherwise, the deposit must be made before the priority date of the application, and the deposit number must be recited in the priority application.

The standard also sets out rules for defining genes in claims, and for deciding inventive step. DNA of a specific sequence involves an inventive step if the protein encoded by the DNA involves an inventive step; if the protein is known, whether or not its amino acid sequence is known, the DNA will be inventive only if it has an advantageous effect compared with other DNAs of different sequence encoding the same protein. (Source: *Australasian Biotechnology*, Vol. 3, No. 6, December 1993)

New patent law proposed for Hong Kong

At present, Hong Kong does not have any patent law of its own, but re-registers United Kingdom patents or European patents designating the United Kingdom, within

five years of the date of grant. It is now proposed that independent Hong Kong patents should be granted, based on registrations of a European patent, designating any country, or of a Chinese patent. Registration would have to be sought within six months of publication of the patent in Europe. Once registered, the patent would be independent, and a patent bill based on the UK Patents Act 1977, which is compatible with the European Patent Convention, has been proposed. (Source: *Australasian Biotechnology*, Vol. 3, No. 6, December 1993)

Amendment to Patent Law in Taiwan

The first reading of a draft patent law amendment was completed in July 1993. This includes new novelty requirements excluding from patentability inventions which have been put into mass production other than for experimental purposes, and providing for patentability of micro-organisms in applications originating in countries with reciprocal agreements with Taiwan; deposit of micro-organisms in a depositary in Taiwan; priority claims on applications originating in countries having reciprocal agreements with Taiwan; and patent term extension for patents originating in countries with reciprocal agreements with Taiwan. (Source: *Australasian Biotechnology*, Vol. 3, No. 6, December 1993)

Industrial Property Bill passed in Brazil

This Bill, originating in 1991. was finally approved by the Brazilian House of Representatives at the beginning of June 1993, and has been referred for approval by the Senate. In addition to procedural streamlining, the Bill provides for elimination of pre-grant oppositions or appeals by third parties, to be replaced by post-grant opposition, a patent term of 20 years, and pipeline protection for inventions relating to chemical products, pharmaceutical products or foodstuffs, or processes for their production, provided that the patent in the country of origin has not been granted at the time of filing in Brazil. Micro-organisms will only be patentable in respect of a given process generating a specific product; the approved text is apparently unclear, but is understood to limit protection to specific use applications; there is no mention of plants or plant varieties, but it appears that animals as such will not be patentable. (Source: *Australasian Biotechnology*, Vol. 3, No. 6, December 1993)

Legal protection of biotechnological inventions in European Community

On 16 December 1992, the EC Commission published its *amended proposal for a Council directive on the legal protection of biotechnological inventions (Proposal)*. The Proposal covers such matters as patentability of biological material, including parts of the human body and transgenic animals.

Although the Proposal has the potential for considerable impact on the biotechnology field, it suffers, in its present state, from a number of deficiencies discussed below. Some argue that the Proposal creates an unfavourable climate for European biotechnology when compared to the position in the US and Japan.

Patentability of human body parts

Article 2.3 of the Proposal provides that inventions are not to be considered patentable where publication or exploitation of them would be contrary to public policy or morality. More specifically, it states the human body or parts of the human body *per se* shall be unpatentable on this basis.

The explanatory notes to the Proposal state that it is intended that parts of the human body *per se*, means parts of the human body as found inside the human body. The notes then list certain patents for products or parts of the human body, being implicit that these should continue to be patentable. The list includes a human cell line, recombinant DNA molecules, molecular cloning and characterization of gene sequence coding processes and certain processes for producing human antibody and human protein of therapeutic value. The notes then go on to say that if the applicant simply wishes to patent a mere part of the human body *per se*, e.g., a human gene whose function or protein product is not known, exclusion from patentability would apply.

It seems clear that the Commission intends to extend patent protection to microscopic parts of the human body such as genes subject to the normal requirement of the existence of a commercial application, but not to parts found on human inspection, e.g., a liver or a kidney. However, the Directive and the notes do not themselves make the macroscopic/microscopic distinction. It is unfortunate that there is not greater clarity on this vital issue.

Transgenic animals

While under Article 3 biological material including transgenic animals are to be patentable, Article 2.3 (c) states that processes for modifying the genetic identity of animals that are likely to inflict suffering or physical handicaps upon them without any benefit to man or animal shall be unpatentable. The explanatory notes refer to the Preamble to the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes of 1986 to assist in providing criteria for what will be acceptable animal suffering in terms of patentability, although these are not mentioned in the Proposal itself.

As with the case of patentability of parts of the human body, efforts to encapsulate popular morality and ethical considerations into patent law serve only to confuse rather than generate legal certainty. Whether the Oncomouse suffers and even if it does, whether the benefit to man overrides that suffering is a highly subjective consideration.

Amendments to the R&D block exemption

Collaborative research and development agreements between biotechnology companies and pharmaceutical firms frequently embrace both the R&D phase and also specify the respective rights of the parties covering commercial exploitation. Inevitably there are restrictions on competition within the scope of Article 85 (1) of the Treaty of Rome, particularly with the grant of some form of exclusive rights. Such restrictions are void and unenforceable and may render the parties liable to fines and third party action.

Under Article 85 (3) certain agreements and restrictions can be exempted from the application of Article 85 (1), and in 1984 in Regulation 418/83 the European Commission granted a block exemption for agreements entered into for the purpose of joint R&D and, to summarize, joint exploitation of the results by manufacture but not by distribution. This severely limited the application of the block exemption in the biotechnology sphere. The R&D block exemption has recently been amended, and the amendments came into force on 1 April 1993.

The amendments seek to extend the scope of the block exemption to include joint distribution of products resulting from joint R&D in certain circumstances. However, the usefulness of this amendment for the biotechnology or pharmaceutical company is limited, and in most cases, it will probably still be necessary to notify joint R&D agreements to the Commission to avoid invalidity pursuant to Article 85 (2) and/or fines. There are three key reasons for this:

Co-promotion/co-marketing. The new provisions in the block exemption dealing with distribution do not refer to co-promotion or co-marketing arrangements, which are becoming increasingly common as a vehicle for market entry by biotechnology companies. Accordingly, any collaborative agreement envisaging commercial exploitation of this nature should be notified to the Commission and an individual exemption sought rather than risking reliance on the block exemption.

Pre-existing intellectual property and know-how. The joint exploitation for which the block exemption provides must relate only to results that are protected by intellectual property rights or constitute know-how which substantially contributes to technical or economic progress. The results of collaborative R&D must be decisive to the manufacture of the new products or the application of the new processes.

However, many R&D joint ventures within the biotech field include the contribution by one or both of the parties of pre-existing intellectual property or know-how, e.g., a product patent that is critical to the exploitation of the results. In those circumstances the joint exploitation does not only relate to the results of the R&D. While not entirely clear, the safer course must be to seek an individual exemption from the Commission in these circumstances.

Five-year term and 20 per cent market share limit

If the parties are not competing manufacturers of products capable of being improved or replaced by the results of the R&D (which is frequently the case with the biotech company), the exemption applies for the duration of the R&D programme and, in the case of joint distribution, for five years from the time the products resulting from that R&D are first put on the market.

After the expiration of that five years, the exemption only continues to apply as long as the production of the products of the R&D, together with the combined production of equivalent products by the parties that are considered by users to be equivalent, does not exceed 20 per cent of the total market for such products in the Common Market. A new biologic might well be said to be in a market of its own and thus there is no guarantee that restrictive provisions will be enforceable five years into commercial exploitation just when most pharmaceutical products are beginning to reach their peak market share. The risk of key provisions of the agreement becoming unenforceable at that stage dictates notification for exemption rather than reliance on the block exemption.

In short, the amended R&D block exemption still leaves much to be desired from the standpoint of collaborative arrangements in the biotechnology/pharmaceutical field. Frequently, individual application to the Commission for exemption will still be the recommended course, using the block exemption as a yardstick when drafting such agreements as to clauses that are and are not acceptable. (Source: *Genetic Engineering News*, 15 May 1993)

F. BIOINFORMATICS

Biotechnology priorities, planning, and policies: A Framework for Decision-Making

(ISNAR Research Report No. 6 by Joel I. Cohen)

Executive Summary

Developing-country Governments are having to make decisions about investments in biotechnology at a time of widespread downsizing of state institutions, liberalization of markets, increasing privatization and deregulation of prices. The rapid expansion of public agricultural research institutes of the 1970s has ended and a reversal of this trend is unlikely. Economic adjustments, meant to help national programmes deal with these financial realities, have underscored the importance of increasing the effectiveness of the agricultural sector and raising the productivity of agricultural land. Science-based innovations such as biotechnology are a key investment to help achieve these goals.

Decisions about agricultural research allocations need to be directly linked to economic objectives. Many programmes and projects compete for limited budgets. For example, biotechnology can compete with conventional agricultural research for fund allocation. Thus priorities and funding for biotechnology are best determined by structured information and discussion between scientists at both the research and management levels, in conjunction with policies determined by decision makers at the national level.

This variety of financial, technical, and institutional issues highlights the complexity of the task facing national policy makers for agricultural research. It is all too easy to establish research programmes that lack focus and accountability and are hampered by duplication. However, the speed of technological change in agriculture and the need for focused applications of new technologies necessitate informed decision-making.

This report is aimed at national policy makers, administrative managers, and directors of research who make investment and institutional decisions regarding biotechnology for the National Agricultural Research System (NARS). Its purpose is to consider the potential costs and

benefits of biotechnology-based research through a four-phase planning process. The decision-making framework presented considers the national policy environment and the institutional, financial and programme issues involved in setting priorities and determining needs for biotechnology-based research. The framework will help decision makers and research leaders ensure that resources allocated to biotechnology, including those activities supported by the international biotechnology programmes and donors, are consistent with national objectives of efficiency, equity, security or concern for the environment.

The four phases are as follows:

- Setting policies and identifying priorities that address constraints on agricultural productivity for which biotechnology offers a comparative advantage;
- Formulating a national programme to address these priorities and policies;
- Implementing and monitoring the research programme;
- Transferring and delivering technologies to end-users.

In this report, the decision-making phases are introduced through an implementation sequence for agricultural research, as this emphasizes biotechnology's dependence on a strong conventional research base. Special attention is given to various aspects of biotechnology-based research where complications in planning can be anticipated. These complications include the need to develop priorities for application of the new technologies, the technology's relation to areas of public perception, such as biosafety requirements, and the additional technical expertise, funding and institutional capacity required.

In conjunction with the four phases, the decision-making process is also analysed from the perspective of three levels within a national programme. These levels are as follows:

- Research level, composed of scientists carrying out activities that may become or are already part of a national biotechnology initiative;
- Management level, composed of administrative and research directors who are responsible for helping to structure the interface between research and policy; and
- National policy level, composed of decision makers from various ministries or departments responsible for national policies seeking to implement biotechnology.

Information on each phase can be used separately by national programme leaders at various stages of the development cycle. In fact, topics covered in one phase relate to those discussed in others, making the development cycle a dynamic, interactive process. Time frames and objectives indicate appropriate expectations throughout the process.

In phase I, decision makers use priority-setting methods to first identify the constraints to productivity where biotechnology offers a comparative advantage and, second, to demonstrate that needs of end-users are considered. These methods are discussed in chapter 2 as well as key features of the public policy setting affecting the manner in which biotechnology research is undertaken and in which national initiatives will be planned.

In phase II, the design and development of a national biotechnology programme is considered by management and research leaders in relation to relevant priorities and policies identified in phase I. As presented in chapter 3, critical programme elements are identified for management's consideration. Scientific review of both conventional and biotechnology-based research is discussed in relation to the proposed research initiative.

In phase III, special monitoring and evaluation needs are analysed. As covered in chapter 4, this also includes the importance of scientific accountability in relation to the priorities and programme objectives established.

Phase IV discusses options to be considered by research, technology transfer agencies, and end-users such that these considerations become part of the programme's operational context and can be considered early in the planning process. As presented in chapter 5, this includes options for public and private technology transfer.

This report is the third in a series of related research and programme-management reports from the Intermediary Biotechnology Service that appear as ISNAR Research Reports. Each IBS report elaborates issues involved in biotechnology research programme management and policy formulation, including needs assessment. One provides a comparative description of the different approaches taken by developing-country governments to stimulate biotechnology research. Another reviews the current international debate on intellectual property protection and assesses the policy options and implications for developing countries. A forthcoming report will give an overview of international initiatives that have as a common goal the application of biotechnology to tropical agriculture. It will also review opportunities for national institutions in developing countries to collaborate with international biotechnology programmes. Other forthcoming reports will address future needs and priorities for biotechnology research on livestock, and the potential effects of biotechnology on tropical beverage crops, small-scale producers and international markets.

Further information may be obtained from Intermediary Biotechnology Service, ISNAR, P.O. Box 93375, 2509 AJ The Hague, The Netherlands. Tel.: (31) (70) 349-6100. ISSN 1021-4429; ISBN 92-9118-015-1.

IBS BioServe Database

A survey conducted in the period June to October 1993 was undertaken to help fulfil the Intermediary Advisory Service's (IBS) objective of compiling a registry of expertise in international biotechnology. This registry, named *BioServe*, currently includes information from international agricultural biotechnology programmes, defined as organizations or programmes that conduct, fund, or coordinate biotechnology-related research, focusing on developing-country agriculture.

The first aim of *BioServe* is to provide IBS's primary clients with up-to-date details of international biotechnology programmes. Primary clients include national policy-making bodies, NARS, and other research organizations, both public and private, in developing countries. *BioServe* may enable them to identify prospective partners

in particular regions or in specific areas of biotechnology research, research management, or policy formulation.

In order to obtain the relevant information systematically and to ensure utility for analysis by national programmes, three different survey forms were designed for the categories of organizations identified below:

- Research-based biotechnology programmes at national or international public institutes, including the IARCs;
- International or regional biotechnology networks;
- Bilateral or multilateral donor organizations that finance biotechnology initiatives for developing countries.

Respondents included 17 programmes, six networks, five IARCs, and four donors. This was a combined response of 32 from a total of 38 survey forms mailed. Each survey requested information on, among other things, overall goals and priorities, agricultural and regional focus, training opportunities, research management, research and development, funding, and expenditures. The analysis of data is based on completed surveys checked for accuracy. Upon receipt by IBS, the information collected was reviewed and then entered into a computer database using REFLEX.

Summing up the programmes and IARCs provides data for 22 international biotechnology programmes. Total funding level cited is derived from the total expenditures analysed from all sources mentioned above. The figures are based on calculations from the information collected from the 22 international biotechnology research programmes, excluding the figures submitted by networks and donor agencies. The figures given on programme funding sources are averages for non-recurrent research grants, which is by far the predominant type of finance for international biotechnology programmes. It excludes (annually) recurrent funding. Figures for recurrent and non-recurrent funding have been standardized by IBS, to make valid calculations for expenditures by programme element.

The 22 international programmes submitted information on 167 distinct research projects, out of which 131 have an identified primary route for technology transfer.

A complete analysis of *BioServe* issues and implications is planned as a forthcoming IBS publication. It will be distributed with a complete directory of the international programme networks and donors that participated in the IBS exercise.

Cultivating knowledge: Genetic diversity, farmer experimentation and crop research
(Eds. Walter de Boef, Kojo Amanor and Kate Wellard, with Anthony Bebbington)

For thousands of years farmers have been adapting crops to diverse environments and experimenting with and developing new varieties. The interaction between people, the environment and their food crops has provided the world with a wide range of crops and a remarkable diversity of varieties within single crops. This diversity encompasses both the varieties farmers have selected, or landraces, and their wild and weed relatives. These interactions have also resulted in a human capacity to further develop crops through a process of continuous adaptation and experimentation.

The international debate on biodiversity has resulted in renewed interest in the role of farmers and local communities in the management of natural resources and crop genetic diversity. The local varieties of crops which have been developed by farmers have made a great contribution to plant breeding genetic resources in the North. In recent years it has become apparent that local crop diversity in the South is threatened by the promotion of modern varieties promising higher yields. This book reflects new approaches and concepts in the field of conservation and the development of local crops.

Agricultural modernization, commercialization, intensification of production, and destruction of habitats are promoting genetic erosion, and threatening both this diversity of local crops and the processes which sustain it (Frankel, 1970; Harlan, 1984; Kloppenburg and Kleiman, 1987). This also results in a loss of farmers' knowledge of crops and of their capacity to maintain and develop diversity (Warren, 1991; NRC, 1992). Institutionalized crop breeding relies to a great extent on landraces originating in the major centres of diversity in the South. The genetic material available for this modern crop breeding is therefore being diminished. While genetic erosion threatens the world's base of food plants, the erosion of knowledge threatens the human capacity to maintain and further cultivate this diversity.

Case studies from Africa, Latin America and Asia address these issues from different angles, examine the significance of local knowledge, and documenting new approaches and methodologies. The book looks at the policy issues raised by the expansion of agribusiness, and the need to consider the interests of small-scale farmers.

The authors come from a variety of backgrounds, from plant breeders to anthropologists, international researchers to NGO development workers and lobbyists, and present a number of different views and perspectives on the subject. The editors work at Wageningen Agricultural University and the Centre for Genetic Resources in The Netherlands, and the Overseas Development Institute, United Kingdom.

This collection of papers examines the threat to global agricultural diversity and the implications for agro-ecosystems. It addresses the need to develop appropriate research and development strategies which build upon both the capacities of farmers to experiment with crops, and the knowledge they have acquired of diversity. Farmers' experiences with diversity provide an important framework for the development of conservation strategies. An appreciation of these experiences can complement and add new dimensions to current conservation and crop improvement efforts, which frequently fail to realize the significance of interactions between farmers and environments in the development of biodiversity and emergence of local varieties. Farmer experiments with crops have been important in promoting diversity and the conservation of species and varieties. A challenge facing the agricultural sciences is to develop methodologies and institutional forms which will enable farmers to build upon their skills in adapting crops to the environment.

Landraces have made vital contributions to crop science, but the role farmers have played in their development has been largely unacknowledged. Apart from the need to understand and revalidate farmers' knowledge of

crop development, this raises institutional and policy issues concerned with the value and appropriation of people's knowledge, the commercialization of plant breeding, and the marginalization of small-scale farming communities.

Cultivating Knowledge will be of interest to researchers from biological and social backgrounds, as well as people with a more practical interest. The book will be of use to university teachers and students in the agricultural, biological, and social sciences. It places farmers at the centre of crop development and genetic diversity, and through this focus challenges the dominant models in formal crop research.

224 pp. approx. November 1993. ISBN 185339 207 3 hb £22.50, ISBN 1 85339 204 9 pb £8.95.

Cultivating Knowledge may be ordered from IT Publications Ltd., 103/105 Southampton Row, London WC1B 4HH, United Kingdom. Tel: +44-(0)-71-436-9761; Fax: +44(0)-71-436-2013.

Compendium of Good Practices in Biotechnology

Butterworth-Heinemann has recently published another book in their BIOTOL series. Good practices in biotechnology are extensive and far reaching. Some issues are product or process specific, other are more generic. This text brings together a discussion of many of the key issues and regulations, thereby providing a valuable resource for those practising, or intending to practise, in biotechnology. It is particularly useful to anyone involved in the biosciences in industry and education who needs a resource containing all relevant regulatory information.

It begins by providing an overview of the administrative organization and tools of the EC and its member States as a backdrop to a description of key directives and guidelines. Topic coverage includes good laboratory and manufacturing practices, safety issues of gene manipulation, the cultivation of micro-organisms, the use of animals, procedures using radioactive isotopes, market authorization for medicinal products and food ingredients and intellectual property rights. Primarily designed as a reference source, the added commentaries and distillation of key elements provide a valuable back-up to the technical texts of the BIOTOL series.

The contents cover: introduction to regulation and science based industry—rationale for regulations; protection of workers; protection of the environment; protection of the public; protection of product quality; legal systems and regulatory systems; approaches to and the tools of regulation; structure and relationships between legislative and regulatory bodies; handling techniques—micro-organisms; laboratory animals; genetic manipulation/DNA technology; cell line/hybridoma technology; radioactive isotopes; hazardous chemicals; product development guidelines—good laboratory practice; good manufacturing practice; quality control; pre-marketing testing; quality assurance; market authorization; health and safety at work; waste disposal; classification, labelling and packaging; transportation; catalogue of EC directives and guidelines including examples of member State-related regulations.

The book is a paperback, and for 300 pages with illustrations is a bargain at £29.95. ISBN 07506 1600 8. Orders may be placed at Reed Book Services Ltd., P.O. Box 5, Rushden, Northants, NN10 9YK. Tel.: (0933) 58521; Fax: (0933) 50284. Telex: 312504.

Biotechnology in agro-food quality

The Commisson of the European Communities has released the final report of a case study on "Characterization and measurement of quality in agro-industrial production".

The report focuses on the gap between the requirements for safety and quality management in agricultural output for feed, food and industry and the reality of tests available. On the whole, the potential of biotechnological techniques is not being fully exploited or realized. Government regulation, not pursuit of appropriate quality, drives the development of tests and enforces markets, such as those for aflatoxin assays. There is also an absence of a test validation system within the EC, leading to lack of confidence by the food industry.

Consequently, the agri-industrial sectors are seen as unattractive by most diagnostics companies, compared with the human health-care sector. There are additional problems of engineering tests so that they fit into agri-production flows. In the absence of a philosophy of total quality management, the future development and application of tests and systems is likely to be inadequate without active and strategically oriented support from the CEC and member States.

The report, over 250 pages of review, strategy, recommendations and data is now available from the CEC, L-2920 Luxembourg, catalogue number CD-NA-14721 (EN-C for the English edition).

Newsletter on release of GMOs

The European Community has recently funded publication of *Screen Quarterly*, a newsletter intended to speed communication amongst researchers (both academic and commercial), regulators and others active in the area of release of genetically modified organisms (GMOs). Initially, the publication will cover both the EC and EFTA, with the possibility of wider coverage in later years. The newsletter is intended to provide a fast, easily read channel through which all those interested in the release of GMOs can exchange information. Besides listing all relevant research programmes and all release permits, the newsletter will include such items as brief summaries of individual programmes, practical advice on applying for release permits in member States, invitations to tender and other announcements. Attention will also be given to the increasingly important question of consumer acceptance of GMOs as food or fodder.

The newsletter will be issued free of charge, but recipients will be asked, in return, to provide half a page or so annually describing their own interests.

Those wishing to be included in the circulation should contact: Joint Editors Rarfon Limited. (Mr. J.F.A. Thomas), Elm Tree House, Southover High St., Lewes BN7 1 JB, United Kingdom. Tel.: 0273-474744; Fax: 0273-474828.

Superbugs and superweeds

"Genetic engineering is creating plants which have never occurred in nature", says a new 24-page Panos Media Briefing, *Genetic Engineers Target Third World Crops.*

"Some of these plants kill the insects which try to eat them, disable viruses as they attack, manufacture their own fertilizer or grow on marginal lands. Some of these plants are already being tested and some will be sold to farmers soon."

Although the potential is great, Panos warns that there are also dangers. "Engineered crops may pass their properties on to wild relatives making 'superweeds'. A research priority is to create herbicide-resistant plants, so that more weed-killer can be sprayed on crops; this will increase the use of highly toxic herbicides". Panos also warns that bioresearch in the North fails to focus on the needs of the South. Worse, some of that research will produce products that displace valuable developing country exports (vanilla, pyrethrum, rubber) in developed country markets.

Panos is worth listening to because its briefings are aimed at journalists and the media world-wide, with the goal of fostering "informed debate on issues of environment and development".

Among the "newspegs" it lists are the final agreement on GATT (which limits the use of genetically engineered plants by Southern farmers), 27 December 1993 (when the biodiversity Convention comes into force), February 1994 (US Senate debates approval of Biodiversity Convention), April-May 1994 (first signatories of Convention meet to discuss a biosafety protocol), the first marketing of the Flavr Savr tomato and demonstrations in India and elsewhere against the patenting of seeds. Local newspegs, it suggests, would include field testing of genetically engineered crops and the advertising of recombinant seed. Details of Panos Media Briefing No. 7, published December 1993, from: Panos Institute, 9 White Lion Street, London N1 9PD, United Kingdom or Tel.: 071 278 1111. Fax: 071 278 0345.

1993 Edition of ATCC diskette catalogue

American Type Culture Collection (ATCC) has released a 1993 edition of all sections of the ATCC diskette catalogue. The new edition will be distributed until the end of 1993 with an option to subscribe for two supplements scheduled for July and October. The diskette catalogue is IBM compatible and available on high density 3.5" or 5.25" floppy disks. Current users of the diskette catalogue can replace their previously purchased sections at half the price of a new section purchase.

Catalogue sections include: (1) bacteria, phages and media; (2) cell lines and hybridomas; (3) clones, vectors, libraries and hosts; (4) filamentous fungi and media; (5) protozoa, algae, and media; (6) viruses and antisera—animal; (7) viruses and antisera—plant; (8) yeasts and media.

For further information contact: ATCC Marketing, 12301 Parklawn Drive, Rockville MD 20852, USA. Fax: +1 301 816 4367.

BioCommerce on-line directory updated and growing

In a dynamic industry like biotechnology with many emerging companies, it is essential to ensure that the latest accurate information is available. The BioCommerce Abstracts and Directory File (286 on Dialog, CELL on Data-Star) is an up-to-date and cost effective source of business and financial information and also provides news of recent scientific and clinical developments.

The directory portion of the database, now with nearly 2,000 entries, is verified and extensively revised annually as well as continuously amended to reflect the latest personnel changes and major takeovers described in more detail in the abstracts. All the 690 UK directory entries were updated prior to the recent publication of the *UK Biotechnology Handbook '93*, a printed directory derived from the database, and 430 of the European, North American and Australian entries were revised in July and August. In addition to revising the remaining entries over the next few months, many newly public US biotechnology companies are being added.

The 100,000+ abstracts in this file summarize more than 250,000 articles published since 1981 in newsletters, journals, magazines and newspapers, and cover all aspects of the biotechnology industry from biopharmaceuticals to bioremediation as well as legal, ethical and public opinion issues, financing and strategic alliances. Since some events may be reported in up to 30 different news sources, the unique "multicitation" abstracts mean your results are already "de-duped", saving time and money.

The on-line database is supported by a copyright cleared document delivery service, through which photocopies of most abstracted articles can be supplied on request and the Biotechnology Manager's Mailing List facility which gives you targeted access to the nearly 9,000 executives listed in the directory and offers customized lists based on job function, location, type of organization and areas of biotechnology. For further details of these services, assistance with searching or a free list of the major sources abstracted (including addresses and subscription prices), contact Customer Services, BioCommerce Data Ltd., 95 High Street, Slough, Berkshire SL1 1DH, UK. Tel.: 0753 511777; Fax: 0753 512239.

Facility for high resolution graphics

Molecular interactions form the basis of biological processes. Understanding how the molecules interact is aided by the use of computer graphics. Nowadays, macromolecules such as proteins and nucleic acids can be manipulated and studied in terms of their function and structure.

Sophisticated molecular modelling programmes and visualization software allows researchers in biology to easily create proteins on a computer screen and experiment with them bringing other molecules up close to them and discovering how they interact or changing something in a protein's composition and watching how that affects its three-dimensional structure and hence the function of the molecule.

Such studies based on a structural approach have led not only to enhancement of our basic understanding in biological sciences but have also led to the development of drugs and vaccines. Increasingly pharmaceutical firms and biotechnology companies in other countries are supporting structural based biological research in a substantive way.

In order to increase the developmental efforts in molecular modelling from sequence analysis and the use of structural approach to research at the molecular level, a

high resolution graphics facility has been set up at the Bioinformatics Centre, Department of Biotechnology, Madurai Kamaraj University. This has been funded by the Department of Biotechnology, Government of India as a National Facility for High Resolution Graphics.

A Silicon Graphics Crimson Elan machine along with the required molecular dynamics and visualization software from BIOSYM is available for use by researchers interested in structural aspects of molecules. The Bioinformatics Centre also provides access to databases of protein and DNA sequences and computational analysis on the microvax. Bibliographics referral and retrieval services are catered to using both CD-ROM and on-line databases. The Bioinformatics Centre forms part of the Biotechnology Information System that has been set up by the Department of Biotechnology, Government of India. Those interested in using the facilities can contact: The Bioinformatics Centre, Department of Biotechnology, School of Biological Sciences, Madurai Kamaraj University, Madurai 625 021 or by email to "bioinf%bic-mku@imtech.ernet.in".

Bioline offers online access to bioscience information

Bioline Publications, in the UK, is aiming to make scientific information available more easily and at lower cost than at present. In a collaboration with the Tropical DataBase in Brazil, Bioline is working closely with publishers of journals and newsletters, and authors of papers and reports world-wide to provide easy on-line access to information in the biosciences (biotechnology, biodiversity, biopolicy, bioinformatics).

Through the Internet network, readers may browse and search without cost through large quantities of contents lists and abstracts using keywords and phrases to search across the whole system. Full text and associated graphics of material of interest can be ordered on-line and e-mailed to the reader's computer. Bioline uses state-of-the-art, easy to use gopher software which is growing in application throughout the world's scientific community.

Access to journal abstracts, report summaries and contents lists is available free of charge and without registration; readers must register with Bioline Publications in order to receive full text/graphics of documents of interest. The charge for that service is US$ 50 per annum. Additional registration with the publishers of commercial journals is necessary if full text and graphics of scientific papers is required; the cost of this will be considerably less than the cost of the printed version.

Bioline is up and running, providing access to 10 journals, 14 reports and 13 newsletters as well as on-line links to three other bibliographic resources for biologists on the Internet. During the first two days of operation there were 1,000 accessions to Bioline; 40 requests for more information and a number of requests for subscription information. Bioline welcomes requests from publishers, editors, authors and conference organizers interested in using the system for distribution of their material.

For more information contact: Bioline Publications, Stainfield House, Stainfield Bourne, Lincolnshire PE10 ORS, United Kingdom. Tel.: +44 778 570618; Fax: +44 778 570175. E-mail: bio@biostrat.demon.co.uk.

Fujitsu to launch gene database

Fujitsu Ltd. and G-Search Corp., the computer maker's database affiliate, will begin to provide a genetic data-search service via E-mail.

The two firms, in cooperation with a foundation that promotes the use of genetics, have constructed a database on the latest information on genes for supplying genetic data, analysis methods and expertise. When users establish contact with G-Search on their personal computers, they can request database searches and analyses.

Results are delivered by E-mail. The service will be made available for 50,000 yen per month for up to ten searches and 5,000 yen for each additional search.

OECD group of national experts on safety in biotechnology publications

This OECD group has been working to update and develop the principles for the safe development of genetically modified organisms (GMOs) first set out in the 1986 "Blue Book". The results of this work now appear in three new OECD reports:

Field releases of transgenic plants, 1986-1992—An analysis reviews the 1,180 experimental releases of GMOs that took place during the period from 1986, when Belgian researchers carried out field trials of genetically tagged tobacco plants. Subsequent field trials have been made in 15 OECD countries, for 30 different crop hosts (oilseed rape, potato, tobacco, etc.) and for 10 categories of traits (such as herbicide resistance, virus resistance, etc.). The report concludes that "there have been no surprises in the behaviour of transgenic plants in relation to what might be expected from the characteristics of the host and the nature of the genetic insert. Some disappointments (the desired effect inadequate); no surprises". (40 pages, OECD, Paris, 1993, ISBN 92-64-14046-8 (93-93-07-1), FF 50 or $12.

Traditional Crop Breeding Practices: An Historical Review to Serve as a Baseline for Assessing the Role of Modern Biotechnology reports on the physiology, toxicology and environmental behaviour of 17 major crops and their parent species, prime targets for genetic modification projects. (236 pages, OECD, Paris, 1993, ISBN 92-64-14047-6 (93-93-01-1), FF 270 or $60.)

Safety Considerations for Biotechnology: Scale-Up of Crop Plants focuses on safety, risk assessment and risk management. The report includes as a preamble the "General Principles for Safety in Biotechnology", released in 1993 by the OECD as a separate document. These recognize that the safety of an organism is independent of the process of genetic modification *per se*. It is the characteristics of the organism, including new traits (however introduced), the environment and the application that determine the likely risk. (40 pages, OECD, Paris, 1993, ISBN 92-64-14044-1 (93-93-08-1)). For further information contact Dr. Mark Cantley, Biotechnology Unit, OECD Directorate for Science, Technology and Industry. Tel.: +33 1 45 24 93 31.

Irish Biotechnology Sourcebook 1994

The first comprehensive guide to Irish biotechnology is about to be released. Published by BioResearch Ireland the *Irish Biotechnology Sourcebook 1994* is packed with

information on organizations operating within the biotechnology field in Ireland.

Details on over 160 companies based on biotechnology including key contacts within the companies are included.

Thoroughly cross-referenced and indexed, the *Irish BioTechnology Sourcebook 1994* is an invaluable source of information for any biotechnology organization. Its easy to read format and attractive covers will make this book a must on every biotechnologist's desk.

It will be available from April 1994 at 777 schillings plus postage. Orders to BioResearch Ireland, Forbairt, Dublin 9, Ireland. Tel.: 00353-01-8370177; Fax: 00353 01 8370176.

For further information contact: Dr. J. Ryan. Tel.: 00353 01 8370177.

BioCommerce Financial Abstracts

Ernst & Young and BioCommerce Data have launched a new information service covering the financial aspects of biotechnology. BioCommerce Financial Abstracts, published twice monthly, will monitor company results and performance, analysts' buy/sell recommendations on stocks, public and private offerings, share price movements, strategic alliances, key appointments and relevant legal and regulatory issues.

Based on the popular news monitoring service Abstracts in BioCommerce, the new publication is targeted at Chief Executive Officers, Chief Financial Officers and the investment community and will provide condensed up-to-date reports of recent financial developments summarizing articles appearing in over 50 newsletters, journals and major newspapers.

BioCommerce Financial Abstracts will be distributed free in the UK to a controlled circulation list with the compliments of Ernst & Young, but is also available on subscription at £195 (UK and Europe)/$300 (elsewhere) including airmail postage. The complete library edition of Abstracts in BioCommerce which also covers other company news, product developments, research advances, patents, legislation and appointments is available in print with quarterly indexes at £419 ($796) and on floppy disk (£790/$1,500).

For further information about Ernst & Young's services to the biotechnology industry contact: Jason Avery, Ernst & Young, Apex Plaza, Reading, RG1 1YE, UK. Tel.: (0734) 500611. Fax: (0734) 507744.

For further information on BCD's products or a sample copy of BioCommerce Financial Abstracts, contact: Anita Crafts-Lighty, BioCommerce Data, Prudential Buildings, 95 High Street, Slough, SL1 1DH, UK. Tel.: (0753) 511777. Fax: (0753) 512239.

Education news

The Chemical Industries Association, UK, has produced a series of information leaflets entitled *Chemical Issues*, several of which cover biotechnology. The biotechnology titles are: *This is Biotechnology*; *Regulation of Biotechnology*; *Biotechnology and the Developing World*; *Industrial Uses of Biotechnology*; *The Patenting of Life*; *Risk-Benefit Balance of Biotechnology*.

Plant biotechnology and molecular biology

The following three reports, all on the above subject, are available on request to the CO-BIOTECH Information Centre, at the Bio-Engineering Centre of the Russian Academy of Sciences:

1. First Symposium "Trends in Plant Biotechnology", USSR, 20-22 November 1991, 223 pp.;
2. Second Symposium "Trends in Plant Biotechnology", Russia, 18-20 May 1993, 482 pp.;
3. "Plant Biotechnology and Molecular Biology, the Latest Bioengineering Methods", Moscow, 1993, 105 pp.;

Editor-in-chief for each of the collections of papers is Academician K.G. Skryabin, Director of the Centre.

The two symposium reports comprise the collected abstracts, in Russian and in English, of the papers presented, almost all from scientists in research institutes of the countries formerly comprising the USSR.

The 1991 Symposium lists 71 papers organized into five sections:

1. Transgenic plants resistant to viruses, herbicides and insects (53 papers);
2. Plant cell technologies (40 papers);
3. Chromosome technology (2 papers);
4. Plant molecular biology (21 papers);
5. Problems of transgenic plant regulations (two titles, no abstracts).

The 1993 Symposium lists 217 papers organized into five sections:

1. Transgenic plants (58 papers);
2. Plant molecular biology (37 papers);
3. Plant cell technologies (82 papers);
4. Plant chromosome technologies (34 papers);
5. Progress in plant molecular biology and bioengineering in CIS (four titles, two abstracts).

The third report is a review containing nine articles, including illustrations, on current problems of modern plant gene and cell engineering, together with a "Chronicle" section giving information on the Biotechnological Academy of Research, the CO-BIOTECH Information Centre and the Institute of Cell Biology and Genetics of the Academy of Sciences of Ukraine.

The reports are available without charge but subject to availability of stocks from: Professor K. G. Skryabin, Bio-Engineering Centre, Vavilova Str. 34/5, 117334 Moscow, Russia. Tel./Fax: (7) 95 135 06 71.

Biotechnology for the twenty-first century—A report by the FCCSET Committee on Life Science and Health

This 90-page report by the Federal Coordinating Council for Science, Engineering and Technology (FCCSET) of the Office of Science and Technology Policy (OSTP) describes the presidential initiative in biotechnology research. The stated goal of the initiative is to sustain and extend US leadership in biotechnology research for the twenty-first century to enhance the quality of life for Americans and the growth of the US economy.

The 12 agencies participating in the biotechnology research initiative have developed an integrated research strategy and identified four strategic objectives:

- Extend the scientific and technical foundations for the future development of biotechnology;
- Ensure the development of the human resource foundations for the future;
- Accelerate the transfer of biotechnology research activities to commercial applications;
- Realize the benefits of biotechnology to the health and well-being of the popuation and the protection and restoration of the environment.

The biotechnology activities of the 12 federal agencies are included with a FY 94 budget of $4.3 billion. The Biotechnology Research Subcommittee (BRS) has proposed that research related to health and the environment be highlighted in FY94.

For further details contact: Office of Recombinant DNA Activities, Building 31, Room 4 B II, National Institutes of Health, Bethesda, MD 20892.

Biodiversity Convention debates

The Convention on Biological Diversity was adopted at the "Earth Summit" in Rio de Janeiro in June 1992. Debate on its ratification and follow-up, on its implementation and implications, is preoccupying policy-makers worldwide, and these policy debates have many implications for biotechnology. We offer below a short selection of the more recent very numerous articles and publications relating to the activities triggered by the Convention, and the issues surrounding it. Beyond the general consensus on the central aim of conserving biological diveristy, the issues in debate concern:

1. Funding the Global Environment Facility, and the mechanism for controlling the financing and choice of scientific priorities;
2. Scientific aspects of bio-diversity: how will national inventories be made, how will the international scientific communities (particularly specialists in taxonomy, nomenclature and systematics) be involved;
3. Ownership of, and access to, germplasm and rights (patents or other) over its exploitation, linked with questions of patents in biotechnology relevant to such use (a problem highlighted by the reluctance of the previous US Administration to sign the Convention);
4. Consideration of the need for a binding international safety protocol covering GMOs harmful to conservation and bio-diversity.

Of these issues, the third especially concerns Article 16. On germplasm and its exploitation, the World Resources Institute produced the book "Biodiversity Prospecting: Using Genetic Resources for Sustainable Development", in conjunction with INBio of Costa Rica, Rainforest Alliance and ACTS, the African Centre for Technology Studies. The report offers guidelines to policy-makers, industry and researchers on the design of organizations, legislation and contracts for biodiversity prospecting.

A four-page article in "Biotechnology and Development" (BDM) No. 15, June 1993, summarizes the same issues: "Are the interests of the drug companies compatible with those of the tropical developing countries?". Their article reviews the Merck-INBio agreement; the US National Cancer Institute's Letter of Intent; and the Biotics-Polybiotika agreement. The last is a specific example of the model agreement developed by Biotics (with Commission co-finance) in the mid-1980s for collaborative exploitation of phytochemical resources.

On biosafety, Article 19 of the Convention is open-ended, and the UNEP Panel 4 report divided; between those advocating world-wide extension of a mechanism similar to the EC field release Directive 90/220, and those fearing stigmatization of biotechnology, and resulting delay to the diffusion in developing countries of the much needed technologies.

The panel reports are addressed to the Executive Director of UNEP, Canadian Elizabeth Dowdeswell, who is required to convene a first "Conference of the Parties" (to the Convention), and in preparation for that Conference, an Intergovernmental Committee on the Convention on Biological Diversity has been created. The first meeting was held in Geneva from 11 to 15 October 1993.

The African Centre for Technology Studies, ACTS, has played a prominent role; organizing (in cooperation with the Stockholm Environment Institute) an international conference on the Convention. The Director of ACTS, Calestous Juma, has written significant books such as "The Gene Hunters: Biotechnology and the Scramble for Seeds" (1987: Zed Books and Princeton University Press) and co-edited "Innovation and Sovereignty: the Patent Debate in African Development" (1989: ACTS). More recently, ACTS has produced a series of "Biopolicy International" booklets, of which the following (all at $7.50/ K Sh 50.00) are particularly relevant:

No. 2: Genetic Resources and Sustainable Agriculture Creating Incentives for Local Innovation and adaptation, by W. V. Reid;

No. 3: Conservation and Use of Agro-Ecological Diversity, by J. I. Cohen;

No. 7: Property Rights, Biotechnology and Genetic Resources, by M. H. Khalil, W. V. Reid and C. Juma.

For more information contact: ACTS, P.O. Box 45917, Nairobi, Kenya. Tel.: 2542 74-40-47/ 40-95; Fax: 2542 74-39-95.

The Bacillus thuringiensis Production Handbook: Laboratory Methods, Manufacturing, Formulation, Quality Control, Registration

The *Bacillus thuringiensis* Production Handbook is the first comprehensive guide to the commercial production of *Bacillus thuringiensis (Bt)* products. The handbook provides detailed item-by-item and step-by-step descriptions of the methods and materials used to manufacture *Bt*. It explains how to raise and store cultures, which media are best suited to large-scale fermentations and which culture conditions and quality control criteria should be applied. The Handbook guides you through the various legislative procedures that have to be negotiated to bring products to market, including safety assessment and registration.

Contents

- The Organism, Commercial Production, The Market, Using This Handbook;
- Laboratory Methods—storage, spore stock production and QC, competence, potency, viability,

purity smears, wet slide preparations, minimal sporulation medium, alternative media;
- Commercial (large-scale) Production—outline, plant, inoculum, seed and main fermenter, harvesting, drying, alternative commercial media, costs;
- *Pro forma* Safety Data Sheet for Use at Production Plant—product information, first aid, safety of fermentation ingredients;
- Formulation—powder, dust, water- and oil-based, *Bti* granules, physical analysis, ingredients;
- Liability and Safety—positive and negative liability, safety and health;
- Complete *Pro forma* Quality Control Manual—includes product specifications and methods;
- Product Registration & Approval—time, expense, safety, US regulations, EC Pesticides Directive.

Further information is available from: CPL Scientific Ltd., Science House, Winchcombe Rd., Newbury, Berks, RG14 5QX, UK. Tel.: +44 (0) 635 524064. Fax: +44 (0) 635 529322.

Conference proceedings literature

The Institute for Scientific Information (ISI) announced today that it has extended the coverage of its Biotechnology Citation Index by adding the bibliographic data from published scientific and technical conference proceedings. ISI will index the proceedings on the paper level, providing complete conference title, date, location and sponsor identification for each. Included will be proceedings publications in which the majority of the material is being printed for the first time and those which contain complete papers, not just abstracts.

The Biotechnology Citation Index™ provides extensive coverage of the world-wide journal literature from all areas of biotechnology, including basic research in genetics, molecular biology and microbiology, and applications in medicine, agriculture, industry and the environment. It is published on compact disc and issued every other month. Although each issue is cumulative, an annual cumulation is included in the subscription. The index is available for the IBM and 100 per cent compatibles, the Apple Macintosh, and the NEC PC 9800 Series.

For more information about ISI®'s Biotechnology Citation Index™ or any of ISI's other products or services, write to: ISI, 3501 Market Street, Philadelphia, PA 19104 USA or Fax: +1 215 386 2911.

Understanding Biotechnology Law

Gale R. Peterson (Ed.)
Marcel Dekker Inc., New York, 1993, 488 pp. $135 (hardback), ISBN 0-8247-8935-0

The vague title of this book is clarified in its Subtitle *Protection, Licensing, and Intellectural Property Policies.* Although written in a biotechnology context, it deals with much more besides and is essentially a guide to US patent law and practice illustrated with discussion of some important biotechnology patents and lawsuits.

Addressed not to lawyers but to research scientists, it sets itself the ambitious but worthwhile aim of enabling scientists to make "informed rational choices as innovations appear". Sustaining the interest of research workers in legal matters is a most challenging task especially in relation to academic institutions, with which much of the book is concerned.

Individual chapters are contributed from US experts in industry, patent attorney firms and universities, providing a wide-ranging practical approach to the handling of inventions from initiation of the idea to eventual commercial exploitation. This aims to create an awareness of the patent dimension in the mind of the scientist at the bench and the development of formalized strategies for positive action in place of the usual haphazard approach to legal protection.

G. SPECIAL ARTICLE

An Honest Broker's Look at Issues Related to Biodiversity Prospecting

*by H. Walter Haeussler**

Looking behind the words of a contract

Natural resources—plants, insects and animals are being reduced throughout the world as each day passes. Conservation of these resources is surely in the world's best interest. This concept is almost universally held. Most also see these resources as a benefit to the human race to be explored and utilized. The commercialization of products based on biodiversity exploration is one of the ways of benefiting society while also being a potential for generating income, which can in part be used to conserve biodiversity.

It must be said at the outset that profits from biodiversity prospecting alone are simply not sufficient to pay for the conservation and exploration infrastructure on the scale usually considered to be necessary initially. Usually profits from biodiversity prospecting are not even sufficient to create the kind of infrastructure that is necessary in a source country to supply material samples.

Historically, there has been mistrust between source countries and the organizations that develop new products based upon biodiversity prospecting. These organizations, usually commercial companies in the developed world, want a foundation of predictability, i.e. good science, a stable legal environment and an understanding of the practical needs of the company. On the other hand, source countries do not want to be exploited. They do not want to feel they are being forced to do things they otherwise would not wish to do. There is therefore clearly a place in the biodiversity preservation and development discussion for an honest broker to help overcome mistrust and mis-

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perceptions, and one who will be listened to by both sides. The broker should be someone who can bring sensitivity to any negotiation and who, through counselling the negotiating parties privately, can avoid the "face-saving" rhetoric that sometimes invades negotiations and causes parties to take stances they wish they could have avoided, but feel compelled to publicly announce.

There are any number of issues that are frequently common to a company/source country relationship, that should be examined in depth before beginning negotiations, and that must be resolved before negotiations can be concluded.

One of the first issues is a clear identity of the parties. Is the negotiation going to be with the Government at the highest levels or with a Governmental agency, or a quasi-governmental agency, or a non-governmental organization (NGO) that has the government's tacit support? On the other hand, is the company dealing from its international headquarters, a branch or subsidiary in a specific country, and does it involve a branch or subsidiary in the source country? Additionally, are there third parties involved, such as universities in the source country or elsewhere, and what is the relationship of that university to the remainder of the parties? Finally, is there a public funding source in the source country, or an international group such as a United Nations agency, the World Bank or others? Each of these parties will express opinions and may want a voice in the proceedings and nature of the negotiations. The final agreement will vary, depending on the parties. One can then rapidly see why the identity of the parties must be quite precise.

Next, the goals of the parties must be clearly identified and stated. If the goals of all the parties involved are not clearly stated and understood, the result will at best be an agreement that is flawed, and at worst no agreement at all.

There follows the decision-making process to arrive at an agreement, which must be clearly understood by all the parties. Again, this will vary significantly depending on who the parties are. If it is only private parties, then they can merely go into a room and negotiate, reaching a conclusion to be memorialized by the lawyers representing the parties. If Governments or governmental agencies are involved, the procedures for final agreement, approval and even authorization to negotiate must be clearly understood and be communicated to all parties. It is extraordinarily frustrating to negotiate for a significant period of time and reach what appears to be an agreement, with one side having made concessions in order to reach that point, and then to be told only at that point that now, of course, we cannot commit ourselves as we are required to submit this to the legislative body, or whomsoever, for approval.

The last point progresses to the next issue, which is that the person, or persons, who have the authority to commit each of the parties must be clearly identified. Again, the frustration level is exceedingly high when walking into a negotiation to discover that the person across the table is incapable of truly negotiating because he or she only has a very limited authority. No deal can be made until the persons capable of binding the parties are present in the room.

In other words, when the parties enter into a negotiation for commercial development of bioresources there must be congruity between policy, planning and implementation. The policy makers, the planners and the implementers must have a common vision and must stay in constant communication with each other so that finally all segments of the source country's Government and general public feel they can support the final agreement because they had a voice in its formulation.

Next, in order to reach an agreement, the working relationship between the source country and the commercial organization and any additional parties must be defined. Who is expected to do what and in what time-frame? What events must occur before a relationship can reach a stable point and operating situation? Part of this discussion involves a definition and evaluation of the subject under negotiation. What is it that is being bargained for? What are the expectations of the parties and are they realistic? What are the financial obligations of the source country and the commercial concern with respect to the initial implementation and the continuing functioning of the relationship? Who are the people involved? What initial training must they have? What training will be given to them in the process of the relationship, and is there going to be a planned reallocation of people and resources over a period of time? What is the technology? How many samples are there, and from where? How are they prepared and preserved? Are the equipment, people and strategies realistic? Lastly, is the infrastructure in place so that the finances, the people and the technology can meet the policy and planning expectations of the source country while satisfying the negotiated and perceived working relationship? The end effect is what is expected by both sides under the contract and whether it can reasonably be anticipated that at the end of the day these will occur as bargained for, be it money, equipment or people flowing in one direction, or samples or information flowing in the other. That is ultimately what contracts are about—expected delivery. Promises that cannot be kept should not be made. Neither should they be made before a clear evaluation of the parties' identities, the goals, the commitment making process, the identification of the working relationship and a definition and value of the subject matter. Financing, staffing, technology and infrastructure can then be thought out. That is how the expected delivery can be accomplished. This is true for both sides, whether the source country organization is governmental, quasi-governmental or private.

Assuming that the fundamentals of the agreement are organized, there are additional points necessary for a good working relationship, which should be set out in detail in the contract. The first is that of communications. Who is going to be talking to whom and how often? There should be technical-level discussions and policy-level discussions. The frequency of these is sometimes crucial. There is a natural tendency not to talk to one's partners when problems arise, as a tenant tries to avoid the landlord when the rent is overdue. This is absolutely the wrong thing to do. Should problems arise, that is when communications should be more frequent and not less frequent.

Remuneration for the association has to be detailed, not only for the financial commitment of the basic continuing operation, but also for the commitment to create a preliminary infrastructure of eventual increased infrastructure if

planned, as well as any personnel training envisaged. Each of these aspects should be clearly identified with the remuneration itemized separately. This compensation is separate from the rewards accruing from the commercialization of bioprospecting, which will be discussed further on. The agreement should also cover rights given whether they are exclusive or non-exclusive, and if exclusive for how long—for a limited period or for the life of any patents. What are the parties' options if the agreement is only partially successful or is unsuccessful?

The legal issues have also to be decided. If there are problems will there be arbitration? If so, how will the arbitration be accomplished? If there is to be litigation, where is the permissible site of the litigation and who is responsible for the payment of legal fees?

There are also liability issues. If legal liability arises from the contract for injury to workers, or harm to people from drugs introduced to the market as a result of the bioprospecting relationship, who will bear the liability for each of these events?

Perhaps attention should be drawn as to this point: there has so far been little discussion about the commercialization of technology. This is deliberate, as there is a substantial time span between the beginnings of biodiversity prospecting and the introduction of a commercial product to the marketplace. Not until the bioprospecting relationship is established and has functioned for a significant period, can any commercialization be expected or any flow of rewards therefrom.

Whether it is set out in one document or several, there are two distinct relationships. Sample collection and analysis on the one hand, and product commercialization on the other. The two issues require separate management.

At this point it is worth while examining what some call the "billion dollar syndrome". First, it is very important to put commercial rewards for bioprospecting in a time-perspective. In the United States of America it costs about $25 million and takes about seven to ten years to bring a pharmaceutical product through the FDA (Food and Drug Administration) for approval. From a biodiversity prospecting standpoint, from the time the sample is first collected to the time a product is introduced to the market-place, a time span of ten to fifteen years can be expected. The present value of money to be realized fifteen years from now is not very high. How much money put in the bank today and left to accumulate and reinvest interest would be required to generate a million dollars fifteen years hence! This amount is the discounted value available from the commercial company to conceivably underwrite the infrastructure to carry out biodiversity preservation and exploration, as measured against their expected returns. If one predicts that one in ten thousand, or one in five thousand samples proves a "hit", then that cost/return expectation must be spread across all those samples.

The building of infrastructure to reduce the "hit ratio" is then extraordinarily important. But this usually requires early money on a substantial scale.

The "billion dollar syndrome" may be illustrated as follows:

> "Clearly, the sample we provide will generate a billion dollar pharmaceutical product, which will stay in the market-place for the full life of the patent, and will have no competition. The pharmaceutical company will capture $100 billion per cent of the market and we are entitled to a 10 per cent royalty. The $17 billion in sales over the seventeen-year life of the patent at 10 per cent royalty should translate to $1.7 billion in royalties over the life of the patent. But we will be generous and only ask for half our royalties up front. You can pay us the rest later. Therefore, immediately upon signing we expect you to pay us $500 million dollars".

The example given is an exaggeration, but it is the mental attitude of many. Reality based upon the "hit ratio" discussion above, demonstrates that finding any commercial product is not easy. Most commercial products do not generate sales in the billion dollar range, and the true billion dollar products are few and far between. Most products are in the area of one, or two, or three hundred million dollars in sales and are sustained in the market-place for far less than the life of the patent because there is competition. Reasonable royalty rates are very much lower than 10 per cent. Clearly then, the money for infrastructure development must be provided very early or has to come from another source, whether it is money derived from taxes, or international donor money. It cannot be expected to come from an organization that is accountable to its shareholders to show a profit. This is unfortunately a reality.

It can be seen that one of the major contributions an honest broker can make is to help the parties understand the actual structure of the market and the market/business issues that on the one hand can irrevocably separate the parties, yet on the other hand can bring the parties together. Once there is an understanding and a certain level of trust, the source country and the commercial concern together can look for the additional money required to build an infrastructure. They will form a creditable team with far more magnetism than either one singly, because by forging the team they can demonstrate that many of the issues discussed above have already been resolved and that the relationship is therefore well on the way to being a success.

What is left is the issue of valuing technology and the intellectual property. First, who is going to own the intellectual property? The original material? The improved material? Who is going to own patents? What rights are the parties to have in any intellectual property? Is the right exclusive or non-exclusive? What kind of compensation and how is it paid? How does the original compensation paid for sample collection and infrastructure building interact with the compensation that will be derived from commercialization? Who manages the compensation? Who makes the decision when patents should be obtained and who does the actual patent work? Who manages the intellectual property and its licensing? Inside the source country, who is responsible for receiving the money and to seeing that the money received is actually used for the purposes intended in the agreement (for example, used to support conservation measures)? These are all questions that have to be addressed in the initial agreement because no commercial concern proceeds without having a definition of these issues and answers to those questions.

A contract of this nature defines the beginning of a relationship and not the end of a deal. It is a living docu-

ment that defines milestones, i.e. when certain events are expected to occur. The agreement may have financial rewards tied to those milestones. It is an agreement that sets time-frames. It is an agreement that defines courses of action that may be interdependent. It is a document that provides for auditing the performance of the parties. Not only financial auditing, but auditing of people, technology and infrastructure. Ultimately it is an agreement for the transfer of information about technology, as well as the transfer of technology itself. It is a document that at one level contains business confidences which may not be widely distributed in exact terms since the commercial concern will be unwilling to have its commercial advantage diluted because its competitors, knowing all the facts, can more effectively compete. On the other hand, it is a document which, because of public participation, frequently must be, at least in part, public. Finally, any document must provide for those parts that are private and those that are public so that reasonable levels of information can be publicized without abusing the actual commercial concerns of a company.

I have attempted to describe the issues that go into a biodiversity prospecting contract. Many of these are issues where an honest broker can make a contribution towards helping the parties resolve conflicts and form an agreement that both parties can be proud of and is beneficial to both.

Source Country Issues

In addition to the mutual contract issues discussed above, there are issues that a source country must examine before it approaches a bargaining table. What is the objective of the country? What is its planned strategy to save its biodiversity resources, to understand and catalogue what they have, and to develop those resources for the good of the country and the world?

Is there an appropriate set of laws in the country that support biodiversity prospecting? Do the laws deal with ownership of technology and to access and control of the biodiversity? And is there a mechanism whereby the biodiversity infrastructure of the country benefits from biodiversity prospecting?

Is there a court system to enforce agreements? Is it credible, consistent and even-handed? Are government policy and attitudes appropriate? What are the positions of the NGOs in the country? There has to be a commitment from government at a political level, a financial level and an educational level. Universities and research institutes have to be prepared to be participants.

Finally, what internal partnerships exist or can be created so that there is multisectoral and multidisciplinary interactions within the country to maximize the intellectual resources of the country towards supporting the creation of a relationship and utilizing the benefits of the relationship to the best advantage of the country.

I have not set forth many answers. What I have set forth is hopefully a broad overview of the questions that must be answered before credible interactions are possible.

A University Viewpoint

Cornell Research Foundation, Inc. the patents and technology marketing arm of Cornell University, served as the honest broker that brought InBio of Costa Rica and Merck together in an agreement. That was essentially the first agreement that compensated a source country for its bioresources. Through this event Cornell has networked with a number of companies and countries to begin to understand the complexity of bringing these deals together. Cornell University is fortunate to have some outstanding researchers who are deeply committed to the process of biodiversity preservation and exploration. Professor Thomas Eisner had been bioprospecting for many years before it became a popular thing to do. Professor Jerrold Meinwald is a renowned natural products chemist. These two renowned scientists organized the Cornell Institute for Research in Chemical Ecology (CIRCE). In the past Professor Eisner has proposed a data/honest broker agency that would perhaps be funded by about $250 million (conceivably a $10 million dollar contribution from each of 25 pharmaceutical companies). This agency would be a clearing house that could supply seed funding to start new relationships and help countries having resources, people or data to make contact with companies that are looking for opportunities. Clearly, such an organization, serving as a sort of "marriage broker", would facilitate the coming together of interested parties, an event which is presently often time-consuming and frequently leads to frustration rather than successful completion of an interaction.

Events, such as the development of new biochips where receptor molecules or enzyme segments are bound to a solid surface so that they can be used to separate candidate molecules from a sample broth, are rapidly changing the economics of bioprospectives. Technology exists in which perhaps forty of these activity sites can be mounted on a single biochip. This single biochip then replaces 2,500 square feet of laboratory space and nine technicians performing 40 screens. It compresses time, space and money and allows bio-rational approaches to sample evaluation. As discussed above, the smaller the "hit ratio", the more money that is practical for a pharmaceutical company or a pesticide company to invest in infrastructure. The more knowledgeable we all become, the larger the reward. So, from a science standpoint, the economic reward for biodiversity exploration can be expected to increase in the course of time, but it is doubtful the reward will ever be adequate to fund the entire infrastructure that is necessary to start a source country in the field of biodiversity preservation and exploration.

Broader Understanding of the Issues is Essential

One final thought to consider, is that when all is said and done, self-interest both in the source country and in industry, should enhance biodiversity preservation, exploration and utilization. The key is to educate the various segments of society on both sides of the equation, government officials, technical people, the legal community and the business community, as to the problems and potential of the business of biodiversity preservation and development. Then it can be hoped that if there is disagreement between the parties, the disagreement will be over the right issues and can become the subject of rational negotiations.