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Genetic Engineering and Biotechnology Monitor

Issue No. 2 December 1989

The *Genetic Engineering and Biotechnology Monitor* proposes to accept industry-related advertisements from companies interested in reaching planners and policy-makers as well as entrepreneurs and members of the scientific community in some sixty developing countries throughout the world and inform them about their products and services.

The *Monitor* is published four times a year and distributed free of charge to individuals and institutions on an approved mailing list which includes at the moment 2500 entries. The *Monitor* has been published since 1982 and has built up a sound reputation both in developed and developing countries.

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Advertisements will be printed in black and white and in English only. Prices in Austrian Schillings or the equivalent in $US will be AS 5,000 for a full page; for half page advertisements, AS 3,700; and for a quarter page, AS 2,500. Requests for placing of advertisements, accompanied by a layout, illustrations and text, should be submitted to the Editor, *Genetic Engineering and Biotechnology Monitor*.

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A. POLICY NEWS AND OTHER EVENTS

UNIDO News

Research safety standards proposed

Three United Nations organizations - the World Health Organization (WHO), the UN Environment Programme (UNEP) and the UN Industrial Development Organization (UNIDO) - have launched a co-operative programme to evolve strict new safety guidelines for the proliferating science-based industries of the developing regions which are about to embark on genetic engineering in a big way. The proposed new guidelines are intended to minimize medical and other hazards which might arise from the release of genetically engineered organisms into the environment.

The promise of profitable and potent new drugs, forestry and agricultural practices, diagnostic techniques and industrial processes which may soon be created by means of genetic engineering has stimulated enormous interest, leading to the establishment of the UN's International Centre for Genetic Engineering and Biotechnology.

Medicine and agriculture in the hungry world are likely to be the greatest beneficiaries from the bio-revolution, which is expected to boost health and nutritional standards, incomes and output there, concludes an authoritative new study published by the International Labour Organisation.

For example, one third of the world's food potential is currently lost to insects, diseases and weeds - as much as 40 per cent in Africa alone. New pest- and disease-resistant plants will soon reduce this loss considerably.

Clonal propagation of timber crops could greatly alleviate the fuelwood and deforestation problems of the Third World. New strains of micro-organisms will more efficiently convert biomass - which is the earth's most abundant resource - into primary energy substances. Improved medicines will become available while some existing ones, like insulin and interferon, will be cheaper and more plentiful.

But genetic engineering has also "raised concerns about possible risks to humans, animals and the environment," adds a spokesman for the scientific group working on the safety code.

"Its impact is global in scope", he goes on. "An international approach to safety offers the advantages of harmonizing genetic engineering rules and preventing costly duplication of effort in assessing risks and in developing guidelines."

The UNIDO and the UNEP are expected jointly to review all recorded experience on the successful and unsuccessful release of genetically manipulated material into the environment and evaluate existing national guidelines. The WHO is to review all relevant health and environment protection legislation.

The WHO is expected also to "twin" its bio-safety collaborating units at various institutions with the new Centre and its affiliates in order to develop expertise in biotechnology safety programmes in the developing countries. (Source: Development Forum, No. 3, March/April 1989)

Turkey's healing herbs

The Medicinal Plants Research Centre at the University of Anatolia in Turkey is spearheading a drive to turn the country's immense variety of flora into medicaments and essential oils. Greater use of domestic medicinal and aromatic plants could reduce Turkey's imports of raw materials for pharmaceuticals, resulting in substantial foreign-exchange savings.

In spite of a well-developed pharmaceutical sector, Turkey had little experience in extraction and processing of medicinal plants on a pilot-plant scale. To bridge this gap between laboratory and commercial production, the Government turned to UNIDO for assistance. With more than $275,000 from the UN Development Programme (UNDP), UNIDO provided experts, equipment and training. An information service was also set up to help local pharmaceutical firms.

The successful two-year-old pilot plant and laboratory is now offering training to students from other developing countries. Building on the Centre's rapid advances, UNIDO/UNDP assistance will be extended into a second phase to isolate and purify herbal extracts and essential oils. (Source: Development Forum, No. 9, March/April 1989)

United Nations and other organizations' news

UNESCO seeks role in genome projects

The United Nations Education, Scientific and Cultural Organization (UNESCO) is seeking to play a central role in co-ordinating global research efforts into the mapping and sequencing of the human genome. In particular, it wants to focus its activities on the ethical questions raised by such research, and on increasing the involvement of scientists from third world countries.

UNESCO Director-General Federico Mayor, a former biochemist, is planning to propose to the agency's 148 member States that the agency allocate $500,000 over the next two years to support such activities.

The money would be used, in part, to provide fellowships and travel grants to enable scientists from developing countries to visit laboratories in the industrialized world to learn about mapping and sequencing techniques. It would also support the distribution in both developed and third world countries of information about the research programmes.

UNESCO's interest in co-ordinating activities relating to human genome research has received encouragement from several members of the recently formed Human Genome Organization (HUGO), including its president, Victor McKusick of Johns Hopkins University in Baltimore. HUGO is a loose-knit international group of scientists involved in genome sequencing projects.

Mayor, who helped secure the agency's support for a meeting held in Valencia last October to discuss the scientific and technological basis of future genome sequencing projects, has established an advisory panel of 20 leading scientists in the field. It includes McKusick; French Nobel laureate Jean Dausset, the director of the Centre des Etudes du Polymorphisme Humaine in Paris; and molecular

biologist A. A. Bayev of the USSR Academy of Sciences, which has recently started its own, relatively modest, programme of genome sequencing and mapping.

A further meeting will be held in Moscow at the end of June, at which it is hoped that detailed proposals will be worked out for submission to UNESCO's General Conference in October. UNESCO itself is clearly hoping that a close association with the topical field of human genome research will raise its profile as an international scientific organization; and that this in turn will help persuade both the United States, which left the organization at the beginning of 1985, and the UK, which followed a year later, to rejoin.

Meanwhile, the European Commission in Brussels is revising its plans for a three-year research programme aimed at boosting European research into the human genome in light of a number of amendments proposed by the European Parliament. The Parliament wants the Commission to increase its support for studies of the social and ethical aspects of the research, and for public information campaigns on both its benefits and potential dangers. Despite objections from the new commissioner for research, Fillipo Pandolfi, the Parliament overwhelmingly approved virtually all of the amendments, which had earlier been passed by its energy and research committee.

It is now up to the Council of Ministers, representing the Governments of the 12 member States, to decide how many of these amendments should be included in the Commission's revised programme. One amendment the Commission has already said it will adopt is to change the programme's name from "predictive medicine" to the apparently less-threatening title of "human genome analysis".

One specific proposal made by the European Parliament is that at least 10 per cent of the training contracts funded under the new programme should be earmarked for research workers from developing countries. (Source: Science, Vol. 243, 17 March 1989, p.1431-1432, D. Dickson. Copyright 1989 by the AAAS)

Social issues

Third world science groups form network

Spurred in part by the United Nations mixed record of success in stimulating third world scientific endeavours - especially R&D and information exchange - concerned scientists have launched their own initiative. Last October, they inaugurated the Third World Network of Scientific Organizations (TWNSO), meeting at the Third World Academy of Sciences' (TWAS) headquarters in Trieste, Italy. Although TWAS has yet to establish a firm programme, its main priorities include third world participation in global scientific efforts (e.g., the human genome project), encouraging biotechnology transfer to facilitate economic and social development of third world countries, and improving lines of communication with developed countries through bilateral links and exchanges.

TWNSO has grown quickly from concept to reality. In 1986, TWAS invited national science academies and research councils in developing countries to sign an agreement to strengthen their co-operative links with TWAS. Out of 30 groups contacted, 23 responded favourably.

Encouraged by this positive feedback, TWAS president Abdus Salam of Pakistan, the director of Trieste's International Centre for Theoretical Physics (ICTP) - speaking at the opening of the 1987 TWAS Second General Conference in Beijing, China - proposed extending the scope of the TWAS initiative to form a network linking scientific institutions in developing countries. To enhance overall communication and collaboration, he called upon the Ministries of Science and Technology and Higher Education in developing countries to participate.

During the Beijing meeting, representatives of over 40 ministries, research councils, and scientific academies discussed Salam's "network" proposal. An ad hoc committee, chaired by Nigeria's Minister of Education Jibril Aminu, was established to further explore the network's formation. Ninety-four scientific organizations from 60 third world countries have since agreed to become members of TWNSO.

The main business of the October 1988 founding meeting was to elect officers and approve the charter statutes. The members also adopted the "Trieste Declaration on Science and Technology as an Instrument of Development in the South", which resolves that its members will "work toward giving science and technology a position of highest priority in their own countries and to strengthen their collaboration with other countries of the South as well as the North".

In addition to its main offices at TWAS, the network established four regional offices to facilitate its operations - in Nigeria, Tunisia, Mexico, and Malaysia, the home countries of the four TWNSO vice presidents. (Source: Bio/Technology, March 1989)

WHO plans for trials of future AIDS vaccines

The World Health Organization says that planning must start now for large trials of potential vaccines to protect recipients against AIDS, even though no vaccine yet shows sufficient promise to enter large-scale tests. Specialists who met at the WHO in Geneva drew up a set of guidelines for testing such vaccines when they become available.

The consensus statement produced by the group recommended that:

- Scientists should give priority to developing a suitable animal model for testing vaccines;
- Trials should observe basic ethical principles of biomedical research, particularly the rights of participants to refuse to take part, or to withdraw from a trial;
- People taking part in trials should receive full counselling, particularly to ensure that they have given fully informed consent.

Testing of candidate vaccines to protect against AIDS is likely to pose some exceptionally difficult ethical dilemmas. For example, people taking part would need full instruction on how to avoid becoming infected with the virus that causes AIDS, which would immediately make the trial a less powerful means of testing the vaccine. (Source: New Scientist, 11 March 1989)

Regulatory issues

Biotechnology industry frets over proposed rules

Representatives of the burgeoning biotechnology industry are not pleased with the proposed US Environmental Protection Agency's regulations for micro-organisms under the Toxic Substances Control Act. Both the Industrial Biotechnology Association and the Association of Biotechnology Companies stated at a public hearing on the draft regulations recently that the regulations would seriously hinder future biotechnology developments. The IBA president Richard D. Godown told the EPA that the proposed rules would not allow companies enough latitude to design manufacturing facilities and would greatly burden the fermenting industry. Regulation of any new use for a naturally occurring organism would put an extreme load on industry and research facilities, according to the ABC. It recommends that the EPA continue with its present policies. The ABC also recommends that research results be presumed confidential and that the EPA should not require "burdensome substantiation" for confidentiality claims. (Reprinted with permission from Chemical and Engineering News, 2 January 1989, p. 25. Copyright 1989 American Chemical Society)

Federal Republic of Germany's cabinet agrees gene guidelines

The Federal Republic of Germany's federal cabinet has approved guidelines for a law to control work in genetic engineering. The guidelines, drawn up by the federal Ministry of Health, will form the backbone of a bill establishing uniform rules for companies and scientific groups working with recombinant DNA technologies.

The law would regulate only basic conditions for using the technologies and separate detailed regulations would be applied to individual projects according to risk.

The regulations would control the use of technologies in closed systems as well as the release of genetically manipulated micro-organisms. It would apply to industry and science alike. Companies or independent scientists working with the techniques or releasing manipulated bacteria would be held responsible for any damage caused to health or the environment.

The federal states would continue to be responsible for approving new projects but would have to consult federal institutions such as the Ministry of Health before making a final decision. All plants which fulfill the requirements will need approval.

The cabinet has disagreed with the enquiry recommendation of a five-year moratorium on the release of genetically manipulated micro-organisms.

In a parallel but separate move, the cabinet has called for the federal Ministry of Justice to draw up criteria for a new law regulating the use of genetic engineering in reproductive technology and genome analysis. (Source: European Chemical News, 12 December 1988)

Biotechnology regulation update

The first International Conference on the Release of Genetically Engineered Micro-organisms (REGEM 1) was held in Cardiff, Wales, UK from 5 to 8 April 1988. The wide-ranging programme contained sessions on mechanisms to monitor deliberate releases from the point of view of survival, persistance and detection; interactions of genetically engineered micro-organisms, including horizontal and vertical transfer of genetic material in the environment; a series of case studies of both deliberate and accidental releases and ecosystem modelling and long-term ecological studies.

Just over 80 papers were presented over the three-day period, dealing with the state-of-the-art situation regarding actual releases as well as predictive or simulation studies. Once again, consensus was reached in an extremely multidisciplinary audience that the method by which an organism is engineered is less important than its effect on the environment. Hence, regulatory controls should be structured accordingly. The proceedings from the conference are available through Academic Press.

In the US, a product liability bill (H.R. 1115) known as the Uniform Product Safety Act cleared the House Energy and Commerce Committee in August 1988. Whilst there is little likelihood of a house vote within the calendar year, this is the first time a product liability bill has ever progressed through this phase in Congress.

Some of the provisions of the bill will have extremely important implications for drug manufacturers, particularly with regard to punitive damages. For example, the bill permits the states to determine when and where punitive damage awards will be allowed. Pre-market approval by the Food and Drug Administration (FDA) of drugs and medical devices will provide a complete defence for manufacturers. Similarly, drugs with packaging in compliance with federal tamper-resistant packaging laws will provide manufacturers with a defence against claims for punitive damages.

Product sellers will also be affected by the bill since they will be liable for a manufacturer's error when the manufacturer cannot be brought to court or lacks the funds to pay a judgement. Otherwise product sellers will be responsible only for their own negligent acts.

The issue of applying genetic engineering to humans in Australia was dealt with relatively painlessly by the National Medical Health and Research Council (NHMRC). The Council's Medical Research Ethics Committee concluded in November 1987 that gene therapy to make inheritable changes is ethically unacceptable. Somatic cell therapy is considered acceptable but experimental and hence subject to the NHMRC's prescribed procedures for experimental research. By contrast, the British Medical Association recently decided to establish a working party to draw up a set of ethical guidelines; it is expected to take at least two years to report.

The NHMRC has also broken new ground by endorsing a set of guidelines developed by its Food, Science and Technology Sub-Committee to assess foods and food additives produced by biotechnological means. The Sub-Committee acknowledged that principal consumer concerns centre around the possible introduction of pathogenicity or toxicity and unacceptable changes in the nutritional value of food stuffs. The NHMRC intends to utilize existing processes to ensure that foods, food additives and food processing aids produced by recombinant DNA

technology and other biotechnological means. The products will be assessed by the Sub-Committee to ensure they are safe and fit for human consumption. (For further information, contact Dr. Gordon Cean, (062) 980307). (Source: Australian Journal of Biotechnology, Vol. 2, No. 2, September 1988)

France introduces bioethics law

France has announced that it is to become the first Western nation to introduce a wide-ranging law on bioethics, defining how the "dignity of the individual" should be protected in an age of rapidly advancing medical technologies.

In a bill that seeks to balance the freedom of research and the requirements of progress with the rights of man, the French Government has published legislative proposals that would, for example, outlaw any sale or trade in human organs, and confirm an existing ban on commercial surrogacy arrangements. The bill would also forbid any attempt to maintain a human embryo in vitro for more than seven days. In exceptional circumstances, the bill permits an extension to 14 days, provided France's National Ethical Committee gives its consent.

The new law is based on a report on "The Life Sciences and the Rights of Man" commissioned by the Government. It is intended to provide a broad juridical base from which detailed regulations covering specific areas of medical technology will subsequently be elaborated. (Extracted with permission from Science, Vol. 243, p. 1284, 10 March 1989, D. Dickson. Copyright 1989 by AAAS)

Guidelines produced for the use of transgenic animals in research

With transgenic animals finding increasing favour in both biomedical research and biotechnology, the UK Advisory Committee on Genetic Manipulation (ACGM) has produced detailed guidelines on their use. The guidelines, which the committee hopes will set an example for other countries, are particularly concerned with the consequences of the deliberate or accidental release of transgenic animals into the wild, and the hazards of using viral, and especially retroviral, vectors for transgenes - that is, the use of genetically modified viruses to introduce new genes into animals.

For animals that are to be released, there will be a ban on the use of any viral vector that contains even a partially functional oncogene and on any form of vector that has even a remote potential to replicate. Plans to use equivalent vectors to produce contained transgenic animals will be considered individually.

Among the considerations will be the precautions that have been planned to ensure containment. For large animals, ACGM takes the view that a well-fenced field is sufficient. Extra care will be needed for fish and other aquatic vertebrates because of the relative ease with which they or their gametes can escape. Even greater precautions are necessary for work with invertebrates that "crawl, jump or fly".

Some of the guidelines on genetic manipulation anticipate changes in the official Health and Safety Regulations, which were drawn up in 1978. Revised regulations suggested by the Health and Safety Commission in October 1987 have since been modified, and now await approval by the Secretary of State and parliament. Their main intent is to establish a legally backed compulsion both to notify ACGM of the production and use of transgenic animals and to set up and operate local risk assessment committees at any establishment that carries out genetic manipulation.

ACGM's guidelines also cover aspects of work with transgenic animals that fall outside its own purview. The welfare of such animals is "dealt with adequately by existing legislation", the guidelines say, pointing out that breeding from transgenic animals is regulated as though an animal experiment until it can be demonstrated that the progeny are not likely to suffer any adverse effects.

The guidelines advise that the consumption of transgenic animals or their products by humans or animals or their products by humans or animals would be subject to consideration by the Advisory Committee on Novel Foods and Processes, which may in turn seek advice from ACGM. (Source: Nature, Vol. 337, 26 January 1989)

General

Twenty-four new cloned viruses and viroids from ATCC Plant Virus Collection

Intensive efforts in the Plant Virus Collection at the American Type Culture Collection (ATCC) are paying off as shown by the recent accession of 24 molecularly cloned viruses and viroids. Eight clones are currently available for distribution, while the remainder are being processed for planned distribution from June 1989. The available clones are: cauliflower mosaic viruses (2), tobacco etch virus (2), beet curly top virus, brome mosaic virus, cassava latent virus and tobacco mosaic virus. Details from: American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD 20852 1776, USA or on + 1 (301) 881-2600. (Source: Biotechnology Bulletin, Vol. 8, No. 2, March 1989)

ATCC Revised Culture Fees (1 January 1989)

	Price per Item (SUS)
ATCC Cultures	
Algae, Bacteria, Bacteriophages, Fungi, Plant Tissue Cultures, Plasmids, Protozoa, Vectors and Yeasts (Except Preceptrol and Uniplus) US and Canadian Non-profit Institutions	45 00
Other US and Foreign Institutions	70 00
ATCC Preceptrol and Uniplus Cultures All US and Foreign Institutions	12 00
ATCC Cell Lines and Oncogenes	
US and Canadian Non-profit Institutions	50 00
Other US and Foreign Institutions	80 00
Contract Cell Lines All "HTB" cells and "HB" 1 to "HB" 7999	
US and Canadian non-profit Institutions	40 00
Other US and Foreign Institutions	64 00
ATCC Viruses, Animal & Plant, Rickettsiae and Chlamydiae	
US and Canadian Non-profit Institutions	40 00
Other US and Foreign Institutions	64 00
Animal and Virus Antisera All US and Foreign Institutions	25 00
Plant Virus Antisera*	

US and Canadian non-profit Institutions	40 00
Other US and Foreign Institutions	64 00

* Selected antisera are priced higher

ATCC/NIH Human Chromosome-Specific Libraries (57700-57999)

Non-profit Institutions	100 00
Other Institutions	150 00

ATCC/NIH Repository Probes and Cloned Genes (57000-57699, 59000-59999)

Non-profit Institutions	40 00
Other Institutions	64 00

Cell lines ordered as flasks, protozoa sent as test tubes and others specially ordered as test tubes carry an additional laboratory fee of $35.00. Minimum invoicing is $45.00. Orders received for lesser amounts will be invoiced at the minimum. Prices are in US dollars. Terms: Net 30 from date of invoice. No COD orders or Letters of Credit accepted. Quantity discounts 10 per cent on $1,400 to $2,100; 15 per cent over $2,101.

Shipping charges

Perishable or pathogenic materials which by their nature require special packaging, handling and/or shipping are shipped FOB origin, freight prepaid via carrier of our choice.

The address is: American Type Culture Collection,
12301 Parklawn Drive,
Rockville, MD 20852 USA
Telex: 908768 Fax: 301-231-5826
(Source: ABA Bulletin, Vol. 4, No. 1, February 1989)

Humane gene therapy on the way

The first experiment involving the introduction of foreign genes into humans got back on track through the institutional review process when it was approved by a sub-committee of the Recombinant DNA Advisory Committee (RAC) of the US National Institutes of Health (NIH).

On 29 July 1988, three scientists at the NIH proposed a plan to treat patients suffering from melanoma - a virulent form of skin cancer - using cells called tumour-infiltrating lymphocytes (TILs). The scientists proposed taking these cells of the immune system from patients, fortifying them in the laboratory with interleukin-2, and injecting them back into the donor, where they would attack tumours.

Before injecting the cells back into the patient, the scientists planned to infect the cells with part of a mouse retrovirus that carries a gene conferring resistance to neomycin, an antibiotic. The gene has no therapeutic value, explains Michael Blaese, who shares credit with French Anderson and Steven Rosenberg for devising the experiment. Instead, the gene will help doctors to track the TILs in the body. The team considered this to be a modest and safe first step toward real gene therapy and a test of their ability to splice a working gene into human cells. The Recombinant DNA Advisory Committee (RAC) at the NIH debated the experiment in public on 3 October 1988, then deferred a decision twice and was ordered on another occasion to review it yet again.

Another panel, the NIH's Institutional Biosafety Committee, which reviews experiments on humans, deferred its decision once, then asked the researchers for more data on safety and whether they should try experiments on animals first.

Tests on animals subsequently proved that scientists could retrieve genetically labelled TILs from blood. Blaese's team has tried without success to induce mutations in tissue culture using the gene.

Blaese says that only those patients with less than three months to live can participate in the experiment. Rosenberg has shown already that therapy with TILs that lack the foreign gene can reduce tumours in patients with melanoma, one of the most difficult forms of cancer to treat. However, because the tests of gene therapy with animals "had not been fully developed", the Biosafety Committee said, only ten patients should participate. The RAC approved the test by mail and the NIH gave its final authorization for the test to go ahead in January. (Source: Nature, Vol. 336, 15 December 1988 and New Scientist, 4 February 1989)

More money needed for human genome mapping project

The US Administration is seeking an almost fourfold increase in spending for 1990 on a project to map and sequence the human genome, up from the $27.6 million the National Institutes of Health (NIH) will spend on genome activities this year. If this huge increase is approved by Congress it will mean much extra responsibility for the newly christened Program Advisory Committee on the Human Genome, chaired by Norton Zinder of Rockefeller University. NIH are counting on the committee for guidance as they work to sequence the 3,000 million bases that make up the human genome.

NIH director James Wyngaarden gave his agency an active role in the genome project last year when he established NIH's Office of Human Genome Activities and chose as its director James Watson, director of the Cold Spring Harbor Laboratory.

The National Science Foundation and the Department of Agriculture will also support human genome research, although the Department of Agriculture's contribution will be small, at less than a million dollars. The Howard Hughes Medical Institute will also play an important role in the project, with its support of genetic databases and mapping efforts.

At the advisory committee's first meeting last week, four working groups were set up: one on training chaired by Joseph Goldstein of the University of Texas Southwestern Medical Center in Dallas; one on centres that will work on the project co-chaired by Phillip Sharp of the Massachusetts Institute of Technology in Cambridge and Maynard Olson, Washington University School of Medicine, St Louis; another on ethics chaired by Nancy Wexler of Colombia University in New York; and the fourth on databases chaired by David Botstein of Genentech, Inc., in San Francisco. (Source: Nature, Vol. 337, 12 January 1989)

Biotechnology in microgravity

With NASA's Shuttle programme apparently back on its feet, low- or zero-gravity research opportunities may once again be coming the way of biotechnologists. Microgravity conditions attained in space vehicles represent a new, unique and under-exploited environment for conducting

scientific experiments. Much has been written on the "immediate" industrial applications, without a clear definition of the implications in terms of cost, resource needs and any likely commercial benefits.

The UK Biotechnology Group of the Society of Chemical Industry (SCI) is organizing a meeting which will aim to: identify and define the potential of microgravity experiments; provide an update on experimental results to date; provide information on how to mount experiments in microgravity; and provide a forum for discussion. (Source: Biotechnology Bulletin, Vol. 7, No. 11, December 1988)

DNA and defence

Genetic engineering is blurring traditional distinctions between chemical and biological warfare, according to Graham Pearson the director of Britain's Chemical Defence Establishment at Porton Down. As a result, he said, countries could circumvent the existing international treaty banning biological weapons.

New techniques of gene splicing and recombinant DNA technology can modify natural biological toxins that are banned under the Biological Weapons Convention of 1972. Some countries could take the view that the modified toxins are not therefore covered by the convention.

Examples of classical chemical weapons are mustard gas, and the nerve agents such as soman. Potential biological weapons include anthrax, plague, influenza and smallpox. But emerging in the middle is a new class of biological toxins and bioregulators that can upset human metabolism. These are often derived from natural compounds or as a result of modifying designer drugs.

Bioregulators are substances that are produced naturally in the human body as part of its metabolism. But when introduced in an unnatural way they can induce a variety of adverse effects, such as change to blood pressure, pain, sleep, and even death. New techniques in biotechnology can synthesize such agents cheaply and in large quantities.

One example of a toxin that concerns the defence establishment is that derived from the bacterium Clostridium botulinum. The toxin causes weakness, double vision and dizziness and can be fatal. Even with medical attention, the toxin kills 25 per cent of those who swallow it.

The Chemical Defence Establishment is also worried about a number of other toxins that could be used in warfare, such as neurotoxin from cobra snakes, ricin from castor oil and tetrodoxin from puffer fish. Such toxins could be converted into fine powders and sprayed over troops. (Source: New Scientist, 17 December 1988)

Investigators track HIV from East to West

Health officials around Europe have agreed to begin a research programme to monitor the spread of HIV, the virus which causes AIDS, by reporting cases of infected people. Up to now, countries have reported only cases of AIDS, but epidemiologists fear that this represents earlier patterns without reflecting the present level of infection. The officials, from 32 countries in both Eastern and Western Europe, debated options for a programme to monitor the spread of HIV.

They agreed that each country should supply statistics on numbers of people infected with the virus, as well as numbers of AIDS cases. The Paris office of the World Health Organization will co-ordinate the monitoring programme and collate data. Each country is to decide the sort of surveillance it wants to undertake; for example, whether it should be totally anonymous testing where all identifying details of the person are removed from the blood sample, or whether it will be compulsory screening, which is confidential but not anonymous.

Data released by various European Governments revealed that there are two very distinct epidemics of AIDS and HIV infection in Europe. In West Europe, AIDS affects mainly homosexual men, although an increasing number of heterosexuals are becoming infected, mostly through the the use of intravenous drugs. In some countries in southern Europe, such as Spain and Italy, this last mode of infection is now the most common.

The second type of epidemic is occurring in East Europe, where the virus has only been present since the early- to mid-1980s. Here, people who are infected are mostly the heterosexual partners of people who have had some contact with the West or with Africa. But now, the virus has become established in the general population and is beginning to sustain its spread.

In the USSR, for instance, the number of Soviet citizens who are infected with HIV has risen sharply in the first few weeks of this year. (Source: New Scientist, 25 March 1989)

International Network for the Promotion of Genetics

The science of genetics has a very vital role in meeting the increasing needs of food, feed, fodder and fibre requirements of the human kind particularly in the developing world which supports nearly 80 per cent of the population. It has, therefore, been felt that this important discipline needs promotion in an organized way. During the XVIth International Congress of Genetics held at Toronto in Canada, Professor V. L. Chopra of the Biotechnology Centre, Indian Agricultural Research Institute, New Delhi and Dr. Anwar Nasim of the National Research Council of Canada, convened a meeting of scientists contributing to the philosophy of promoting genetics in the developing countries under the chairmanship of Dr. M. S. Swaminathan. The largely attended first meeting was followed by many informal discussions and a formal meeting in which it was decided to launch an "International Network for the Promotion of Genetics". Prof. Abdus Salam, President of the Third World Academy of Sciences, Trieste, Italy, has agreed that the Network can function under the aegis of the Academy. It is proposed to seek support of other organizations such as UNIDO, ICGEB, UNDP, UN Centre for Science and Technology for Development and the International Genetics Federation.

The Network will take up the following initial activities:

(a) Promotion of regional co-operation;

(b) Organization of seminars for policy makers;

(c) Work on technology transfer mechanisms designed to bridge the growing gap between the technological capabilities of developed and developing countries;

(d) Stimulating young scientists and helping them in appropriate ways:

(e) (i) Mobilizing third world debt for promoting science in general and genetics in particular through debt for genetics swaps;

(ii) Significance of genetic research for food and health in the third world;

(f) Publication of a newsletter.

Further information may be obtained from the Network's co-ordinators, Prof. V. L. Chopra, Professor of Eminence & Head Biotechnology Centre, Indian Agricultural Research Institute, New Delhi - 110012, India and Dr. A. Nasim, Division of Biological Sciences, National Research Council Canada, Ottawa, Canada KIA 0R6.

Port-a-Lab

A thousand dollars may not go as far as it used to, but it will buy a newly-developed complete mini-medical laboratory for a 100-bed hospital. A researcher at the University of Texas Health Science Center at San Antonio spent ten years developing the laboratory for use in remote areas. It fits into two portable typewriter-sized cases and weighs less than 30 pounds. The unit contains chemical reagents and miniature instruments needed for diagnostic work. Solar energy kits - they are included - can recharge the batteries that power the electrical instruments, which also run on local electricity. But how can someone make a laboratory for $1,000 when a centrifuge alone costs $1,500? Improvise. Using a flashlight, a model airplane engine and velcro, the laboratory's inventor created a centrifuge which takes half an hour to assemble and costs $6.39. For more information, contact David Bernert or Ken Slavin, Dublin-McCarter & Associates, 512/227-0221. (Source: BioBytes, San Antonio Biotechnology News & Information, produced by Dublin-McCarter & Associates)

Drugs from plants

Important pharmaceuticals, such as anti-clotting agents and growth hormones, could soon be produced on a large scale by genetically engineered plants, according to an announcement from Plant Genetic Systems (PGS) of Belgium. Pharmaceutical peptides can now be produced in the seeds of oilseed rape, using a technique developed jointly with scientists at the University of Ghent.

The company foresees itself becoming a "molecular farmer". It plans to grow transgenic plants and sell the peptides to pharmaceutical companies. It says an agreement has already been reached with one major pharmaceutical firm.

Although animals are also being engineered for the production of pharmaceuticals, PGS believes plants are more cost effective. The extraction and purification processes are also said to be efficient. (Source: Chemistry and Industry, 6 March 1989)

Participants needed for ASTM Task Group on Membrane Characterization

Participants are needed for a new ASTM task group on membrane characterization. This activity is sponsored by E48.03 on Unit Processes and Their Control, a sub-committee of ASTM standards-writing Committee E-48 on Biotechnology.

The group will develop standards in bioprocessing using membranes, including membrane reactors and membrane separators. Of particular interest are cell separation and proteins concentration using microfiltration devices, and measurement of control of membrance biofouling. Membrane manufacturers will benefit from this activity, and industry and consumers will be able to properly select and test devices, and satisfy traceability.

All interested parties are welcome to participate. For more information, contact Subhas K. Sikdar, National Institute of Standards Technology, 325 Broadway, Boulder, CO 80303, 303/497-5232; or John Vowell, ASTM, 1916 Race Street, Philadelphia, PA 19103, 215/299-5496.

Committee E-48 is one of 134 ASTM technical standards-writing committees. ASTM is a management system for the development of voluntary consensus standards for materials, products, systems and services, and the promotion of related knowledge. Currently, ASTM has 30,000 members from around the world representing industry, governments, academia and consumers. Participation in ASTM is open to any interested party. The Annual Book of ASTM Standards contains over 8,000 test methods, specifications, practices, guides, classifications and definitions developed by ASTM standards writing committees. (Source: ASTM News Release, 3 February 1989)

An open market in developing countries

Because large corporations in industrialized countries have dominated biotechnology research efforts, products have largely been geared to Western markets. But the message coming out of a recent conference in Bangkok is that many developing countries, blessed with an abundance of natural biological resources, can also benefit greatly from these advances.

Several common threads emerged from among the 200 participants at the September 1988 International Symposium on Application of Biotechnology for Small Industries Development in Developing Countries. First, that small industries in developing countries form the strongest foundation of biotechnology development - they are economically and socially best suited to provide the greatest benefits to the most people. Also, industries should emphasize market-driven, not technology-driven, product development, and improve connections between the business and scientific communities.

Several speakers discussed applications suited to small industry areas in South-East Asia and elsewhere that already show potential. These include fermented products such as soy sauce and beer - which can be generated from the 1.5 billion

tons of agricultural residues produced in developing countries each year - and traditional starch products, which can be upgraded using fungi to boost their protein content.

Biotechnology can also provide livestock industries with improved feeds, vaccines, therapeutic agents, diagnostic aids and growth hormones. Demand for animal protein products is increasing throughout the developing world and producers must develop local sources for industry inputs, many of which are currently imported.

Finally, tissue culture was cited by many participants as a technology well-suited to many developing countries. Already widely used in South-East Asia in the orchid industry, rapid advances are being made with other horticultural crops. Steps are even being taken to develop tissue culture kits that can be used by farmers in propagating potatoes and other crops.

Selecting an appropriate technology demands knowledge of existing technology. Speaker after speaker stressed the need for linkages between entrepreneurs and scientists - and lamented that these linkages currently are weak. (Extracted from: Biotechnology, November 1988)

Asian commercialization of biotechnology

While most discussion on Asian biotechnology focuses on Japan, other fast-growing nations in Asia - South Korea, Singapore and Taiwan - are poised for rapid commercialization of biotechnology. The presentations by Government, research and industry leaders at the Pacific Rim Biotechnology Conference (5-9 September 1988) organized by these three Governments and the USA, demonstrated the strong focus and economic commitment of these Asian countries to biotechnology as their next emerging industrial wave.

These three Asian countries now have export markets almost equal to those of the entire EEC. Taiwan has the second highest trade surplus with the USA after Japan. Thus, they have the economic resources if properly focused to succeed in developing biotechnology. For example, the accumulated cash reserves in Taiwan now exceed US$77 billion.

Asian government strategies to develop biotechnology are rather straightforward. A new research infrastructure is being quickly developed. To do this, these Governments have established new molecular genetic research institutes, academic research departments in existing universities and new medical centres. These are state-of-the-art facilities with the latest equipment. Moreover, the establishment of new facilities bypasses the politics of the established academic groups who are reluctant to change and rapidly adopt the new technology.

To staff these new facilities, Asian Governments have sought to tap the growing pool of Asians living in the USA who are well trained in science. Taiwan has over 100,000 immigrants in the USA, 70 per cent of whom have scientific, engineering or commercial training in high technology. Korea is sending increasing numbers of students to the USA for higher education as well as establishing industrial laboratories in the USA staffed by Koreans. Singapore, with a much smaller population, is enticing scientists with high salaries and benefits to work at its institutions.

Government funding for biotechnology research is dramatically increasing in these Asian countries. As the research pump is primed, there is increasing emphasis also on technology transfer. The concept of the Singapore Conference was to lay the foundation to expedite such transfers. These Asian countries will rely heavily on technology imported from the USA and Europe to provide the basic technology and manufacturing capabilities. If the USA and Europe are not willing to transfer technology, then these countries will turn to Japan. Obviously, with US$77 billion accumulated cash reserves Taiwan will have considerable economic clout. Thus, initially one does not anticipate any earth-shattering discoveries to come out of Asia, but rather biotechnology products made more cheaply.

Although Asian Governments are willing to invest in biotechnology, their industrial and private investors have not shown similar enthusiasm. To stimulate such private investments, government tax and commercial incentives are being offered. There will probably be no immediate investor rush, but a slow, steady increase over the next several years. As electronic industry sales begin to wane, investors will be forced to seek new technology to invest in

The success of biotechnology is based on international interchange, co-operation and support. The rapid growth of biotechnology has occurred through numerous transnational interrelationships and financial arrangements. A small US biotechnology corporation which teamed up with a Japanese food concern and a Swiss multinational drug company produced the cancer-fighting Interleukin-2. In the USA there are over 160 joint ventures between small US biotechnology companies and foreign multinationals. Canada, Europe and Asia also have an increasing number of joint ventures, as well as small biotechnology companies being formed and financed. Australia too has a predominance of smaller biotechnology companies with excellent technology which are therefore capable of such joint ventures. (Source: Australian Journal of Biotechnology, Vol. 2, No. 2, September 1988)

The Biotechnological Revolution
by Salomon Wald

(Reprinted from The OECD Observer, No. 156, February/March 1989)

Biotechnology is not an industrial or agricultural sector - it is a broad, generic technology. It is the third technological revolution this century, after nuclear energy and information technology. For hundreds of years its evolution was slow, and empirical, as small advances were made at the margins of knowledge. But modern R&D (in particular, recombinant DNA, cell-fusion and other scientific breakthroughs of the last decade) have transformed biotechnology into an efficient and swiftly growing set of tools and applications. 1/

1/ See Bruna Teso, "The Promise of Biotechnology ... and some Constraints", The OECD Observer, No. 118, September 1982.

The next ten years will see even more changes in a discipline intimately linked with man and life. These are early days.

Biotechnology in industry

Biotechnology has the potential to improve the international competitiveness of advanced countries, and to open up entirely new markets. The leaders will be the big multinational corporations primarily concerned with chemicals, pharmaceuticals and food processing, although small companies will continue to make vital contributions to science and technology. For the large corporations, biotechnology will provide the means for improving or consolidating their competitive position. With time, there will be a growing diversity of biotechnological products coming from a variety of industries, and demand for them is expected to grow.

Many of the companies that are not already developing and using contemporary biotechnological techniques plan to do so in the coming years. While biotechnology remains but one tool in their corporate strategies, a remarkably large proportion of firms see in it a new generic technology that, like the computer, calls for a permanent pool of in-house expertise. The move of industry into biotechnology is correspondingly broadly based, rapid - and probably irreversible.

The considerable resources required in biotechnological R&D favour highly industrialized countries and large companies. Yet the fruits of this new technology have a particular interest for the third world, although many of the companies concerned (Japanese ones apart) seem to show little interest in that potential market. Biotechnology could help developing countries deal with their health concerns and meet their food requirements.

Biotechnology will not be the predominant technology for most industries and services this century, and is not likely to become the main basis for new investment and economic growth until the second or third decade of the 21st century. Yet it will bring a further reduction in the use of materials and energy per unit of GDP in OECD economies and make for a more rational innovation process. In any case, its effects on society, on the way people live, are likely to be more important than its quantitative impact on economic performance.

Capital, investment and patents

Far-reaching transformation of the technologies currently in use must inevitably lead to large-scale investment in the new, perhaps at the expense of the old. But changes in capital stock, in the "skill profile" and organizational structure of industry will not occur overnight. And recognition of the length of the time-scale involved will help avert two opposing dangers: "technological super-optimism", which tends to ignore the hard economic realities of relative costs, profitability and consumer acceptance of entirely new products, and "technological conservatism", which fails to recognize the enormous potential at stake.

Commercial investment in biotechnology was given a big boost by court decisions to grant patent protection to its inventions, on the grounds that the new technology, often derived from genetic modification, was ascribable to human ingenuity. But it is widely argued that the large-scale diffusion of biotechnology will depend critically on better international harmonization of patent protection. 1/

Drugs, disease and diagnosis

Understanding of the mechanisms of life and the causes of disease will continue to grow through the study of genes, revolutionizing the underlying concepts in this still new area of research. To judge from past experience, future progress might again be distinguished from that in other technologies by the rapidity of scientific and technical developments, which has often confounded the forecasts of experts and observers. Some important recent discoveries are already being applied. Genetic or DNA-finger-printing, which was developed in the early 1980s and enables individuals to be identified from the DNA contained in their body fluids or hair, is now being used in paternity suits and crime detection.

For the time being, advances in biotechnology are taking place first and foremost in pharmaceutics and health care. A number of products have already emerged, such as insulin produced by bacteria, interferons for the possible treatment of diseases such as cancers and leukemia, the human growth hormone, a natural enzyme for dissolving blood clots and a hepatitis-B sub-unit vaccine. Animals can now be used as bioreactors to produce rare proteins. The combination of genetic- and protein-engineering technologies will allow drugs to be more specifically targeted, to have fewer adverse side-effects and to be more efficient. And most importantly, more than 200 diagnostic tests have been developed for detecting diseases.

In health care, indeed, the main general trend is towards disease diagnosis and prevention (through new vaccines) rather than cure, although diagnostic advances will also require other changes, not least the automation of sampling and the instrumentation necessary to analyze organic material from a large number of people. Biotechnology is playing a key role in enhancing understanding of AIDS and biotechnologically generated products may provide a solution to this most urgent of public health concerns before the end of the century. 2/ In the longer term, gene therapy, which will be revolutionized by the development of recombinant DNA techniques, may offer the prospect of curing genetic disorders at a time when the number of disorders recognized as being of genetic origin has already jumped to over 3,000, compared to an estimated 400-500 some 30 years ago.

But such advances could bring their own problems. One of the biggest killers in the third world is hepatitis-B. Simple diagnostic and preventive treatments have already been devised, but are currently too expensive to be widely deployed; once they can be produced more cheaply, there will

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1/ See Ebba Dohlman, "International Piracy and Intellectual Property", The OECD Observer, No. 154, October/November 1988.

2/ See Carl Wahren, "Can AIDS be Contained?", The OECD Observer, No. 154, October/November 1988.

obviously be enormous additional pressures on family planning programmes. 1/

There will be changes, too, in the health care systems of the industrialized countries. Home-testing for pregnancy is now perhaps one of the best-known domestic applications of biotechnology. But what of potentially terminal diseases, such as AIDS or cancer? Home-testing is now theoretically possible but can it be recommended in such instances, where medical and psychological counselling is of prime importance? And will the medical establishment - a powerful lobby in most developed countries - acquiesce in a loss (even marginal) of its power? The defence of corporate interests, too, could slow down the diffusion of new techniques, and not only in medicine and pharmaceuticals.

The transformation of agriculture

Agriculture is one of the world's largest sectors and it, too, will be transformed by biotechnology, which has the potential to boost food production substantially, both through increasing crop growth rates and improving the growth efficiency of livestock, and to reduce residues from pesticides and other agro-chemicals. Man wil be able to create plants that are resistant to disease, insects and herbicides, or are capable of surviving in inhospitable climates. The momentum is accelerating, and the next decade will see enormous advances in the development of plants and trees - not least, maize, wheat and rice - that offer high growth rates and improved seed qualities and tolerate salt or stress.

Livestock is also benefiting from the products of biotechnology. Biotechnologically produced natural hormones can increase the milk yield for the same amount of feed, and can enhance animals' growth rates. Better vaccines are being produced for foot-and-mouth disease and other animal illnesses. Sex-specific semen might also be used in animal reproduction to produce the desired quantities of each sex - giving rise to ethical concerns that this technique could be used in human reproduction.

Many of these advances are also applicable in the food and feed industry. Applying molecular biology to wheat breeding could improve its bread-making qualities. Improved enzymes for food processing will lead to more efficient and cost-effective industrial food production. Biotechnology products and processes may be used as thickening agents and natural preservatives or to enhance flavour.

Concern has been expressed on how the powerful new tools of biotechnology could exacerbate current problems of agricultural surplus. To avoid this complication, agricultural biotechnology should be directed more towards qualitative than quantitative goals: food with better taste and aroma that is safer, has fewer chemical residues (which implies the replacement of present agro-chemicals by biological techniques), and further specialization and diversification of food products in order to respond to specific demands.

Moreover, the development of new and economically viable, and particularly industrial, uses of agricultural products has become a vital challenge. Biotechnology could become a decisive tool in the transformation of the agriculture necessary in OECD countries. For example, the growing importance of biodegradability and environmental compatibility might be better satisfied through products based on transformation of biomass than through synthetic products.

What Effects on Trade?

Biotechnology is already making itself felt in agricultural trade. A maize-based sweetener, high fructose corn syrup (HFCS), derived from starch through the use of enzymes, is now having an effect on the international sugar trade, since HFCS production costs have fallen in recent years, partly as a result of a sharp fall in the cost of enzymes. World HFCS consumption was equivalent to over 6 per cent of world sugar consumption in 1985, up from under 1 per cent in 1975. As a result, industrialized countries have managed to reduce their imports of sugar, while developing countries saw their share of internationally-traded sugar plunge from 90 per cent in 1975 to 67 per cent in 1981.

In vitro propagation of plants and cell tissue culture could increase the supply of many plant species, speeding up the production of large numbers of plants or clones, making them available all the year round instead of on a seasonal basis, improving their quality, and facilitating the reproduction of species that are hard to propagate naturally once they flower. Such techniques might improve the supply of palm trees, for example, helping producers respond to the rapid rise in world demand for palm oil. Palm trees can only be grown in tropical countries, but they have to be replaced every 25 to 30 years and are hard to propagate in the wild. Producers from industrialized countries might thus compete against suppliers of alternative oils and fats derived from coconuts, sunflowers and cottonseed.

Countries, especially industrialized countries, that previously had to rely on commodities imported from others, are therefore likely to be able to produce some of them competitively themselves. The effects on world trade could be profound. And where a developing country relies heavily on a single crop (as, say, Bangladesh once did on jute) employment effects, too, could well be traumatic. Moreover, such countries often tend to rely on earnings from agricultural exports to service their external debt; if this source of income disappears, or is severely attenuated, it may not be long before another debt crisis figures on the agenda of world economic summits.

Yet new products, awaking unexpected consumer demands, will also create entirely new markets and new trade. It is presently not possible to estimate all likely net results of the various trade-disturbing and trade-creating effects of biotechnology.

A marriage of technologies?

Molecular electronics and biochip technology are concepts which have arisen from discussions on how electronic or computer components could mimic living cell capabilities to store and retrieve information in a dense form. In the scientific community, there are proponents as well as sceptics

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1/ See Carl Wahren, "Family Planning Costs and Benefits", The OECD Observer, No. 155, December 1988/January 1989.

of the possibility of building a computer made up of proteins and other molecules functioning as electronic devices - and even the proponents do not believe that the possibility could become reality before many decades have passed and before totally new synthetic approaches have been developed. Nevertheless, in recent years, activities in the area of bioelectronics have intensified in several countries despite the technological obstacles. One reason for this interest lies in defence concerns: biochips, biocomputers and the information technologies based on them would not be susceptible to the impact of nuclear radiations. If, in the long term, the linking of biological and information technologies becomes possible, the resulting specific devices would be endowed with much higher capacities for information storage and processing than are possible with current information technologies. This breakthrough would influence economic and human activity more generally, and in ways which are presently difficult to imagine.

Ethics and acceptability

Public acceptance of, and confidence in, biotechnology may prove to be the main factor determining its rate of diffusion. The debate on the potential risks and benefits started long before any new products or processes were developed: it has already been going on for 15 years. The issues involve both the subjective attitude of the public towards biotechnology, which reflects a number of reactions - including emotional ones - and the acceptability of the technology according to scientific criteria approved by the scientific community.

Even where a product or process may be scientifically acceptable, therefore, a company could judge that public reaction to it may be unfavourable, with the result that management may prefer not to market the new product. Some companies have already taken that line of least resistance. Thus both rational and irrational responses could inhibit the diffusion of biotechnology.

There are four main causes for disquiet in the public perception of biotechnology:

- Ethical considerations about genetic modifications, especially in humans;
- Safety concerns about the introduction of modified micro-organisms into the environment, such as modified micro-organisms which would protect crops from frost damage;
- Fears about the (unfounded) reputation of biotechnology as an allegedly radical technology, with unpredictable and irreversible consequences;
- Worries that it may cause unemployment.

* * *

It can reasonably be expected that the increasing number of products arriving in the health and environment markets will influence public discussion in favour of biotechnology. Current developments in biotechnology may suffer delays because of public concerns, whether they are justified or not, and their more or less inevitable political exploitation. In the long term, however, mankind will not be able to solve its major health, environment and perhaps even food problems without the new exciting and steadily improving tools of biotechnology. After all, it is also one of the oldest and safest techniques mankind has known since prehistoric times, and to which it owes bread, wine and beer, amongst other things.

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B. COUNTRY NEWS

Argentina

The Argentine Forum of Biotechnology

The Argentine Forum of Biotechnology is a non-profit organization aimed at promoting research and development in Argentina. The Forum was set up on the inspiration of Dr. Luis Leloir, who was its president until his death.

Activities were formally initiated in December 1987 thanks to the initial economic support of a few national companies. Since then the number of corporate members has grown steadily. At present, there are 25 associated companies coming from different areas of biotechnology such as the dairy and food industries, the veterinary industry, the pharmacological industry, financial institutions, laboratory equipment suppliers, chemical industries and others.

The Administrative Board includes ordinary and extraordinary members, some of which are the presidents of governmental research institutions (i.e., National Institute of Agriculture and Cattle Technology (INTA), National Institute of Industrial Technology (INTI)) or promoting research activities (i.e., National Council of Scientific and Technical Research (CONICET), Secretary of Science and Technology (SECYT)). Associate members come from the scientific community and academic institutions (researchers, students).

The Forum publishes a bulletin three times per year, organizes scientific meetings, conferences and public seminars, and promotes contacts between the actors of technological development and relationships with international centres and biotechnology companies.

For additional information, please contact: María Marta McCarthy, Secretary, Foro Argentino de Biotecnologia, Avda. Callao 2115, 5to. piso F, (1022) Capital Federal, Argentina.

Foreign investment for the development and scale-up of alcohol production in Argentina

On 11 May 1988 the Board of Directors of the National Council for Scientific and Technical Research (CONICET) signed an agreement with the firm AGRIMONT (a limited company), the Agrochemical

Division of Montedison (Italia). The Pilot Plant for Microbiological Industrial Processes (PROIMI) was the executive unit from CONICET chosen for this company to carry out this kind of research. The research facilitiy is located in San Miguel de Tucumán, and will work on the scaling up of laboratory processes of alcohol production using Zymomonas strains isolated at PROIMI. The new strains have been successfully isolated and tested producing between 10-20 per cent of alcohol from carbon hydrate sources at laboratory scale.

Dr. Faustino Siñeriz, Director of PROIMI and the Scientific Director of the Project, pointed out two major objectives of this agreement:

First, the building of a pilot plant to carry out the process of alcohol production through these new bacterial strains in order to evaluate the technical feasibility and economical yield at the industrial level, and second, to study the use of the resulting waste produced by the method mentioned above. The objective of this second study will be to make use of residues, giving an overall economy in the energy required by the alcohol production process and to eliminate environment contamination to the maximum.

PROIMI s alcohol production process involves the use of bacterial strains locally isolated from native species of Zymomonas extracted from juices of sugar cane by a continuous feed process. This makes it very efficient from the point of view of the process and of the time employed. The main characteristic of these new strains is the capacity of flocculation, allowing the elimination of centrifugation due to the changing agent - the bacteria - which remains in the reactor.

After distillation of the alcohol from the supernatant there is a residue called vinaza which has a high contaminating power. It contains organic substances without fermentate which when discarded oxidizes to produce a high level of contamination. The second objective of this agreement is to evaluate the fermentability of vinazas through an anaerobic treatment to reduce the high level of contamination of vinaza. The amount of contamination of the final residues will be done by monitoring the chemical demand of oxygen. The natural gas produced by this way can be used to feed the distillation boilers or generators to produce electricity. The process described becomes interesting as it seems cheaper than the ones obtained from yeasts. (Source: Bulletin Foro Arg. Biot. 2(3), No. 26, 1989)

The Argentine-Brazilian Centre of Biotechnology

The Argentine-Brazilian Centre of Biotechnology - CABBIO - was officially inaugurated on 10 December 1986 in order to use present research and development capabilities in each country and carry out joint projects in scientific research and technological developments and related activities of common interest, using the already existing physical infrastructure.

CABBIO will receive US$20 million during the first five years of activity, each country contributing half this amount. Part of this fund will be used to finance research and development projects.

CABBIO has approved eight projects:

- Production of pre-basic material of potato seeds (minitubers).
- Production of monoclonal antibodies against human leucocyte antigens and for the detection of blood group antigens.
- Purification of human natural and recombinant gamma-interferon for use in human therapy: (1) Laboratory scale; (2) Pilot plant scale.
- Bordetella pertussis Component of tripple vaccines: development of new technologies for production and control.
- Production of fungus cells in semi-solid cultures and their industrial application.
- Production and propagation of virus-free plants in species of agamic reproduction, i.e. garlic.
- Application of cellular and molecular biology for the improvement of maize.

For more information, please contact: Secretary, CABBIO, Avda. Córdoba 831, 4to. piso, (1054) Capital Federal, Argentina, Telex 25272 SECYT AR. (Source: Bulletin Foro Arg. Biot. 1(2):16, 1988)

DNA points the finger at Argentina's past

Mary-Claire King, an epidemiologist, and Cristian Orrego, a biochemist at Berkeley's Museum of Vertebrate Zoology, have begun to take mitochondrial DNA from the blood of children living in Argentina.

During the "dirty war" in Argentina between 1976 and 1983, the military abducted and killed almost 10,000 people. Among the kidnapped were almost 200 children, who were eventually adopted by military families or their friends.

King has joined immunologists at the Durand Hospital in Buenos Aires to compare genetically determined markers in people's white blood cells with markers in the blood of their putative relatives. Knowing the prevalence of these markers in the general population, King and her Argentine colleagues can compute the chances of any matches being merely coincidental.

Some markers are very rare in the Argentine population. If they match, they provide hard evidence that the child is related. In one case, King found genetic markers in an adopted child that matched those of two different adult relatives. The chances that they were coincidental were 0.02 for one match and 0.005 for the other. King calculated that the likelihood of the child's being related was so unequivocal that it convinced the local court to return the child to his biological family. The "adoptive" parents were indicted.

Some 13 years have passed since the beginning of the "disappearances". With parents of the missing children gone and the grandparents now beginning to die, King can often find only one member of a putative biological family for an adopted child. In such cases, conventional methods of tissue typing are often inadequate.

Orrego and King decided that mitochondrial DNA might provide the link needed. It is easy to extract, has been completely mapped, and contains a segment that does not transcribe. That is, it does not create proteins or other substances needed by the body.

Thus the segment, known as the displacement loop or D-loop, has accumulated many harmless mutations. These mutations create variability in mitochondrial DNA from person to person, and, like whorls in fingerprints or the shapes of noses or lips, help to distinguish one person from another.

There is no mitochondrial DNA in sperm, so it passes from one generation to the next through the mother. Because it evolves at a rate only 2 to 4 per cent every million years, a child's version almost never varies from that of the mother, the mother's mother, or aunts, uncles, first cousins and other relatives on the mother's side of the family.

Until recently, only experts equipped with sophisticated and expensive tools could isolate enough DNA to scan it for variations, or polymorphisms, for matching relatives. Now, Cetus Corporation in the US has developed a technique, polymerase chain reaction (PCR), that will reproduce almost unlimited copies of a small stretch of DNA. Synthetic pieces of DNA are attached to the ends of a desired sequence and then allow polymerase, an enzyme that causes DNA to replicate itself, to copy that sequence.

The combination of PCR and mitochondrial mapping is simpler to use for identifying relatives than the DNA fingerprinting invented by Alec Jeffries of Leicester University in Britain.

Orrego's mitochondrial maps can link a child with a single maternal relative with a chance of error of only 0.001, says King. Orrego plans to try the technique in Buenos Aires within the next few months. (Source: New Scientist, 28 January 1989)

Australia

Centre for Molecular Biology and Biotechnology at the University of Queensland (CMBBT)

The Centre was formally established early in 1988. Its primary aim is to foster research in molecular genetics and applications of recombinant DNA and other advanced biotechnologies. The Centre's research activities cover such areas as cell and developmental biology, gene cloning and analysis, genetic and protein engineering, fermentation technology, downstream processing, and biocomputing, among others. These will involve not only the core resources of the Centre but also interdisciplinary interactions and research collaborations with various groups within the biological, physical and health sciences, in such areas as agriculture, biochemistry, botany, chemical engineering, medicine, microbiology, veterinary science, physiology and zoology. The Centre will be actively involved in information and technology transfer and has started publication of a Newsletter called The Restriction Digest which describes the activities of the Centre and news of appointments to the Centre and the services provided by the Centre. Copies of The Restriction Digest can be obtained from the Centre (Telephone: (07) 377 4447 or Fax: (07) 371 7588). (Source: ABA Bulletin, Vol. 4, No. 1, February 1989)

Guidelines for monoclonals

The Australian Drug Evaluation Committee has recently released the final Guidelines for the preparation and presentation of applications for general marketing of monoclonal antibodies intended for use in humans. This document will ultimately be published as an appendix to the Department of Community Services and Health NDFS Guidelines. Although this is a final copy of the Guidelines, the Committee is happy to receive comments on it as it regards change in this rapidly evolving area as normal. (Source: ABA Bulletin, Vol. 4, No. 1, February 1989)

International Depository Authority in Australia

The Australian Government Analytical Laboratories in Sydney have acquired the status of an International Depository Authority under the Budapest Treaty from 30 September 1988. At present, this Depository is unable to accept samples other than bacteria, actinomycetes, yeasts and fungi, other than known pathogens, which can be preserved by freezing or freeze drying. It has been suggested that, because of difficulties of importing samples into the US or Europe, an Australian facility which can accept viral, animal, plant, algal and protazoal etc., samples is urgently needed. It has been suggested, for example, that the University of Queensland should also become a depository institution.

In order for the Association to be able to advise the Department of Industry, Technology and Commerce on this matter, information is urgently needed as to the demand for deposits in Australia, and an indication of any difficulties which have been encountered in the past, and which are anticipated in the future, in making deposits in institutions overseas. Obviously, if a sufficient demand is known to be present, then the establishment of appropriate facilities in Australia is much more likely.

Comments should be sent to Dr. Brent Davey, Director, Australian Government Analytical Laboratories, 11 William Street, Melbourne 3000. (Source: ABA Bulletin, Vol. 4, No. 1, February 1989)

University of Queensland Microbial Culture Collection (UQMCC)

This collection contains some 4,000 cultures, including bacteria, fungi, yeasts, algae, viruses and cell lines. The UQMCC has the expertise, experience and infrastructure to handle a wide range of organisms, including bacterial and fungal pathogens, algae, genetic material and organisms containing recombinant DNA. With appropriate support, and in association with other University facilities, it could also handle viruses, animal and plant cell cultures and hybridomas. Acceptance is limited only by the ability to be preserved by generally applied methods.

The UQMCC has an established national and international reputation, is affiliated with the World Federation for Culture Collections and the Australian Federation of Culture Collections. It has been designated by UNESCO as a Microbial Resources Centre for biotechnology in Australia and the Pacific region, and is a node in the International CODATA/WFCC/IUMS Microbial Strain Data Network.

The UQMCC provides or has available a number of services for science, biotechnology and industry, including: the supply of a diverse range of cultures; reference cultures for Australian standard methods; safe deposit of industrially important strains and cell lines; long term preservation of cultures; and identification of bacterial cultures.

The strength of the UQMCC lies in its repertoire and the fact that it acts as a central facility for the establishment, maintenance and dissemination of microbial cultures for basic and applied research and development. (Source: ABA Bulletin, Vol. 4, No. 1, February 1989)

Human embryo experiment banned

The state government in Victoria has over-turned a decision to permit a controversial experiment on human embryos and one member of the committee to regulate in vitro fertilization (IVF) has resigned in protest. The experiment, designed to test human embryos for birth defects before implanting them in patients, would have been the first to involve embryos older than 22 hours.

The experiment was to have been carried out by the IVF research group at Monash University, headed by Dr. Alan Trounson. It would have involved the biopsy of 11 embryos that had been slow to grow. Trounson says that the experiment was approved unanimously by the committee.

According to Trounson, the government's intervention came in response to public pressure, provoked by newspaper reports saying that the experiment would lead to genetic engineering and cloning. (Source: Nature, Vol. 338, 6 April 1989)

Super shrimp

A super shrimp is being sought for the start of a major genetic breeding project by the Australian Institute of Marine Science (Townsville, Qsld). Specimens are being searched for along the Great Barrier Reef. The institute thinks the optimum shrimp will be larger than average, and have a small head, large tail and ravenous appetite. The experiment may take a decade before results are generated. (Extracted from Machine Design, 9 March 1989)

Austria

Austria pushes biotechnology R&D

Four Austrian majors have set up a biotechnology company to boost the country's research activities in the sector. The new concern, called Biotechnologische Forschungsgesellschaft (BTF), will have a research budget of Sch 16 million/year ($1.2 million/year).

OIAG owns a 22 per cent share of BTF, and Chemie-Holding, OMV and VAIG hold the remaining stake equally.

Research will focus on biomass, fermentation, biocatalysis, and plant genetic techniques.

Chemie-Holding predicts that $2.6 billion biotechnology market, will be valued at $65 billion by the year 2000. (Source: European Chemical News, 27 February 1989)

Brazil

New biotechnology centre established

The Federal University of Viçosa, in Minas Gerais, has recently organized a Biotechnology Centre Applied to Crops and Animal Science, called "BIOAGRO". It is composed of 70 researchers working in the areas of biological probes, biological associations, plant cell and tissue culture, plant molecular genetics, biological control and pheromones of pest insects, industrial fermentations and animal production. The FINEP - a governmental agency for financing projects - is building a 4,500 square metre building for the Centre which is scheduled to be completed by the end of 1989. The Centre is part of a State of Minas Gerais Program of Biotechnology - .IOMINAS - and is expected to be the largest Centre in the area of crops and animal science in Brazil. The FINEP is allocating about 4 million dollars for financing of different projects of the Centre, which is currently under the co-ordination of Dr. Maurilio Alves Moreira.

Canada

Plant biotechnology in Canada - a survey for the 1990s

The Plant Biotechnology Institute of the National Research Council of Canada initiated a national survey to assess the prospects for the 1990s as viewed by members of Canada's plant biotechnology community. Perceptions were solicited from individual community members through 621 nationally-distributed questionnaires and 32 on-site interviews. Sixty per cent of those surveyed responded. The responses were categorized into industry, university and government respondents with plant biotechnology activity and "other" respondents without plant biotechnology activity but active in another biotechnology area.

The survey showed a general consensus among plant biotechnologists in universities, government agencies and industry about prospects for the 1990s. However on some issues strong differences in outlook were noted. Also, biotechnologists with plant biotechnology activity responded differently than those without plant biotechnology activity. From the responses four recommendations emerged.

(a) **Strengthen Infrastructure.** Canada's plant biotechnology community has to prepare itself to deal with many dynamic and contentious issues; moral, ethical, regulatory, environmental, educational, and others. The formation of formal and informal cross-sectorial associations, groups and networks would strengthen the community's infrastructure. This could provide the necessary mechanisms needed to formulate, scrutinize, defend and champion policies, and ideas which may affect the community's direction and well-being.

(b) **Plant Breeders' Rights.** Parliament must be encouraged to pass Plant Breeders' Rights legislation as soon as possible. The plant biotechnology community should ask its professional associations and industrial organizations to discuss this matter with ministers, officials and individual Members of Parliament.

(c) **Regulatory Committee.** A cross-sectorial committee should be formed to examine regulatory issues surrounding the research and release of

genetically engineered plants. This committee should act both as an advisory group to the plant biotechnology community as well as to federal regulatory bodies concerned with these matters.

(d) **Manpower and Training Study.** A committee should be established to project the manpower requirements for each sector and make recommendations on how to meet these demands.

The survey questionnaire solicited perceptions on the prospects of the commercial opportunities in the 1990s. All respondents perceive a high commercial potential for crops genetically-engineered to improve their resistance to diseases and pests. Also, all respondents believe that tissue culture technology will be used for the production of reforestation stock by the end of the 1990s. The university and government respondents see applied and basic research as having a potential for a high return-on-investment while the industry and "other" respondents believe it to be applied research and product development.

Perceptions were solicited on interaction and information exchange in the plant biotechnology community. There is a consensus that the information exchange between researchers and users of plant biotechnology is inadequate and needs improvement. All respondents believe they will use their in-house laboratories for their plant biotechnology research. The industry respondents also indicated they will use federal government and university laboratories. The government and university respondents also indicated they will use each others' laboratories. None of the sectors foresee much use of Canadian private sector laboratories, provincial government laboratories or laboratories outside of Canada. Finally, government, university and "other" respondents indicate that the most suitable methods of interacting with outside research laboratories is through collaborative research with cost sharing and contract mission-oriented research. Industry indicated that they prefer technology transfer through licensing as well as contract mission-oriented research. (Extracted from Plant Biotechnology in Canada, published by the National Research Council of Canada, 110 Gymnasium Road, Saskatoon, Saskatchewan, Canada, S7N 0W9)

Canadian diagnostics company markets research products

ADI Diagnostics Inc., formerly Allelix Diagnostics Inc., has signed twelve agreements and is in the process of finalizing three others for the distribution of its products throughout Europe, the United States, India, South-East Asia and Japan. This is the culmination of 18 months of negotiations to place five diagnostic tests for infectious diseases in the global market by the end of 1989. The ADI Diagnostics test for Strep A is already marketed worldwide and another for detecting syphilis will be launched in the first quarter.

This distribution network marks the final phase of the restructuring of ADI Diagnostics Inc. into an independent company and a fully integrated manufacturer of medical devices.

ADI's products are based on proprietary developments in monoclonal antibody technology. To date the company has filed a total of 53 patent applications and been granted six patents on nine different devices and methods of diagnostic testing. Technical collaborations in Canada, the United States and Japan ensure the expertise will continue. Already second-generation products are in the development stages.

Initially ADI Diagnostics will target infectious diseases, particularly those spread through sexual contact where tests either do not exist or are slow and cumbersome for clinicians. ADI Diagnostics will be able to compete in world markets with more accurate technology adaptable to automation and appropriate for doctor's offices or clinics.

For instance, VISUWELL Strep A, ADI Diagnostics' first product, detects beta-hemolytic Group A Streptococcus. It is the cause of infections of the upper respiratory tract and skin in humans. Left untreated in children, a Strep A infection may lead to complications such as rheumatic heart disease.

Products scheduled for launch in 1989 include kits for gonorrhea, chlamydia and a revolutionary, direct antigen syphilis test which measures directly from the lesion for greater accuracy than conventional tests. In the United States alone 175,000 screening tests for syphilis are performed each day. The need for an automated system is acute. (Source: Company News Release, 10 January 1989)

AGC inoculants joint venture

Agricultural Genetics Co. (AGC) has formed its first overseas subsidiary with the formation of a joint venture with Canada's Rhizo Gen Corp, which produces and markets Rhizobium inoculants.

These products contain naturally occurring bacteria which improve the yield of legume crops by allowing them to utilize atmospheric nitrogen as opposed to fertilizer or soil nitrogen.

The venture will combine AGC's research and technical capabilities, with RhizoGen's manufacturing and marketing ability, and will primarily target the western Canadian market. (Source: European Chemical News, 10 March 1989)

Canadian site for HIV study

ICN Pharmaceuticals (Costa Mesa, CA) is starting up a three-year placebo-controlled, double-blind study on the effect of its antiviral drug, ribavirin, on human immunodeficiency virus, often a precursor of AIDS. About 30,000 Canadians are infected with HIV, according to the Royal Society of Canada, and ICN plans to include about 7.4 per cent of them in its research project. The company says it will determine whether ribavirin can slow or stop the advance of early-stage HIV to AIDS. The study will cost $7-10 million. (Source: Chemical Week, 15 February 1989)

Costa Rica

Costa Rican biodiversity

A consortium of 14 Costa Rican organizations responsible for biodiversity met in San Jose to try to formalize nascent plans for a National Biodiversity Institute. One goal of the institute would initially be to create a collection and catalogue of all the plant and animal species throughout the country, an inventory that would effectively represent something like 5 per cent of the world's biodiversity.

Costa Rican authorities have in recent years become enthusiastic about promoting conservation and ecological research efforts in their country. By the end of next year, little over 25 per cent of the country will be designated as national park land, in half a dozen locations. The parks are significant in a global ecological sense because they preserve not only major rain forest habitat but also stands of tropical dry forest. By comparison with tropical rain forest, which is endangered enough by any standards, tropical dry forest is virtually extinct. Agriculture and ranching have virtually obliterated this unique habitat from Central America.

Costa Rican conservationists are therefore attempting to preserve what remains of the dry forest and restore presently denuded habitat in other park areas, the most ambitious restoration effort currently being in the northwest, the Guanacaste National Park. Initially the inspiration of Daniel Janzen of the University of Pennsylvania, the restoration project is run by Costa Rican organizations and includes economic exploitation of park land. "There is no other way for conservation projects in the tropics to be successful", says Janzen.

The biodiversity institute would be necessary in co-ordinating the countrywide collection effort and the analysis and storing of specimens. Researchers from other countries would be funded to visit the institute, where they would contribute to identifying and cataloging species; and they would be free to take specimens back to their own laboratories for work on taxonomic problems of their choice. Travel and other support funds often limit what researchers currently can do in systematics.

Janzen estimates that the necessary funds - for building an endowed institute, making the collections, and working them into thorough national field guides and identified reference collections - would amount to about $50 million over 10 years. The impetus from within Costa Rica for a biodiversity institute is an outgrowth of the indigenous involvement in conservation and biological science by many organizations there. As a result, Costa Rica has become something of a model for tropical conservation efforts. Crucial to the ultimate success of this internal impetus, says Janzen, is the parallel growth of interest in biodiversity that is currently blossoming in the upper echelons of Government and industry in the Americas and in Europe.

Once Costa Rica's proposal for a National Biodiversity Institute becomes formal, the search for financial support will begin. (Extracted with permission from Science, Vol. 242, 23 December 1988, p. 1637, Roger Lewin. Copyright 1988 by the AAAS)

Denmark

Merger creates biotechnology giant

The Danish drug merger between Novo Industri and Nordisk Gentofte will result in one of Europe's biggest biotechnology companies with a value of about $1.3 billion, 50 per cent of world insulin sales, and a combined research portfolio with many promising products.

The alliance means that Novo-Nordisk, as the new company will be known, could have more efficient production and greater competitive clout in the world market, as well as enhanced R&D. Novo has a new genetically-engineered human insulin and Nordisk Gentofte has regulatory approval in several European countries and Japan for its genetically-engineered human growth hormone.

Although pooling resources the two companies will still be rivals in insulin, which accounts for about 80 per cent of Nordisk's sales and 40 per cent of Novo's. Both will also maintain competing ties with other companies in the US, Japan and the Federal Republic of Germany. (Source: Manufacturing Chemist, February 1989)

European Economic Community

Environmentalists react to EEC draft directive on deliberate release

The European Environmental Bureau (EEB), which represents a wide range of European environmental organizations in Brussels, has responded to the European Commission's draft Directive on the deliberate release to the environment of genetically modified organisms. Among the points made by the EEB are the following:

- The fact that the consequences of deliberate releases may transcend national borders, coupled with the widely different approaches adopted to regulation in different EEC member States, make it essential that the European Commission acts decisively in this area.

- Because modified organisms may give rise to risks to man and the environment, European Community legislation should be based on Article 130 of the Single European Act, which deals with the protection of man and the environment, not Article 100A, which seeks to ensure free circulation of goods within the European Community.

- Although the draft Directive is based on the Commission's earlier chemical regulations, the EEB argues, "our scientific understanding of ecology and genetics is not advanced enough to enable an empirical evaluation of the risks posed by genetically modified organisms in the environment". So there needs to be more funding for the relevant areas of environmental research.

- The deliberate releases already taking place in Europe, the EEB suggests, are premature. The potential ecological risks "are significant, any ecological damage done could be irreversible, there are no meaningful risk assessment procedures and the social implications of the technology are not taken into account".

- Transparency in decision-making will be a key requirement in decisions on whether or not to allow particular releases to proceed. "No application should be granted", the EEB argues, "unless the competent authority concludes that the proposed release will be environmentally benign and ethically, socially and economically desirable". It also argues that indirect impacts should be considered, including increased use of agricultural inputs and shifts in patterns of agricultural production.

- The scope of the draft Directive is too narrow. Products based on genetically

modified organisms, including pharmaceuticals, food and feedstuffs, and plants and animals used in agriculture should not, as currently specified in Article 8, be excluded from the requirements of the draft Directive. And the draft should be amended to cover the transport of genetically modified organisms.

- Competent authorities in all member States should be informed of any application to release a genetically modified organism which could feasibly move or be transported away from its site of release. In all such cases, the EEB insists, risk assessments should be carried out for all member States.

- Any person or body making a deliberate release of genetically modified organisms must be held strictly liable for any damage caused as a result.

Details from: Bureau Européene de l'Environnement, Maison Européene de l'Environnement, rue de Luxembourg 20, B-1040 Bruxelles or on + 32 2 514 12 50. (Source: Biotechnology Bulletin, Vol. 8, No. 2, March 1989)

Fear of 'neo-eugenics' hits Europe

The EEC plans to award molecular biologists 15 million European Currency Units (10 million pounds) to work on human genetics. However, the European Parliament has insisted that the programme be open to public scrutiny so that the results are not misused. The Parliament fears that without accountability, the programme will lead to unethical use of human genes and to "neo-eugenics".

The human genetics programme, as proposed by the European Commission, will co-ordinate the efforts of European scientists to identify where the estimated 100,000 genes to make up the human genome sit on chromosomes. A similar effort is under way in the US.

The US's National Institutes of Health has asked European scientists to participate in HUGO, the American human genome project. Bronwyn Loder, of Britain's Imperial Cancer Research Fund, helped to design the EEC's proposal. She says that a project to map the human genome is too big for one country alone to accomplish, and must be co-ordinated internationally.

In its first three years, the EEC programme aims to simplify the practice of mapping genes. It will help to pay to train European molecular biologists and improve techniques for sequencing genes and managing the resulting databases.

The first goal of the programme is to set up two networks of scientists in Europe. One network will develop a standardized "library" of cloned segments of human DNA. In the next six months, scientists in the working group organizing the programme will decide on a strategy for setting up the library.

The second proposed network, called Euclid, will group researchers working on the "linkage map" of the human genome. The closer genes are to one another on a parent's chromosome, the more often they are inherited together in the children. In very large families, with a large amount of mixing and matching of the same DNA, the frequency of such linkages can reveal the relative locations of genes.

A number of laboratories are now studying the DNA of 40 large families in the US, Europe and elsewhere, in a programme co-ordinated by the Centre for the Study of Human Polymorphism in Paris. The EEC's proposed programme will gather a further 20 families into the project.

The ultimate aim of the project is to use the data generated to predict which people are predisposed to which diseases.

The proposal states that heart problems, psychoses, cancer and other major diseases of the Western world result from the "exposure of genetically susceptible individuals to environmental causes".

Because environmental factors cannot always be changed, says the proposal, the study of genes should lead to the identification of "high risk individuals", to "protect [them from] illnesses to which they are genetically most vulnerable and, where appropriate, to prevent the transmission of genetic susceptibilities to the next generation".

Loder says that the programme could well benefit from strengthened ethical and legal safeguards, especially to prevent the misuse of genetic data by insurance companies. It will not aim to establish correlation between genes and disease in the first phase, she says. (Source: New Scientist, 4 February 1989)

Animals to be patented in Europe

Europe is preparing to make it easier for biotechnologists to patent animals, and other types of "inventions" that result from research in bioscience. The European Commission has decided to press for new patent laws so that biotechnologists in the EEC can rely on the same protection as do their counterparts in the US and Japan.

The European Commission has proposed to ministers a directive which stipulates that it will be possible to grant patents on living organisms "provided that a sufficient degree of human intervention has occurred". The directive makes it clear that the patent will extend to all subsequent generations of the animal, for the lifetime of a patent, which is 20 years.

This overcomes a key difficulty in patenting micro-organisms. Existing patent laws have a provision called "exhaustion of rights", which means that an inventor will be paid only once for the sale of the patented invention. This can cause problems when patenting micro-organisms. An inventor of a novel organism could sell it to a customer, who pays royalties, but the customer could subsequently breed the novel organism and sell further copies without having to pay extra royalties. The new directive aims to stop this.

A new law should make it less likely that one country in Europe would fail to respect a biotechnology patent granted in another state, which can happen now. The aim is to prepare for 1992, when all trade barriers in Europe disappear.

The existing international conventions on patent law were drawn up in the early 1960s, when biotechnology was in its infancy. As a result, countries have tended to adopt different interpretations of the conventions when applied to inventions in biotechnology.

In the US, the Patent and Trademark Office has already granted a patent on a transgenic mouse that has had oncogenes inserted to predispose the animal to breast cancer.

The new patent legislation will also allow inventors to patent genetically enhanced plants. The commission intends, for instance, to protect breeders of new strains of barley for brewing beer. No royalties would be payable for such beer. "But if a purchaser of the patented barley which was sold for the purpose of brewing beer, plants the barley and harvests a crop without authorization, the patent rights would not be exhausted", the commission says. (Source: New Scientist, 15 October 1988)

Federal Republic of Germany

FRG Biocentres identified

Several geographic areas in the FRG exhibit a strong concentration of biotechnology activity. Because of efficient public action on the part of certain regional authorities, private companies have been encouraged to set up and to develop in the vicinity of large cities, in particular Heidelberg, Braunschweig, Hamburg and Berlin.

These firms benefit from a dense scientific environment and have often been attracted by well-structured industrial parks.

The Braunschweig - Hannover area

As the German national centre of biotechnology, the Gesellschaft für Biotechnolgische Forschung constitutes a strong focus of attraction for biotechnology companies. It employs over 500 persons and collaborates with about 50 firms. The area regroups Bissendorf Biochemicals, Pharma Biotechnologie Hannover, Braunschweiger Produktion, Braunschweiger Umwelt-Biotechnologie, amongst others. Two projects are under way as regards bioparks: next to GBF, 4,000 m^2 laboratories are now under construction by an independent entrepreneur, and will be leased to biotechnology companies. Moreover, the city of Braunschweig has a project of a 120,000 m^2 biopark in the same zone. Recently established, the Medical Park Hannover is willing to attract firms operating in the bio-medical area. It is noteworthy that the American firm Invitron is now in the process of establishing a production facility in Hannover.

The Heidelberg Biopark

Created in 1985, this biopark benefits from the presence of excellent centres such as the European Molecular Biology Laboratory or the Max Planck Institutes. The park currently regroups most of the German new biotechnology startups (Gen-Bio-Tec, Orpegen, Progen, Fermigen, Denagen, International Biotechnology Laboratories). Large firms are not permitted, but often participate in the capital of these young biotechnology firms.

Hamburg

BMFT (Bundes Ministerium fuer Forschung und Technologie) and the city of Hamburg have decided to spend DM 200 million on high technology industry in Hamburg. More specifically, the intention is to foster collaboration between the Institute for General Botany and SME in plant selection. Moreover, DM 75 million will be spent on a common platform between the Neurobiology Centre and private concerns. Strengthening this neurocentre lies within the framework of making Hamburg the fifth "Gene Zentrum".

Berlin

Created in 1983, BIG (Berliner Innovations und Gruenderzentrum) was the first German initiative aimed at regrouping high technology firms. BIG expanded in 1985 through TIP, which has taken advantage of roomy buildings recently made available. Special financial incentives exist, and numerous biotechnology firms are present in Berlin (including Schering, Analyticon, Jenning, IAF, Aqua-Tek, and Mikro-Bak Biotechnik). Public research is well-developed in this city with the Institut fuer Ganbiologische Forschung, the first German gene centre, the Free University of Berlin, the Technical University of Berlin, the Max Planck Institut fuer Molekulare Genetik, etc.

Other centres are developing at Cologne, where a Gene Zentrum has been set up jointly by the Max-Planck-Institut fuer Zuechtungsforschung and the University of Cologne (the area also includes the Kernforschungsanlage in Juelich); Munich (Gene Zentrum); Stuttgart (biotechnology priority network). (Source: European Biotechnology Newsletter, 16 September 1988)

FRG establishes protein engineering base

Projects aimed at building a strong national framework capable of fostering the well-being of protein engineering are making progress in the Federal Republic of Germany.

On the one hand, the project for co-ordinating existing activities in protein engineering carried out in dispersed German research centres is expected to be approved soon by DFG (Deutsche Forschung Gemeinschaft). It is anticipated that the network will bring together about 20-30 research groups, and that a budget of DM2-3 million will be earmarked for this network.

On the other hand, the question now arises of establishing a national protein engineering centre, although this project is still at the discussion stage.

The significant role of the Gesellschaft fuer Biotechnologische Forschung in protein engineering should, however, not be overlooked. On top of setting aside a significant part of its total budget to protein engineering, GBF has been granted special funding to acquire protein engineering software and hardware over recent years, thus reinforcing GBF's position.

Major proteins engineered in FRG include: pancreatic secretory trypsin inhibitor, parathyroid hormone, interleukin 2, interferon beta PDGF, aprotinin, hirudin, Bowman-Birk inhibitor, semenal antimicrobial protein, synthetic antibodies. (Source: European Biotechnology Newsletter, 16 September 1988)

Biotechnology field test

The FRG's first experiment with a genetically altered plant is due to begin in May with the planting out of 37,000 manipulated petunias carrying

a "springing gene" which changes the colour of the blossom.

Although the project has not yet been officially approved by the federal health authority, the BGA, it has received the seal of approval of the central commission on biological safety (ZKBS), the scientific body that advises the federal government on the safety of genetic engineering projects.

A parliamentary committee studying the "Prospects and risks of genetic engineering" in early 1987, recommended a five-year moratorium on experiments with genetically-altered micro-organisms or plants outside the laboratory; an informal ban that has been upheld by science and industry in the absence of a framework law.

However, the federal health ministry has indicated that exceptions will be allowed. A spokesman for the BGA termed the experiment "low risk". The health authority generally follows the recommendations of the federal commission. (Source: Chemical Business, 20 March 1989 - 4 April 1989)

Genetic guidance

The FRG's federal cabinet has passed guidelines for a new framework law on genetic engineering. The law is currently being drafted by the federal health ministry and the Government hopes to have binding rules for both industry and science passed by the Bundestag by mid-1989.

In contrast to plans by the EEC to allow r-DNA projects to be approved within 60 days if local authorities do not object, the FRG Government favours a "thorough study of the risks".

However, the guidelines state that all projects meeting FRG construction and safety requirements have a right to be approved.

There is no mention of a public hearing for industrial plants working with r-DNA as set down in a law in effect since September 1988. However, federal states would continue to have the right to approve new projects, but would be obliged to consult federal authorities before approving or rejecting applications. The central commission on biological safety (ZKBS), which advises the Government on genetic engineering research projects, would also be established as a permanent body to judge on the safety of projects. (Source: Manufacturing Chemist, January 1989)

Firm plans biotech unit

Grunenthal GmbH, the FRG drug concern, has announced plans to build a plant for genetically engineered pro-Urokinase, produced from Escherichia coli bacteria, near its research headquarters in Aachen.

The company hopes to begin construction in autumn for completion in 1991. A public hearing, as required under the new terms of the fourth amendment to the FRG's federal emissions control law which came into effect on 1 September 1988, is scheduled for March 1989.

A spokesman for the pharmaceuticals producer said the company had purposely submitted its application after the September cut-off date in an attempt to allay public fears. Some opposition is expected, the spokesman added, but it is too early to say whether this would lead to delays.

Clinical trials on the drug, which the company is to recommend for use in the treatment of heart attacks, are already in progress. To bypass the FRG federal health authority, where registration can take as long as two years, the company says it will take its application directly to Brussels. Under a new EEC ruling, high technology biotechnology products can be approved in all twelve member countries simultaneously. (Source: European Chemical News, 16 January 1989)

Genetics plant opposed

Plans by Hoechst subsidiary Behringwerke to build a full-scale production facility at Marburg for erythropoietin (epo) produced from genetically altered mouse cells have hit a snag.

A public hearing on the project, under the new FRG law on genetic production plants, has been postponed indefinitely while state authorities study additional data on the safety of the plant.

The investigation by the state administration office in Giessen is directed at the possible threat to the environment and public health presented by the cell cultures imported from the US.

Behringwerke voluntarily subjected its plant to a public hearing, despite the fact that its application was filed prior to the September cut-off date. (Source: Manufacturing Chemist, February 1989)

Course on safe handling of genetically engineered organisms

The first course covering the safe handling of genetically engineered organisms has been completed at the DECHEMA Institute (Frankfurt). The course is designed for those with supervisory positions in industry, universities, technical institutes or other organizations, whose work entails various aspects of genetically altered organisms. All of the modules or only one may be completed depending on the person's interest and experience. The first module deals with the safe use of genetically modified material at the laboratory level, the second with the safety aspects of large-scale production processes and the third with various legal issues and federal and state laws covering biotechnology and industrial medicine. The FRG's Ministry of Research & Technology developed the curriculum. The course could eventually be offered to individuals who live outside the country. (Extracted with permission from Chemical and Engineering News, 5 December 1988, p. 31-33. Copyright 1988 by the American Chemical Society)

Hoechst continues

A court in Frankfurt rejected a prevention order filed by opponents to Hoechst's genetically engineered human insulin plant. The company still has to wait for overall approval for the complex.

Work on the three-phase insulin complex resumed last summer after the courts reinstated permits for operating the first stage, the experimental pilot

unit Fermtec, and building the second phase, a DM 70 million ($37.4 million) insulin unit Chemtec.

Local residents believe genetically engineered bacteria used to produce insulin could escape from the plant and cause environmental damage. (Source: European Chemical News, 20 February 1989)

Biogen wins interferon approval

The FRG's federal health authority has approved Biogen's genetically engineered interferon, sold under the trade name Polyferon. Used for treating rheumatoid arthritis, the drug will be sold under licence in the FRG by Biogen's joint venture partner Dr. Rentscher Arzneimittel. The 50:50 joint venture Bioferon Biochemische Substanzen will supply the product to Rentscher.

According to Bioferon, clinical studies with the gamma interferon drug have been encouraging. Around 50 per cent of the arthritis patients given the drug showed improvement and lasting improvement was seen in 40 per cent.

Bioferon holds an exclusive patent in the FRG for gamma interferon used in arthritis treatment. In the FRG the arthritis prescription drugs market is worth more than $500 million/year. (Source: European Chemical News, 6 March 1989)

France

Foetal cell transplant

Doctors have successfully performed the first transplant of human foetal cells to a living human foetus. The operation was performed on a male foetus diagnosed as having bare lymphocyte syndrome, a genetic immune system disorder that is almost always fatal. Immune cells from two aborted foetuses were injected into the patient's umbilical cord at 7 months into the mother's pregnancy in the hopes that early injection would improve the patient's chances. Additional injections were performed after birth. The patient, now 7 months old, has been confined to a sterile environment since birth, but may be able to leave his confinement bubble by the end of summer 1989 since the transplanted cells show signs of multiplying in the patient's bone marrow, liver and spleen (Extracted from Time, 3 April 1989)

Promising discoveries in myopathy research

Following the heels of the American discovery of the gene responsible for myopathy, the French research team of A. Kahn and J.C. Kaplan (National Institute of Health and Medical Research) have identified the genetic messenger (m-RNA) which acts as the link between the relevant chromosome and the production of dystrophine. The discovery was made thanks to PCR, a revolutionary technique which has also facilitated research in other genetic diseases, hepatitis B and AIDS. The French breakthrough may eventually permit scientists to perfect an efficient prenatal diagnostic test. (Source: European Science News, August 1988)

Mérieux proposes vaccines merger

France's Rhône-Poulenc aims to merge its human vaccines business - operated by its 50.5 per cent controlled subsidiary Institut Mérieux - with Connaught BioScience (Toronto) to create the biggest vaccine producer in the world. The proposed merger would result in a $275 million/year company with a 30 per cent worldwide market and a 20 per cent share of the North American market, says Igor Landau, president of Rhône Poulenc Santé, Rhône-Poulenc's pharmaceuticals division. Mérieux's key interest in the deal is the access it would provide to the North American market. An attempt by Mérieux to take full control last year was rejected by Connaught's shareholders and by the Quebec and Ontario Securities Commissions. (Source: Chemical Week, 14 March 1989)

India

Mérieux plans vaccine unit

Rhône-Poulenc subsidiary Institut Mérieux is planning to build what it believes to be the largest human vaccine production unit in the world. The French company has decided to locate the plant near New Delhi, India, so that it can exploit the huge Indian market.

A contract for the unit was signed during President Mitterand's recent visit to India. Construction of a laboratory will start in the next few months, and the whole unit will take up to five years to complete. The engineering contract has reportedly been awarded to France's Technip and local Indian companies.

The unit will be capable of producing 2 million doses of rabies vaccine from cell cultures, 50 million doses of injectable polio vaccine and 20 million doses of measles vaccine made from living cells. The first product to be manufactured will be the measles vaccine. According to Institut Mérieux, measles vaccines cannot be made in large enough quantities in India to fit in with the world vaccination plan for children because of a lack of facilities and technology.

The French healthcare unit will provide technology transfer for the New Delhi facility, covering manufacturing, quality control and training of Indian personnel. The French Government will provide special credit facilities so the Indians can buy necessary equipment for the new plant. (Source: European Chemical News, 13 February 1989)

HIV a problem for Indian blood banks

India is suffering from a wave of public alarm caused by news that human immunodeficiency virus (HIV) is increasingly being transmitted by use of donated blood. This development conflicts with the earlier belief that AIDS is being spread chiefly by prostitutes and foreigners.

Officials say that the Government can no longer postpone compulsory screening of all blood banks, a suggestion that only six months ago was dismissed as unnecessary as well as impracticable.

Last month alone, the All-India Institute of Medical Sciences in New Delhi discovered antibodies to HIV in three haemophiliac patients, and doctors in another hospital said that 10 of their 6,136 voluntary blood donors tested positive for AIDS. Of the 620 confirmed cases of HIV infection in India, about 60 have received blood transfusions in Indian hospitals.

According to the Indian Council of Medical Research (ICMR), which operates some 40 AIDS surveillance centres, blood transfusion has become an important mode of HIV transmission. An estimated

1.5 million units of blood are used each year in India, but ICMR's centres can perform only 30,000 tests, using kits imported from Britain. Complete blood screening would require a 100-fold increase in the number of kits. Although ICMR feels that all donated blood must be screened, the job "cannot be done overnight".

As a first step, all donors in Bombay and Madras are now being screened, and experience from these cities will be used to start screening in other cities in about a year, by which time India hopes to be producing its own test kit. (Source: Nature, Vol. 337, 26 January 1989)

Ireland

Insulin plant for Cork

Nordisk Gentofte A/S, recognized worldwide for the production of high quality insulin, plans to begin production within two years at a specially built plant in Ringaskiddy. This is the foundation's first manufacturing investment outside Denmark and it intends to utilize new developments in biotechnology to produce insulin through a yeast fermentation process, similar to that used for brewery fermentation. The first phase of the Cork plan involves an investment of over 11 million pounds sterling in the first three years with expected build up to more than double this in five years and with a consequent growth in employment from an initial 40 people to 100.

The process to be used in Cork is expensive but is in keeping with Nordisk's emphasis on quality. The third largest insulin manufacturer in the world it is the only company concentrating on producing human insulin and insulin from pork pancreas alone. It stopped the production of beef insulin 20 years ago because of its tendency to provoke immunological side effects. (Extracted from Technology Ireland, November/December 1988)

Japan

Consensus elusive on genome plans

A Japanese government project had been running since 1981 with the aim of developing an automated process capable of sequencing more DNA in a single day than is now sequenced worldwide in a year.

The goals initially set for Japan's project have proved elusive, however, and they have recently been considerably scaled back. Moreover, there appears to be no consensus about whether Japan should pursue a more vigorous effort, or what the country's role should be in an international genome project.

A report issued in January by an advisory group to the Ministry of Education, Science, and Culture (Monbusho) endorsed the concept of sequencing the human genome and argued for international collaboration. Last year, the Science and Technology Agency issued a similar statement. But neither agency has offered specific proposals.

Japan's efforts have been hampered in part by a lack of good molecular biologists. Japanese biologists are also worried that a major commitment by the Government to decipher the human genetic code will divert money from their individual work, echoing a concern that has been voiced by some American biologists.

Meanwhile, the Government's biggest effort related to sequencing - the project aimed at developing high-speed automatic sequencing technology - is continuing The Science and Technology Agency initiated the project in 1981, selecting Akiyoshi Wada, a biophysicist at Tokyo University who will become dean of the Faculty of Science, to conceptualize and direct the effort.

Wada's ultimate aim is to make the decoding process an assembly line operation. A snip of DNA would be inserted into an automated system that links a variety of different machines to perform the repetitive, complicated procedures involved. At the end of the line, the system would print out the string of bases of the deciphered gene. Operating the process would require a minimal amount of scientific input, which would free scientists' time for more creative activity.

While the automation project continues, various government agencies in the past year or so have undertaken some interesting new projects related to sequencing. Monbusho is sponsoring an effort to sequence Escherichia coli.

Some scientists advocate linking a human genome project with the Huam Frontiers Science Programme, an international collaborative effort in basic science proposed by Yasuhiro Nakasone while he was Prime Minister. The programme is now just getting started. As originally conceived, the Human Frontiers programme would have included work in sequencing. But over the years, the focus has shifted to brain science and other areas of molecular biology. (Extracted with permission from Science, Vol. 243, 31 March 1989, p. 1656-1657, (Marjorie Sun). Copyright 1989 by the AAAS)

Bioherbicide joint venture

Mycogen Corp., San Diego, California, has agreed with JT Biotech USA Inc., a US subsidiary of Japan Tobacco Inc., to form a US partnership to jointly develop and commercialize bioherbicide products worldwide.

Mycogen develops and commercializes biopesticides for control of insects and weeds. Japan Tobacco Inc., headquartered in Tokyo, is the dominant supplier of tobacco products in Japan with total annual revenues of $22 billion.

Mycogen and JT Biotech will collaborate through the partnership to develop bioherbicides based on or derived from naturally occurring micro-organisms which are pathogens of specific weeds.

Mycogen will expand its bioherbicide research and development activities at its laboratories in San Diego and Ruston, La. Research and development will also be carried out at JTI's Yokohama laboratory focusing on problem weeds in Japan. JTI will have access to Mycogen's existing bioherbicide technology, and the companies will share new technologies in carrying out efforts to develop products for their respective markets. (Source: Chemical Marketing Reporter, 13 March 1989)

Synthetic CD derivatives developed

Akira Harada's research group at Osaka University has synthesized cyclodextrin (CD) derivatives that have properties similar to those of antibodies. Cyclodextrins are circular polymers of glucose that can be used as carriers for drugs and

other molecules since they have hollow, relatively hydrophobic centres. The synthetic CDs are bifunctional: they can recognize and bind specific molecules ("antigens") and - similar to real antibodies - become cross-linked and clump together or precipitate from solutions upon binding multivalent "antigens". These bifunctional CDs may be useful in sensors to detect specific molecules in solution or to remove harmful molecules from the blood. (Source: Bio/Technology, Vol. 7, February 1989)

Musk oil synthesized

Musk oil (together with sperm whale ambergris) is one of the most expensive ingredients in perfume. In fact, this scent is becoming more valuable all the time: there has been a dramatic decline in the population of musk deer, which once ranged through China and Central Asia; moreover, a single male deer yields only 30 grams of musk oil. Now, scientists at Nippon Kogyo Inc. (Tokyo), which produces petroleum and non-ferrous metal, have developed a method for synthesizing musk oil from petroleum products. Normal paraffin (isolated from petroleum) is fed to a special strain of yeast (isolated from an oil field in Akita Prefecture), which converts it to cyclopentadecanone, the substance that gives musk oil its unique odour. (Source: Bio/Technology, Vol. 7, February 1989)

Artificial vegetable seeds

Scientists at Kirin Breweries (Tokyo), working in collaboration with researchers at Plant Genetics, Inc. (Davis, CA), have developed "artificial seeds" that produce whole celery and lettuce plants. Mass-production of artificial seeds will aid the development of new strains of commercially important plants by allowing growers to raise large numbers of first-generation plant hybrids. Artificial seeds consist of tissue derived from plant embryos or shoots, encapsulated in alginate with growth nutrients.

Several innovations underlie this success. Large quantities of plant tissue are produced by growing celery or lettuce callus in cultivation tanks. From a single gram of callus, the scientists raise enough tissue for 10 million celery seeds or 100 thousand lettuce seeds in a period of six months. (Conventional methods produce only 200-300 sprouts per gram of callus in six months). The scientists also developed a high-speed encapsulation device. In a recent test, 20,000 artificial seeds grown under carefully controlled conditions sprouted with approximately the same speed and efficiency as natural seeds. The next step will be to test the efficiency of the artificial seeds' growth under ordinary field conditions. (Source: Bio/Technology, Vol. 6, November 1988)

Biodegradable plastic

Researchers at the Tokyo Institute of Technology have developed a method for synthesizing plastics using bacteria. The plastics, which can vary in elasticity, are biodegradable: they are completely detroyed after being buried in soil for six weeks. Developed by Yoshiharu Doi, the method uses hydrogen-fixing bacteria to convert 4-hydroxybutyric acid to polyesters, which accumulate in large amounts inside the bacteria under the proper culture conditions. Scientists extract the compound with chloroform and add methanol to precipitate it as a white powder. The polymer is gum-like and very elastic when 40-50 per cent 4-hydroxybutyrate is used. Plastics of varying degrees of hardness can also be synthesized by using 1,4-butanediol.

The fact that the plastic is biodegradable may make it suitable for use in slow-release containers for pesticides or fertilizers. The bioplastics are also highly compatible with human tissues, and may find medical and cosmetic applications. (Source: Bio/Technology, Vol. 7, January 1989)

Mexico

Mexican research centre closed

An internationally known research centre dedicated to the study of Mexico's tropical ecology has been dismantled, a victim of the economic crisis that is squeezing indigenous research throughout Latin America.

The National Research Institute for Biotic Resources (INIREB), based in Xalapa in the state of Veracruz, supported an extensive botanical garden and compiled one of the largest herbaria in Mexico as well as unique collections of native fauna. The centre also funded research in basic and applied ecology, and worked to transfer environmentally sensitive practices to Mexico's poor farmers. At its closing last year, the institute had an annual budget of about $3.5 million, employed 100 scientists and technicians, and maintained a network of regional research centres scattered throughout Mexico.

In recent years, however, the institute floundered somewhat, burdened by union strife, a bloated bureaucracy, and the pressure to support large programmes with less money, according to sources inside and outside of Mexico. INIREB was officially closed in November, on the last day of the outgoing administration of former President Oscar de la Madrid.

The institute's famous garden and herbarium will be taken over by the National Institute of Ecology, which is moving its headquarters from Mexico City to Xalapa in April. But the fate of many INIREB scientists and their research projects remains unclear. The graduate students of INIREB are left wondering where they will complete their educations, since the Institute of Ecology cannot issue diplomas or academic degrees. (Extracted with permission from Science, Vol. 243, 31 March 1989, p. 1654, W. Booth. Copyright 1989 by the AAAS)

The Netherlands

Mogen wins funds

Dutch plant biotechnology concern Mogen International is to receive funding from the Dutch Ministry of Economic Affairs for two of its projects. The ministry has implemented a ruling to stimulate Dutch-based innovation by granting subsidies.

One of the ministry-backed projects is aimed at obtaining breeding rights for genetically modified potato varieties conducted in co-operation with the government institute for research on varieties of cultivated plants.

The second project concerns the development of a genetically modified potato as an economic production system for high value industrial and pharmaceutical proteins. It will be carried out in co-operation with the Dutch potato starch and derivative company Avebe. (Source: European Chemical News, 21 November 1988)

Sweden

New system to synthesize DNA

Sweden's Pharmacia has developed a new system for synthesizing DNA, which it claims will make life easier for researchers working in the field of recombinant DNA technology, diagnostics and plant breeding. The unit has been developed jointly with LKB Biochrom, of Cambridge, UK, and can be used for studying and developing gene structures and as a tool for developing new biotechnological products. (Source: European Chemical News, 13 February 1989)

Thailand

Reforestation problems

Environmentalists say reforestation using eucalyptus trees is counterproductive due to the damage done to soil and water springs. Even though Thailand has recently suffered from floods stemming from a lack of trees, peasants are ripping out eucalyptus seedlings and burning down tree nurseries. In 1950, about 66 per cent of the country was covered by forest. Much of the forest has been lost to illegal logging, clearing for farm land, and a campaign by the Government in the mid-1970s to fell trees being used as hiding places by insurgent guerrilla forces.

After experiencing a devastating flood in November 1988, the Government has been persuaded to ban logging and the Royal Forestry Department is considering restoring tree cover to 40 per cent of the nation's land. Because the Government cannot handle reforestation on its own, private interests are being invited to take part. However, their primary concern is monetary, and the eucalyptus produces quick earnings. The tree can be harvested in as little as five years, can thrive on poor soil, has a high germination rate and is resistant to pests. The Government is actually encouraging the use of eucalpytus trees by offering a per-acre subsidy to growers. Villagers vow to continue their fight against the trees, which they say destroy their farmland. (Extracted from Wall Street Journal, 14 February 1989)

United Kingdom

Co-ordination of biotechnology

Four research councils are involved in UK biotechnology: the Agricultural and Food Research Council (AFRC), the Medical Research Council (MRC), the Natural Environment Research Council (NERC) and the Science and Engineering Research Council (SERC). The four Councils co-ordinate their programmes through the Biotechnology Advisory Group (BAG).

BAG was established by the Councils in 1987, under the chairmanship of Prof. Roger Whittenbury (Department of Biological Sciences, University of Warwick). The Group advises the heads of the Councils and has a particular interest in strategies for the optimal future development of biotechnology research. Each of the four Councils is represented on BAG and there is an equal number of independent members with expertise in various areas of biotechnology, including representation from industry.

In its recent discussions, BAG has identified protein engineering as a key field for investigation and a working party, including representatives from the Department of Trade and Industry, which was set up to consider the possibility of a nationally co-ordinated programme of research, has recently reported to BAG. The heads of the Research Councils have accepted the importance of this area and are hoping to participate in the LINK programme in protein engineering, as well as to increase their support for basic and strategic research.

Another need recently identified by BAG is for easier retrieval of information on the training of research students in particular areas of biotechnology. The heads of the Research Councils are currently considering how this can be achieved, with the possibility of a joint studentship data base for all areas of research training including biotechnology. (Source: Biotechnology Bulletin, Vol. 7, No. 11, December 1988)

Report proposes future SERC support for biotechnology

A major review of the Science and Engineering Research Council's support for biotechnology over the last seven years has been carried out by a panel under the chairmanship of Prof. T. Blundell, FRS, of Birkbeck College. SERC set up the panel in January 1988 to review the work of the SERC Biotechnology Directorate - and advise on SERC's future role and activities in this area. The main conclusions are that:

- The Biotechnology Directorate has made significant achievements in support of biotechnology research and should maintain a biotechnology programme;

and that SERC should:

- Support a biotechnology programme through a separate Biotechnology Directorate for a further six years to 1995, with its position to be reviewed in 1994;

- Plan for an increase in staffing to allow the essential enhancement of strategic planning and the co-ordination of the managed programme;

- Co-operate with the Department of Trade and Industry (DTI) in the formation of a joint advisory body for biotechnology, under a single overall director;

- Continue active involvement in the Biotechnology Advisory Group, and any other activities needed to ensure good co-ordination with the other Research Councils, including cross membership of committees.

Copies of the report can be obtained from The Biotechnology Directorate, Science and Engineering Research Council, Polaris House, North Star Avenue, Swindon SN2 1ET.

The second corporate plan produced by SERC spells out the Council's strategy for the funding of

research in science and engineering and of manpower training. In the three years since the publication of the last plan, research grant expenditure has risen from 28 per cent to 33 per cent and the Council wishes to raise this percentage to 40 per cent by 1991-1992.

In addition to biotechnology, fields earmarked for high priority are: novel materials; optoelectronic processing systems; the exploitation of information technology in engineering; the underlying computer science of software engineering; molecular sciences; polymer science and technology; the understanding of atmospheric processes; the application of new parallel processing architecture; and the improvement of the understanding of cognitive processes. (Source: Biotechnology Bulletin, Vol. 8, Nos. 1 and 2, February and March 1989)

Law to contain engineered organisms

By the end of the year, the UK will have a law controlling the release of genetically engineered organisms into the environment. At present, researchers have only a list of voluntary guidelines to follow if they want to experiment with transgenic animals and plants outside the laboratory.

William Jones, a senior administrator at the Health and Safety Executive (HSE) which, as the watchdog on occupational safety, is also concerned with genetic engineering, predicted that the Government would introduce legislation towards the end of the year. He said that the legislation would probably take the form of a statutory instrument to extend the existing rules governing the safety of research using potentially dangerous micro-organisms.

The law would force researchers to notify the HSE of planned experiments outside the laboratory 30 days before the work began. The legislation would also include measures to ensure that scientists undertake studies to assess the risks that would be involved in releasing a genetically engineered organism into the environment.

The HSE has already sent out a consultative document to interested parties that outlines the sort of measures that the Government could bring to the statute book. The principal benefits of legislation the document says, are to reassure the public, and to continue to oversee genetic engineering as it moves out of the laboratory. (Source: New Scientist, 28 January 1989)

Genetic toxicology guidelines revised

Revised guidelines on genetic toxicology testing are to be published later this year by the UK Committee on Mutagenicity. The main change from the CoM's previous guidelines, issued in 1981, will be that for chemicals to which humans are not going to be exposed at high or moderate levels for long periods, such as pesticides, there will no longer be a requirement for an in vivo mutagenicity test, provided that three standard in vitro tests are all negative. For chemicals to which humans are more exposed, such as food additives and pharmaceuticals, the CoM is still recommending in vivo mutagenicity testing.

The change reflects a change in philosophy in the CoM. Genetic toxicologists no longer expect, as they did a decade ago, that in vivo tests will pick up mutagens that cannot be detected by a good battery of in vitro tests.

The three basic in vitro tests are a bacterial mutagenicity test (e.g. Ames), and two mammalian-cell assays, for chromosomal aberrations and gene mutations. If any of these are positive, then the CoM does recommend conducting a couple of in vivo tests for chromosome damage in bone marrow cells. If either of these is also positive, the chemical's development is likely to be abandoned. If they are negative, then the CoM recommends further tests that are not as yet routine. (Source: Chemistry and Industry, 20 February 1989)

New NERC centre to focus on deliberate release

A new Interdisciplinary Research Centre (IRC) in population biology is to be established at Imperial College, London, according to the Natural Environment Research Council (NERC). The IRC will be located at Imperial College's Silwood Park campus, already an international centre of expertise in ecology, and will be linked with the Population Genetics Group at University College, London, the NERC Sea Mammal Research Unit at Cambridge and other NERC institutes.

Problems that will be tackled by the IRC include the release of species, such as genetically manipulated organisms, into the environment; the effects of pollutants on populations; the conservation of species and restoration of habitats; the harvesting of renewable resources; and the control of pests and infectious diseases. A key IRC facility will be building housing a number of highly sophisticated chambers in which environmental conditions can be closely controlled and which will allow, for the first time, the creation of simple terrestrial communities within the laboratory.

Prof. John Lawton, currently at York University, has been selected as director. Details from: Natural Environment Research Council, Polaris House, North Star Avenue, Swindon, Wiltshire SN2 1EU or on 0793-411561/411708. (Source: Biotechnology Bulletin, Vol. 8, No. 1, February 1989)

Human genome project

The Clinical Research Centre (CRC) of the Medical Research Council (MRC) has been chosen as the hub of Britain's part in mapping and sequencing the human genome. CRC will house a resource centre responsible for assembling and distributing data bases and DNA libraries as well as for substantial technical developments, both in computing and sequencing.

The planners hope their decision will also attract the administrative centre of the Japanese Human Frontiers Science Programme and the European office of the Human Genome Organization (HUGO)to the same site at Northwick Park in north London.

MRC's decision follows the British Government's allocation of extra research funds for the next three years, of which 11 million pounds sterling has been earmarked for the genome project.

MRC plans to guide the overall direction of British human genome research by a co-ordinating committee and a scientific advisory board, whose priorities will influence which projects it finances. The board will be much like that which, since 1987, has co-ordinated the human genome interests of MRC and the Imperial Cancer Research Fund (ICRF).

ICRF, which has been keen to bid to provide the MRC resource centre with a DNA probe bank, has developed a particular interest in the European Community project and is also a partner in the EUREKA project to automate DNA cloning and sequencing. (Source: Nature, Vol. 338, 9 March 1989)

Plant genome mapping

Five European seed companies will help UK plant scientists complete restriction fragment length polymorphism (RFLP) maps of wheat and barley, Europe's two major cereal crops. In return, over the next three years the companies will gain sole access to new RFLP probes and the maps they generate.

The deal has been negotiated in the form of license agreements by Agricultural Genetics (Cambridge, UK), which is exercising its right of first refusal to exploit biotechnological research at the Agricultural and Food Research Council's Institute of Plant Science Research (IPSR) in Cambridge.

According to Mike Gale, head of the Cereal Research Department at IPSR, the RFLP maps of both wheat and barley should be close to completion by the end of the three-year license period.

Conventional mapping has already placed about 20 genes on each barley chromosome, but nearly all the genes are recessive, and of no use to the breeder. Far fewer wheat genes are mapped at present, but those that are tend to be useful. To the five genes already mapped on wheat chromosome 7, the IPSR scientists have now added 18 RFLPs, which should greatly assist the mapping of additional genes.

Making RFLP maps of wheat and barley will progress in parallel. Wheat arose only 10,000 years ago, and so there has been little outbreeding of the plant. Because it has three times as many chromosomes, and less of the variation in DNA sequence that enables RFLPs to be found, making RFLP wheat maps will be more difficult.

IPSR's stocks of wheat - each lacking one pair of the 21 chromosomes - and other stocks that carry single barley chromosomes will greatly aid the RFLP mapping process. (Extracted from Bio/Technology, Vol. 7, March 1989)

New research centre

Chemists at the University of Exeter, together with microbiologists and biochemists at the Universities of Warwick and Kent, have formed an inter-university Biotransformations Centre. Supported equally by public and private funds, the centre will develop the potential of enzymes and micro-organisms as substitutes for traditional synthetic techniques used in the chemical and pharmaceutical industries.

In particular, university scientists are seeking to establish the advantages of enzymes in the production of optical isomers of complex organic compounds. By working in "reverse," they will also explore using enzymes that normally break carbon-carbon bonds to synthesize them instead. A third focus will be on oxidases and dehydrogenases - enzymes involved in oxidation and reduction.

The precise nature of the centre's core projects is as yet not revealed. Seven were chosen from 20 put forward to a management committee on which all the industrial sponsors sit. The 10 sponsors - including Glaxo, Beecham (Brentford, Middlesex), ICI (London), and Shell (London) - have each agreed to pay $80,000 towards the projects over three years: Matching funds are provided by the Department of Trade and Industry and the Science and Engineering Research Council on a 50:50 basis.

Companies are also free to sponsor postgraduates or postdocs to work on specific, confidential projects supported by matching public funds. In all, the Biotransformations Centre - which has been set up under the UK Government's LINK scheme to encourage collaboration between industry and universities - already has been guaranteed about $1.8 million for its first three years. (Source: Bio/Technology, Vol. 7, January 1989)

Britain backs work on HIV-2

The Medical Research Council in Britain may award a grant of almost a quarter of a million pounds to its unit in the Gambia, West Africa. If approved, the grant will buy new equipment and support preliminary research to establish a test for infection with HIV-2, the second human immunodeficiency virus.

The unit, one of the most technologically advanced and sophisticated research facilities in Africa, began work on HIV-2 in 1986, when scientists first identified the virus in the Gambia. HIV-2 is found mainly in a belt of sub-Saharan African countries that stretches from Senegal to the Central African Republic.

Researchers at the unit in the Gambia have completed a one-year study of the pattern of HIV-2 infection in the country. They have asked for a further 200,000 pounds sterling over two years. (Source: New Scientist, 25 February 1989)

AFRC and Edinburgh University join forces on transgenic animal biology

A 10-year research programme on transgenic animal biology has been announced by the Agricultural and Food Research Council (AFRC). The Centre will focus on basic research on how genes work in animals and how they are controlled. It will also work on such techniques as gene manipulation and gene transfer between species.

The new Centre will be established in conjunction with the Edinburgh Station of the AFRC Institute of Animal Physiology and Genetics Research. Close collaboration is also envisaged with the Medical Research Council's Human Genetics Unit and with the Scottish Agricultural Research Units. The Centre will build on the strengths of the University in agricultural, biomedical and veterinary sciences.

The Centre brings together groups in Edinburgh already working on gene transfer in animals. One of these, funded by AFRC, has recently bred sheep that produce Factor IX in their milk, the human blood clotting factor required by haemophiliacs. A company, Caledonian Transgenics, has been set up to market such products. (Source: Biotechnology Bulletin, Vol. 8, No. 2, March 1989)

Cranfield Biotechnology Centre leads "in-body" microsensor consortium

The Biotechnology Centre at the Cranfield Centre of Technology has been chosen by the Commission of the European Communities to lead an 11-country, 25-centre consortium established to investigate the use of chemical microsensors within the body. Dr. Tony Turner, head of the Bioelectronics Division at Cranfield, will head the consortium.

The idea behind in vivo chemical sensors is that they should operated within the body of the patient, in contrast to ex vivo sensors which require the delivery of the substance for analysis to a sensor outside the body.

This action was initiated by the Biomedical Engineering Committee for Concerted Action (BME COMAC), which falls under the auspices of the Directorate General XII. Following an expert meeting and workshop in 1988, at which 35 experts from all EEC member countries met to discuss the interface between biology and sensors, it was concluded that a Concerted Action proposal should be pursued.

To begin with, the work - for which the EEC has provided initial funding - will focus on the analysis of the clinical problems, identify suitable analytes and consider sites within the body suitable for continuous monitoring.

The Cranfield Bioelectronics Division is involved in the development of a wide range of biosensors. For example, it is working on biosensors based on intact micro-organisms, including carbon monoxide sensors, herbicide monitors and antibiotic screening devices incorporating micro-organisms. These systems attempt to use the specificity of biocatalysts, whilst avoiding the comparative instability of the respective isolated enzymes.

A new pen-sized glucose biosensor has recently been launched on the market by Baxter Travenol. The technology is based on a ferrocene-mediated amperometric glucose oxidase configuration invented jointly by Cranfield and Oxford University. (Source: Biotechnology Bulletin, Vol. 7, No. 12, January 1989)

ICI to expand its biotechnology business

In a drive to expand and diversify its operations, ICI Biological Products is concentrating its efforts on fermentation. The company is installing a multipurpose unit in Billingham, which together with associated harvesting facilities will cost up to $20 million. Completion is planned for the middle of next year.

The decision points to the changing profile of the chemical industry in general and of ICI in particular.

Biodegradable plastic, for instance, could become commercially significant in the light of growing concern over the environmental impact of plastic waste.

ICI Biological Products emerged recently as a spin-off from ICI's former agricultural division. It will draw on the fermentation experience gained from production some years ago of single-cell protein as an animal feed supplement. (Extracted with permission from Chemical and Engineering News, 13 February 1989, p. 38, by Dermot O'Sullivan. Copyright 1989 by the American Chemical Society)

Joint venture for commercialization of collagenase inhibitors

British Bio-technology Limited, the UK-based health science company, announced its signing of a licensing agreement with SmithKline Beckman Corporation for the development and commercialization of collagenase inhibitors as new treatments for arthritis.

The human enzyme collagenase is a protein responsible for bone and cartilage destruction in the joints of sufferers of rheumatic and osteoarthritis.

The two companies have been engaged in collaborative research in the field of arthritis since entering a research and development agreement in late 1987.

In this latest collaboration, British Biotechnology's chemistry department has been designing and building collagenase inhibitors. The properties of these potential new drug molecules are currently being tested at SmithKline's pharmaceutical R&D laboratories in Upper Merion, Pa. (Extracted from Chemical Marketing Reporter, 20 March 1989)

BTG microcarrier

UK technology transfer organization, British Technology Group (BTG) is seeking firms to test and/or produce a new type of microcarrier that can increase yields of biotechnology products. BTG has recently obtained a patent for the microcarrier, trademarked Cellfast and invented by scientists at Queen's University, Belfast.

Using the microcarrier, scientists have achieved a 74 per cent increase in virus yields. (Source: European Chemical News, 27 February 1989)

United States of America

US EPA's deliberate release rules

The US Environmental Protection Agency's long-awaited rules governing the deliberate release of genetically engineered micro-organisms may not see the light of day for some time. Environmentalists note that outgoing EPA administrator Lee Thomas failed to get the rules through before he left office in the Bush reshuffle.

The rules were opposed by the Office of Management and Budget (OMB) as over-restrictive and burdensome for the biotechnology industry. They were intended to support the co-ordinated framework established in 1986 by the White House's Biotechnology Science Co-ordinating Committee. Organizations like the National Wildlife Federation and the Environmental Defense Fund feel it is unlikely that incoming EPA administrator William Reilly will fight for the rules in the near future. The battle is now likely to shift to Congress, where various Congressmen appear willing to draft bills to give the EPA stronger regulatory authority over industry.

Meanwhile, the Industrial Biotechnology Association (IBA) has criticised the draft biotechnology regulations produced by the EPA - under the Toxic Substances Control Act - as "seriously flawed" and "based on unfounded, dramatic environmental fears". The IBA is focusing on three key issues: the scope (types of organisms subject to review and when they would be reviewed) of the

EPA's latest draft: the data and information necessary to support an assessment of the potential for human health and/or environmental risk associated with small-scale testing; and the utility of Environmental Biosafety Committees. The EPA is seeking additional public comments on its proposed regulations on development of biotechnology products under both the Toxic Substances Control Act and the Federal Insecticide, Fungicide & Rodenticide Act. According to the agency, a number of basic issues have arisen since it began developing these rules in 1986. The proposed rules have not been published in the Federal Register yet because of difficulty in getting them cleared by the Office of Management & Budget. There are seven specific issues to be addressed, EPA says, including the scope of micro-organisms subject to review and regulation and the use of independent groups of experts in the review process.

The Association of Biotechnology Companies (ABC) agrees, describing the draft regulations, which cover industrial and environmental uses of micro-organisms, as "overburdensome" and "excessive". The ABC underscores to the recent experience of the biotechnology industry in the FRG. Under a 1988 law there, any biotechnology production plant that uses any type of genetically engineered cell must disclose technical details of its plans and obtain approval in a procedure requring a public hearing. As a result, the ABC notes, three FRG companies - Bayer, BASF and Hoechst - are changing their investment plans. One will build in Japan, while the other two will build biotechnology facilities in the States. Many smaller companies, the ABC claims, have shelved their plans or sold their biotechnology operations. (Source: Biotechnology Bulletin, Vol. 8, No. 2, March 1989)

IBA plans for 1989

The US Industry Biotechnology Association's plans for 1989 provide an interesting insight into some of the key issues likely to emerge in the year ahead. They include:

Animal patents: The call for US legislation imposing an animal patent moratorium or farmers' exemption will surface again in the 101st Congress. The IBA will be campaigning against the legislation, believing that it will hinder the development of commercial biotechnology.

Drug pricing: Congressional hearings on drug pricing are likely to be held during 1989. Questions about the Health Care Finance Administration reimbursement for biotechnology drugs and biologics are expected. The IBA will be highlighting the cost recovery programmes peculiar to biotechnology.

International patent harmonization: The IBA will examine the US and European systems of patenting in relation to the first-to-invent versus first-to-file approaches. The goal is to harmonize patenting regimes in Europe, Japan and North America.

Food biotechnology: Satisfactory US Food and Drug Administration (FDA) procedures for the approval of biotechnology-related food and food products will be the target here.

Human genome: The mapping and sequencing of the human genome - and issues linked with these activities - will be a major priority.

Cell line deposits: Through discussions with the US Patent Office, IBA will work for regulations which restrict access to cell line depositions so that countries without adequate patent protection will not be permitted access.

Biotechnology regulations: The IBA will continue working with the federal agencies to ensure that environmental uncertainties are scientifically defined and solutions are scientifically based.

US biotechnology patent backlog: The IBA recommended an initiative aimed at additional technical training of biotechnology patent examiners, which is now being implemented by the US Patent and Trademark Office.

Biotechnology insurance: The IBA will also continue efforts to make product liability insurance and lower cost insurance coverage available to biotechnology companies.

Details from: Industrial Biotechnology Association, 1625 K Street, NW, Suite 1100, Washington, DC 20006, USA or on +1(202)857-0244. (Source: Biotechnology Bulletin, Vol. 7, No. 12, January 1989)

Milestones in legislation affecting biotechnology

Legislation that passed in 1988

The Process Patent Amendments Act, which became part of the Omnibus Trade Act signed in August, will help protect against infringement of US process patents through foreign manufacture of products.

The Labor, Health and Human Services appropriations bill, signed into law in September 1988, mandates a biotechnology advisory panel.

Amendments to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), signed in late October, step up testing of pesticide ingredients now being marketed, establish a schedule for the completion of the reregistration of pesticides currently required by FIFRA, and provide a formula for charging manufacturers a reregistration fee.

The Generic Animal Drug and Patent Term Restoration Act, now awaiting the President's signature, brings most animal drugs under a 1984 law easing approval of generic drugs. It exempts biotechnology products from such treatment.

The Technical Corrections Act of 1988, also awaiting the President's signature, extends the research and experimentation tax credit through the end of 1989.

Legislation that did not pass

The **Biotechnology Competitiveness Act** sought to create an advisory panel to maintain US industrial leadership in biotechnology as well as panels for overseeing research on the human genome and in agricultural biotechnology. The Senate passed the bill in June but, after clearing the House Committees on Agriculture and Science, Space and Technology, it died in the Energy and Science Committee.

The Animal Patent Moratorium sought to prohibit the patenting of genetically engineered animals either indefinitely (Senate version) or for two

years (House version). The Senate version died in the Judiciary Committee; the House Judiciary Committee defeated its version outright.

The Transgenic Animals Reform Act sought an exemption from payment by farmers of any royalties for use of patent-protected genetically engineered animals. It passed the House in September, but died in the Senate Judiciary Committee.

The Alternative Agricultural Products Research Act would have authorized research programmes studying alternative uses through biotechnology of plants and plant materials. Despite passing the Senate in two forms, however, the House continues to reject the measure.

The Novel Organism Release Act sought to amend the Toxic Substances Control Act to protect human health and the environment by explicitly regulating the release of novel organisms. It died in the Senate Environment and Public Works Committee.

The Food and Drug Administration Revitalization Act sought to enhance agency resources and to establish a biotechnology demonstration project. It died in the Senate after passage by the Labor and Human Resources Committee.

The Commerce appropriations bill had included a request for $2 million for the US Patent and Trademark Office (PTO) to support efforts to reduce the current backlog in reviewing biotechnology patent applications. While the House/Senate Conference Committee approved $109 million for the PTO, that amount did not include the $2 million.

Recent changes to speed the approval of drugs and biologics

FDA revised its regulations for investigational drugs in 1987. (See 52 Fed. Reg. 8798, 19 March 1987; 52 Fed. Reg. 19466, 22 May 1987; 53 Fed. Reg. 41516, 21 October 1988). The Agency's goals were: (1) to shorten the IND phase and increase its efficiency, without sacrificing the quality of review; (2) to make promising new drugs available to desperately ill patients at the earliest possible time; and (3) to define conditions under which drug manufacturers may charge for investigational new drug products.

In late October, FDA publicly announced its implementation of these plans to make available new drugs for life-threatening and severely debilitating diseases as soon as possible. In determining whether to approve such a drug, FDA will weigh its benefits and risks - known or potential. Other factors include the severity of the disease for which the drug is intended, the absence of alternative therapies, and statutory approval criteria. Any unresolved issues - such as the drug's lowest effective dose - can be addressed post-approval. Post-marketing studies will also provide more information on risks, benefits and optimal uses. In particular, FDA's changes addressed the following issues:

Greater freedom during early research. The Agency has narrowed its scope in reviewing Phase I studies to focus on the safety of human test subjects rather than the drug's efficacy. This allows drug sponsors greater innovative freedom during the preliminary studies.

Strengthened adverse reaction reporting. The drug sponsor must notify FDA within 10 days of all adverse drug reactions that are both serious and unexpected. If any of these are life-threatening or fatal, FDA expects to be notified by telephone within three working days. (This extends existing requirements for approved new drugs). Adverse reactions must be reported throughout the research, approval, and post-marketing stages.

Increased consultation between FDA and drug sponsors. FDA will meet with drug sponsors to design animal tests to minimize the time necessary to enter the drug into human Phase I trials. And FDA will help the drug sponsor devise Phase IIs such that they yield data sufficient for product approval. If a preliminary analysis of Phase IIs looks promising, FDA will even provide a treatment protocol so patients can start receiving a drug before its approval. Otherwise, all IND sponsors have the opportunity to meet with FDA officials in an "End of Phase II" conference - to concur on an overall approach for Phase III trials and to design specific studies.

Streamlined procedures. FDA has clarified the format for IND submissions, specified procedures for placing a study on "clinical hold", and streamlined procedures for updating current clinical trial data. The Agency will actively monitor and evaluate clinicals with an eye towards facilitating them. Further, FDA has designed rapid means to resolve any questions that might arise during trials

Exemptions for certain marketed drugs. The new rules exempt from most IND requirements studies on approved drugs - as long as safety is not an issue and the studies are not intended to support changes in the drug's labelling.

"Treatment use" of investigational drugs. Investigational drugs can now be used to treat patients outside of a controlled clinical trial under the following conditions: (1) the drug is intended to treat a "serious" or "immediately life-threatening" disease; (2) there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population; (3) controlled clinical trials of the drug, as an IND, are either underway or complete; (4) the sponsor of the controlled clinical trial is actively pursuing marketing approval of the drug with due diligence.

Charging for investigational drugs. The drug's sponsor can now charge for an investigational drug during a clinical trial, with prior FDA approval. The sponsor must demonstrate that it needs the fees to initiate or continue the investigation. For treatment INDs, sponsors may charge for experimental drugs provided: (1) an adequate number of patients are enrolled in IND-authorized investigations; (2) charging for the drug - which has not yet received marketing approval - does not become a commercial venture; (3) the sponsor is not promoting or advertising the drug; (4) the sponsor is actively pursuing marketing approval with due diligence. For both clinical trials and treatment INDs, the drug's sponsor cannot charge more than what is necessary to recover research, development, manufacturing, and handling costs. (Source: Bio/Technology, Vol. 6, December 1988)

NIH organizes its genetic research

Expenses in 1988 for the National Institutes of Health (NIH) gene mapping and genome analysis initiative have exceeded $17 million. Grants recently awarded by the National Institute of General Medical Sciences (NIGMS) account for $13.5 million out of that total. During the next three to five years, that money will support 55 scientists who will be determining the location of genes on chromosomes and developing new research tools. Gene location can help scientists understand inherited disorders, and may lead to better ways to diagnose, treat and prevent them. The Health and Human Sevices Department says NIGMS's programme is unique because its intention is to map all of an organism's genes rather than searching out and studying specific genes of interest. (Source: Chemical Week, 30 November 1988)

US firm, Chinese set up joint venture

New Brunswick Scientific Co. and the East China University of Chemical Technology (ECUCT) have entered into an R&D agreement for new biotechnology products and equipment. The deal apparently for the first time enables the Chinese scientists involved to share in royalties on products derived from their research, according to Wu Dongdi, vice president of ECUCT.

Under the terms of the agreement, a separate facility, to be called the E-N United Biotechnology Laboratory, will be established on the Shanghai campus of ECUCT. With a staff of up to 20 scientists, the laboratory will initially focus on the development of bioreactors, fermentation equipment, sensors, media for cell cultures and monoclonal antibodies.

ECUCT specializes in the fields of chemical and biochemical engineering, and provides most of the technical personnel for the Chinese pharmaceutical industry. (Extracted with permission from Chemical and Engineering News, 20 March 1989, p. 7, by Ann Thayer. Copyright 1989 by the American Chemical Society)

NSF programme to link biology and mathematics

A novel programme to promote collaborations between mathematicians and molecular biologists has been announced by the National Science Foundation. The project's goal is to advance the use of mathematics in solving a range of questions about the three-dimensional structures of DNA and proteins, as well as other puzzles involving shape and pattern in biological systems.

The Programme in Mathematics & Molecular Biology will receive $2 million over five years from NSF's divisions of mathematics and of molecular biosciences. According to NSF, the programme marks the first time these two divisions have shared support for a programme of this size.

Nicholas R. Cozzarelli, chairman and professor of molecular biology at the University of California, Berkeley, will direct the new programme, which will initially involve an eclectic mix of scientists from nine institutions.

In addition to funding collaborative research among the researchers who are part of the programme, the programme will enable Cozzarelli to set up "mini-conferences" on selected topics in mathematical molecular biology and sponsor courses on modern applications of mathematics to molecular biology.

He also hopes to set up what he calls a "marriage service" to bring together molecular biologists and mathematicians in useful research collaborations. (Extracted with permission from Chemical and Engineering News, 28 November 1988, p. 5, by Rudy Baum. Copyright 1988 by the American Chemical Society)

Bio-information centre

David J. Lipman has been appointed director of the new Biotechnology Information Centre set up within the National Library of Medicine, part of the US National Institutes of Health (NIH). The management of NIH is known to be dismayed that the centre has been established separately from the office established to co-ordinate efforts to map and sequence the human genome.

The centre was established last year by legislation authorizing the human genome project, and will develop software and data base systems for handling the large amount of data emerging from the project. Congress appropriated $8 million for the centre for 1989, some of which will go towards partial support for the GenBank and Protein Information Resource data bases. Twelve bio-informatics specialists will work at the centre, but James Ostell, the developer of the Pustell DNA sequence manipulation software, is the only one hired so far.

Lipman developed software for searching sequence data bases while working elsewhere at NIH, and has served on the advisory board for GenBank. He will be co-ordinating the centre's programmes with the information advisory subcommittee of the NIH Human Genome Office, composed of David Botstein from Genentech, Mark Pearson from DuPont, Jaime Carbonell from Carnegie-Mellon and George Cahill from Howard Hughes Medical Institute. (Source: Nature, Vol. 338, 9 March 1989)

Biotechnology pilot plant for Penn State

A biotechnology pilot plant will start up this autumn at Pennsylvania State University at the school's Bioprocessing Resource Centre. According to Todd Burkhart, pilot plant manager, vitamins, hormones, proteins, flavours, antibiotics and enzymes are some of the products that may be produced there. The plant is part of the Pennsylvania Industrial Resource Centre programme, which has eight resource centres around the state that help regional companies with business problems. The pilot plant will be available for fermentation processes and cell culture, and the separation and purification steps needed for product. Cell culture equipment will range from 1.5 to 60 L, and three different cell culture processes will be available. Equipment for microbial fermentation will range from 1.5-L to 300-L capacity. The plant will meet NIH containment regulations of BL2 LS, the second level designated by NIH. (Reprinted with permission from Chemical and Engineering News, 20 March 1989, p. 16. Copyright 1989 by the American Chemical Society)

Field tests end

One of the first experiments approved in the United States involving the environmental release of a genetically engineered organism has been ended prematurely by its company sponsor. BioTechnica, a biotechnology company based in Cambridge, Massachusetts, has halted its field test of a strain of Rhizobium meliloti engineered to have enhanced nitrogen fixing capabilities because the microbe failed to increase the growth of alfalfa.

Despite local controversy, BioTechnica began the field test of the recombinant Rhizobium last spring on a plot of alfalfa at a farm owned by the

company in Pepin County, Wisconsin. The bacterium contained plasmids bearing several copies of the gene for the production of the enzyme nitrogenase, and was administered to the alfalfa plants in irrigation water. By the end of the growing season, the company could not detect the presence of the recombinant organism in the soil or the root nodules of the alfalfa plants, and plants treated with the engineered Rhizobium grew no faster than those left untreated.

BioTechnica plans to try again in 1989 using Rhizobium with extra nitrogenase genes integrated into its genome, and coated onto the alfalfa seeds or poured into the furrow as the seeds are planted. (Source: Nature, Vol. 335, 13 October 1988)

Collectors of plants for AIDS drugs sought

The National Cancer Institute is seeking proposals from potential contractors who could collect terrestrial plants for the purpose of isolating natural products that would be evaluated for anti-AIDS activity. Such materials, it says, will be used for advanced preclinical development and clinical trials. The solicitation is to enlist new holders of Master Agreements (to be issued about mid-February) from whom proposals to collect specific plants will be solicited by NCI as the need arises. (A Master Agreement is an agreement to accomplish highly circumscribed pieces of work as promptly as possible). Expertise and facilities required would be for collection of 10 to 5,000 kg dry weight; developing methods for collection may be necessary. NCI will supply all known information about the plant material to be collected, including where possible, a voucher specimen. The contractor would be responsible for ensuring correct identity and uniformity of all material collected before it is submitted. Information is available from Brenda D. Hayes, contract specialist at NCI, Research Contracts Branch, Executive Plaza South, Room 603, Bethesda, MD 20892. (Reprinted with permission from Chemical and Engineering News, 9 January 1989, p. 27. Copyright 1989 by the American Chemical Society)

USSR

Monsanto plans Moscow biotechnology laboratory

A new Monsanto biological research laboratory, to be based in Moscow, will concentrate on neurobiological research, human and animal growth hormones and plant genetic engineering. Under the terms of the agreement, the Soviet Union and Monsanto will jointly operate the facility - and would both hold patents on any products. Details from: Monsanto Co., 800 North Lindbergh Boulevard, St. Louis, MI 63167, USA or on +1(314)694-1000. (Source: Biotechnology Bulletin, Vol. 8, No. 2, March 1989)

Cell-free protein production system

A technique to produce proteins without the aid of living cells has been developed by researchers at the Institute of Protein Research (Moscow). The cell-free systems could use genes and amino acids to produce proteins at a rate far greater than previously possible in cell-less systems. The cell machinery and m-RNA copies of the gene are held in a chamber, while fresh solutions of ATP, GTP and amino acids flow through the chamber. The flow also carries away the protein products. Such a reaction has been sustained for over 40 hours, with over 300 protein molecules produced for each copy of the gene. About 2 or 3 copies was the maximum previously obtained. Filters prevent the genes and the protein-making molecules from leaving the reaction chamber. The system may have some drawbacks, such as the expense of providing ATP and the problems of scaling up to commercial scale. The process might also be incapable of making modifications to the proteins that are normally handled by cellular mechanisms. But the process might also allow the production of compounds that are too toxic to produce in living cells. (Extracted from Science News, Vol. 134, 26 November 1988)

Contract for a biotechnology laboratory

Oy Hortus, a Kemira subsidiary, has signed a contract with the Soviet Union's V/O Techmashimport for the construction of a $1.2 million biotechnology research station at Pushino, about 30 miles south of Moscow. The centre will provide Soviet biotechnology scientists with an ultra-modern working environment in which to experiment with applied plant biotechnology, including plant cell culture technology and micropropagation. The laboratory will consist of central administration buildings, glasshouses, [illegible] a reserve heating centre. Control technology will be supplied under subcontract by the Finnish company Itumic Oy. The project should be completed by early 1990. (Source: Chemical Week, 16 November 1988)

Viet Nam

Home laboratories produce better potatoes

Farmers are growing better potatoes using home tissue culture techniques with the assistance of the Institute for Experimental Biology (Ho Chi Minh City). Ten farmers in Dalat have set up home laboratories to produce disease-free plants, using tissue cultivars imported from Peru's International Centre for the Potato. The home laboratories contain 200 growing flasks, an UV light, wooden boxes for growing seedlings and a reactor for producing tissue culture growth medium. Farmers place the plants into a growth medium containing coconut water and transfer the plantlets to a semisterile soil bed one month later. The plants are then topped once a week to provide material for field planting. One family can produce up to 500,000 plants/year using tissue culture methods. In one year, 10 families produced enough plantlets to fill 1,000 hectares of land. The new potato varieties boosted yields to 18 tons/hectares against the usual 10 tons/hectares. The new varieties are resistant to many of the diseases that afflict potatoes and have reduced spraying costs dramatically. Plant tissue culture techniques are also used in Viet Nam to propagate coffee, orchids and sugarcane. Potatoes are helping to offset some of the rice shortage and are intercropped with rice on 100,000 hectares. (Extracted from Bio/Technology, Vol. 7, February 1989)

C. RESEARCH

Research on human genes

Cells lining blood vessels respond to foreign DNA

Gene therapy - the treatment of inherited diseases by restoring the defective gene - moves a step nearer with the discovery that the cells that line blood vessels will obey the instructions on inserted DNA. French Anderson at the National Heart, Lung and Blood Institute in Bethesda,

Maryland, persuaded the endothelial cells of rabbits to manufacture proteins encoded by genes from rats and humans.

There are two components to gene therapy: the therapist must isolate the gene that causes the disease and insert a working version into the body. The cells that have received the working gene must be capable of surviving a transplant because at present it is impossible to send genes to their targets within the body. They must also be able to make the protein encoded by the inserted gene - that is, they must express the gene. In the search for a suitable system, scientists are working on skin cells, white blood cells, hair cells and liver cells. Anderson and his team turned to endothelial cells precisely because they are in constant contact with the blood. They could be engineered to secrete proteins that will work in the bloodstream, or to make enzymes capable of removing harmful toxins from the blood.

The retroviral vectors that Anderson used contained a bacterial gene that made them resistant to an antibiotic, neomycin. The presence of this gene allows scientists to select the cells that are expressing the foreign DNA, because only those cells will survive treatment with neomycin.

In addition to the gene for resistance to neomycin, one vector contained the gene for a growth hormone from rats, while the other contained the human gene for an enzyme called adenosine deaminase (ADA).

The cells infected with the ADA gene made five times more of the human enzyme than of the rabbit version of the same enzyme. Those given the gene for rats' growth hormone secreted large quantities of the hormone into the culture medium. As a first step, then, genetic engineers can make endothelial cells express foreign proteins, at least in culture.

The researchers then grew the engineered cells on the inside of an artificial blood vessel and found that the cells continued to pour out the growth hormone. Their next step will be to see whether the system will work as well when the cells are returned to the body. (Source: New Scientist, 4 February 1989)

Improved PCR

Polymerase chain reaction has been improved to amplify nucleic acid segments even when terminal sequences are not known, according to researchers at Stanford University. Until now, unless both terminal segments were known, the reproduced DNA would be of different lengths, and therefore impossible to purify. Anchored PCR (A-PCR) adds a tail of guanines to the end of the DNA with the unknown sequence. A cytosine tail added to a primer can locate and bind to the guanine tail to provide a terminal sequence. (Extracted from New Scientist, 28 January 1989)

Images of DNA double helix obtained

The first images of individual lengths of native DNA that show the double helix have been obtained using a scanning tunnelling microscope (STM) by a team of scientists at Lawrence Livermore National Laboratory and Lawrence Berkeley Laboratory. Led by LBL materials scientist Miquel B. Salmeron and LLNL materials scientist Wigbert J. Siekhaus, the researchers produced three-dimensional images of deoxyribonucleic acid magnified one million times that reveal in detail the structural features of DNA and support recent evidence that DNA exists in several different helical conformations. The results suggest that even higher-resolution images can be obtained of the nucleotides that make up DNA. According to Salmeron, STMs have been used to image DNA before, but only after the sample had been shadowed with metal. By contrast, the LBL and LLNL researchers deposit a DNA solution onto graphite. Evaporation of the solvent leaves native DNA molecules on the graphite surface where they are probed with an STM. The scientists indicate that they "anticipate that the revolution that the scanning tunnelling microscope and related techniques have caused in the field of surface science will shortly be followed by an even larger revolution in molecular biology and biophysical research". (Reprinted with permission from Chemical and Engineering News, p. 18, 23 January 1989. Copyright 1989 by American Chemical Society)

Protein cleaves DNA sequence - specifically

A sequence-specific DNA cleaving protein completely made up of naturally occurring alpha-amino acids has been designed and synthesized by chemists at the California Institute of Technology. The glycine-glycine-histidine tripeptide, a concensus sequence for the copper-binding domain of serum albumin, was attached to the amino-binding terminus of the DNA-binding domain of Hin recombinase. This resulted in a new 55-residue protein with two structural domains whose functions are distinct. The hybrid protein is capable of sequence-specific recognization and cleavage of double helical DNA. It binds to four Hin sites, each 13 base pairs in length. In the presence of Cu(II), hydrogen peroxide and sodium ascrobate, the protein cleaves DNA at one of four sites. Previously, the researchers had converted the DNA-binding portion of Hin into a sequence-specific DNA cleaving protein by covalent attachment of ethylenediaminetetraacetic acid (EDTA), an iron chelator, to the amino terminus of the protein. (Extracted with permission from Chemical and Engineering News, p. 17, 31 October 1988. Copyright 1988 by the American Chemical Society)

Gene affecting dopamine identified

Oregon Health Sciences University (Portland, OR) researchers have identified a gene that affects the action of the brain chemical dopamine. The discovery could provide insight into such ailments as Parkinson's disease, cocaine addiction, schizophrenia and other diseases thought to be linked to dopamine levels. Scientists found the genetic blueprint for a protein called D2 dopamine receptor in rat brains. The gene enables dopamine to act as a chemical messenger between certain brain cells. According to brain-chemistry researcher J.W. Maas of the University of Texas Health Science Center (San Antonio, TX), the discovery should lead to the development of drugs designed to manipulate dopamine levels. The Oregon research team also reported they made the receptor protein in the test tube by using genetic engineering methods. This will allow for quick screening of chemicals that interact with the protein, making them likely candidates for development into drugs. Drugs currently used to control dopamine levels have trouble discriminating between D2 receptors and other kinds of dopamine receptors, which is probably the cause for a variety of side effects. (Extracted from Wall Street Journal, 22 December 1988)

Individual DNA molecules observed in gels

Individual DNA molecules stained with dye can be observed under a fluorescence microscope wending their way through agarose gels during electrophoresis, according to researchers from the University of Washington, Seattle. Knowing how the molecules migrate can help in improving separation of large DNA strands, say James B. Callis and Paul K. Aldridge from the department of chemistry and Steven B. Smith from the department of genetics. They find that the DNA molecules move through the gel as if they were a string of beads confronting a lattice of obstacles. The DNA molecules alternately elongate in the direction of the field and then contract, sometimes forming a U shape when they get hooked around an obstruction. A videocassette showing individual molecules in motion is available from Instructional Media Services, SB-54, University of Washington, Seattle, Wash. 98195. (Reprinted with permission from Chemical and Engineering News, p. 30, 16 January 1989. Copyright by the American Chemical Society)

Zinc fingers manipulate DNA

Proteins that help to regulate the activity of DNA may contain short pieces that are structured around an atom of zinc. Research by Aaron Klug and his colleagues at the Laboratory of Molecular Biology at the University of Cambridge has shown that the atom of zinc makes chemical bonds with two specific amino acids, cystine and histidine, in such a way that the chain of amino acids becomes folded around the zinc. This structure forms a loop, or "zinc finger", 30 amino acids long.

Proteins that regulate the transcription of DNA to RNA seem to do so through their zinc fingers: if they are absent, the protein cannot bind to DNA and regulate its transcription.

New research suggests that the zinc fingers are actually shaped more like a coiled ribbon than a finger. Grace Párraga and her colleagues at the University of Washington in Seattle, and at the California Institute of Technology in Pasadena, wanted to find out exactly what shape the alleged "fingers" had. The researchers used a protein that was involved in transcribing DNA in a yeast, Saccharomyces cerevisiae. The protein contains two zinc fingers.

Párraga and her colleagues synthesized a single zinc finger, and used various techniques to "visualise" its molecular structure. The researchers found that, once the zinc atom was incorporated, the chain of amino acids around it always folded up in the same way. This structure was very stable. The researchers suggest that, as the zinc becomes attached to the chain of amino acids, it forces the chain into a particular shape.

The researchers in the US also found that the chain contained a short helix, about one third of the total length of the finger. The helical structure meant that the "finger" was not a simple loop; it was shaped more like a coiled ribbon. The zinc atom, they suggest, links across one turn of the helix and across to the other end of the chain.

One zinc finger may not, however, be enough to enable the chain to bind onto DNA. The researchers found that their synthesized zinc finger would not attach readily to DNA. This is not, they believe, because it is the wrong shape, but because the protein needs to have more than one zinc finger to be able to attach properly to DNA. Multiple fingers may be necessary if the protein is to play its role in regulating the transcription of DNA. (Source: New Scientist, 15 October 1988)

Guanylate cyclase sequence determined

Cyclic guanosine monophosphate (cyclic GMP), like its more familiar cousin cyclic AMP, is a messenger molecule triggered within cells in response to external signals such as hormones. Important clues about how this communication system works come from Michael Chinkers and Stephanie Schultz of Vanderbilt University's school of medicine and their colleagues there and at Genentech and the National Institutes of Health. These researchers have determined the DNA sequence for the gene that makes one form of guanylate cyclase, the enzyme responsible for producing cyclic GMP. The researchers cloned and sequenced the gene for the membrane-bound form of this enzyme found in rat brains. The corresponding protein has three regions, they find: a single membrane-spanning region, an extracellular portion that serves as the binding site for a hormone called ANP, and an intracellular portion that catalyzes the formation of cyclic GMP. ANP is a hormone that regulates sodium and water excretion from cells, and earlier studies suggested that it worked by activating the cyclic GMP pathway, a finding that this work now confirms. (Reprinted with permission from Chemical and Engineering News, p. 27, 6 March 1989. Copyright 1989 by the American Chemical Society)

Catalytic antibody cuts peptide bond

An important advance has been achieved in the swiftly moving field of research on catalytic antibodies. Scientists at the Research Institute of Scripps Clinic in La Jolla, California, have developed for the first time a catalytic antibody that catalyzes hydrolysis at a specific site in a peptide. Also, it is the first time that a catalytic antibody has been successfully designed to bind a co-factor non-covalently, in this case a metal complex, along with the substrate. Such co-factors have the potential to provide antibodies with an expanded range of chemical reactivities.

The sequence-specific peptide hydrolysis has important practical applications if it can be achieved on proteins. Such antibodies "have the potential to be the protein cleaving equivalents of the restriction enzymes", says Richard A. Lerner, director of the research institute. Restriction enzymes cleave nucleic acids at specific sequences and have played a major role in the recombinant DNA revolution in molecular biology.

Until recently, most catalytic antibodies have been produced by immunizing animals with stable analogs of the tetrahedral transition state of the targeted hydrolysis reaction. The resulting antibodies, like many enzymes, thus preferentially bind the transition state and stabilize it relative to the substrate and products. Lerner and Brent L. Iverson instead immunized animals with an inert co-ordination complex that resembles a metal co-factor and a peptide substrate in a geometry that would lead to metal-mediated peptide bond cleavage.

Lerner and Iverson produced 13 monoclonal antibodies that could bind this complex, or "hapten". They found that, in the presence of a number of metal complex co-factors, several of the antibodies could catalyze the hydrolysis of the glycine-phenylalanine peptide bond in substrates closely related structurally to the hapten. The antibodies did not cleave the analogous

glycine-phenylalanine bond in substrates that differed from the structure of the peptide portion of the hapten, nor did they cleave alanine-phenylalanine peptide bonds. (Extracted with permission from Chemical and Engineering News, p. 5, by Rudy Baum, 6 March 1989. Copyright 1989 by the American Chemical Society)

Enzyme pulls the trigger on magic bullet for cancer

A new two-stage treatment for cancer, which involves activating a drug only at the site of the tumour, should begin trials in people next year. The treatment has already proved highly effective in mice with tumours.

The therapy is a refined version of the "magic bullet" approach, which uses antibodies to target cancer cells. It allows doctors to deliver drugs precisely to tumour cells, avoiding damage to normal cells.

Kenneth Bagshawe, medical oncologist at Charing Cross Hospital in London, together with scientists from the Public Health Laboratory at Porton Down in Wiltshire, developed the method. A British cancer charity, the Cancer Research Campaign, has supported their work.

The treatment is in two stages. The first is an injection of an antibody which is bound to an enzyme. The antibodies are monoclonal antibodies which identify cancer cells and dock onto the cell surface, holding the enzyme in place.

The second stage is an injection of a "prodrug": a compound which is inactive in the form in which the patient receives it, but which undergoes a change in the body into an active form. In this case, the prodrug is harmless until it comes across the enzyme held at the site of the cancer. When the two meet, the enzyme "arms" the drug by removing a chemical group. The enzyme's activity makes it possible to generate a high concentration of cell-killing (cytotoxic) drug close to the cancer.

The scientists have called the new treatment antibody-directed enzyme prodrug therapy, or ADEPT. The technique's ability to target cancer cells promises to make it much less toxic to the body than more conventional forms of treatment such as radiotherapy, which damages normal cells as well as cancer cells.

ADEPT also has the edge over the original concept of the "magic bullet", in which the antibodies themselves attack the cancer.

The scientists have already applied the method successfully to cure mice carrying human cancers that are resistant to conventional treatment. Researchers at the Cancer Research Campaign Laboratories at Charing Cross Hospital have treated mice which bear human choriocarcinoma, a rare tumour of the womb. They chose choriocarcinoma for the tests because monoclonal antibodies specific for the tumour were already available.

When testing the treatment on the mice, the researchers followed a single injection of the antibody-enzyme complex with three doses of prodrug. Other mice with the same type of tumour received conventional treatment. Whereas conventional treatment had no effect, 80 per cent of the mice treated with ADEPT were effectively cured.

Bagshawe's team hopes to start small-scale clinical tests next year. Patients with advanced bowel cancer are likely to receive the treatment first. The therapy will make use of antibodies produced by the British biotechnology company, Celltech.

Treatment will extend to other cancers as specific monoclonal antibodies become available. Scientists have already identified antibodies to over 50 per cent of common cancers, but many are not specific enough for ADEPT. (Source: New Scientist, 7 January 1989)

Gene loss linked to cancer

Evidence linking some breast cancers to loss of a protective "anti-oncogene" has strengthened the theory that loss of such genes is a major factor in the complex process by which many human cancers arise.

The evidence also illustrates how complicated the role of such genes may be because it shows a link to a gene or genes on chromosome 17, which had not previously been linked to development of breast cancer.

Each normal person has two copies of chromosome 17, one of the 23 pairs of human chromosomes. In the past, scientists have found links between some breast cancers and loss of genetic material from chromosomes 11 or 13.

Scientists generally believe cancer is a multistep process, a cumulative biological disaster in which several things must go wrong in some cells and tissues. This leads to uncontrolled and often chaotic growth.

At the heart of the problem are the genes that control the growth and regulation of cells.

During the past decade oncogenes have been found that apparently contribute to the development of cancers when they become abnormal or are abnormally activated in cells.

Loss or abnormal rearrangement of material in the chromosomes is also believed to be a factor in many cancers. More recently, scientists have discovered a class of "antioncogenes", or suppressor genes that seem to protect against cancer.

They are thought to function as regulators of cell multiplication. Cancers arise when both copies of such a protective gene are lost from some of a patient's cells.

In some cancers that have a strong hereditary basis, the loss or impairment of one copy of the protective gene is inherited, while the loss of the other results from damage at some time after conception.

In the new studies, scientists discovered human breast cancers in which a suppressor gene was apparently lost from chromosome 17. (Source: International Herald Tribune, 12 January 1989)

Mouse model links aging to Down's syndrome

Researchers from the US and Israel have introduced a human gene responsible for some symptoms of Down's syndrome into mice. The researchers found that, after they had introduced the gene, the mice showed signs of premature aging and biochemical imbalances that could indicate mental retardation. The work may provide clues to the molecular basis for both aging and mental retardation.

Down s syndrome is associated with the presence of three copies of chromosome 21 in each cell, instead of the normal two. Until recently, the link between this excess genetic material and the manifestation of the syndrome has remained a mystery. The obvious ethical problems of working on humans, combined with the complexity of this entire chromosome, have hampered progress in the field for almost 30 years. Now two groups, led by Charles Epstein of the University of California in San Francisco and Yoram Groner of the Weizmann Institute of Science in Israel, have used cloning techniques to isolate a key gene on the extra chromosome 21. The researchers introduced this gene both into mice and into a well-characterized colony of cells, endowing the cells with excess copies of the gene.

The researchers studied the way in which the product of this single gene - an enzyme - affected the development and physiology of the animal when it was produced in excess. The technique enabled the researchers to find out more about precise biochemical effects of the gene product on colonies of cells.

The enzyme coded by this gene, copper- or zinc-superoxidase dismutase 1 (SOD1), protects the cell from harmful singlet oxygen and hydroxyl radicals, which are produced during normal cell metabolism. Overproduction of SOD1 appears to upset the delicate metabolic balance of this cell, resulting in a high concentration of active oxygen. This oxygen damages important molecules. In particular, singlet oxygen attacks lipids in cell membranes, in a process known as lipid peroxidation. This process occurs in the brains of people with Down's syndrome.

When Groner and a colleague, Orna Elroy-Stein, introduced the gene for SOD1 into a colony of neurone cells from rats, the cells expressing the extra gene had a greatly reduced capacity to take up neurotransmitters while outwardly maintaining the appearance of neurones.

The researchers found that the ability of neurones to propagate signals was also impaired in neurones affected with Down's syndrome, possibly as a consequence of lipid peroxidation. This conclusion, coupled with Groner and Elroy-Stein's earlier work with the gene for SOD1, demonstrated that an imbalance in just one gene can produce alterations in neurones which would impair the transduction of signals and mimic the deficiencies apparent in Down's syndrome.

Even more intriguing results emerged from experiments on the mice bearing the extra SOD1 gene. Outwardly, the mice appeared normal, without any obvious deformities. However, when Groner's team examined the tongues of the mice under a microscope, they discovered that the synapses betwen the neurones and the muscle cells were abnormal. All the differences reflected inefficient signal transmission. The tongues of people with Down's syndrome have similar abnormalities, and the synapses in this tissue resembled those in the tongues of aging rats.

These results suggest a direct genetic link between mental retardation, Down's syndrome and aging. (Source: New Scientist, 15 October 1988)

Alzheimer's gene evades neurologists

Chromosome 21 does not contain the gene responsible for Alzheimer's disease, as many neurologists had thought. This is the conclusion of a study carried out by Gerard Schellenberg and colleagues at the Division of Neurology at the University of Washington, Seattle.

Alzheimer's disease is a progressive illness. Nerve cells die gradually, leading to loss of memory, confusion and the breakdown of cognitive thought. As the cells die, abnormal "plaques" and "tangles" appear in the brain. People over the age of 30 suffering from Down's syndrome also have plaques and tangles in their brain. This similarity led neurologists to believe that, because people with Down's syndrome have an extra copy of chromosome 21, the gene responsible for Alzheimer's disease might be on the same chromosome.

The plaques appearing in the brains of people with Alzheimer's disease and Down's syndrome both have deposits of the peptide amyloid β.

The gene for amyloid β is located on chromosome 21 so scientists began to think that the gene responsible for Alzheimer's disease was located on the chromosome.

Peter St. George-Hyslop and his colleagues at the Massachusetts General Hospital came close to finding the gene when they looked for genetic markers on chromosome 21.

The researchers at Massachusetts showed that, in four families where Alzheimer's had affected people of different generations, the disease was linked to two small marker sections of DNA in a band of chromosome 21 called q21. One of these two sections has in turn been linked with the amyloid β gene, so the theory that the gene was on chromosome 21 seemed to be correct.

Schellenberg and his colleagues carried out a larger survey of Alzheimer's disease in families. They studied 15 families in which the disease had been clinically diagnosed in at least two generations. The researchers also had evidence from postmortem examinations of bodies from 14 of the families. The evidence showed plaques and tangles in the brain, confirming that the disease they were looking at was indeed Alzheimer's disease and not some other type of dementia. However, Schellenberg's team did not find any link between inherited Alzheimer's disease and the q21 markers.

The two teams may have obtained different results because they were looking at different types of Alzheimer's disease. St. George-Hyslop studied people who were between 40 and 52 years old when they developed the disease. Schellenberg, by contrast, studied people who were between 41 and 68 when they became ill. Perhaps there is a gene on chromosome 21 that accounts only for familial Alzheimer's disease that has a very early onset. However, it is unlikely that these studies have found two types of Alzheimer's disease with different causes, because the two studies did not show up any pathological differences in the brain. Schellenberg and his team suggest that St. George-Hyslop's results are a chance occurrence, and that susceptibility to familial Alzheimer's disease is not written in the genes. (Source: New Scientist, 15 October 1988)

Olfactory damage may lead to Alzheimer's diagnosis

Researchers in the US have discovered abnormalities in cells from the olfactory nerves in the noses of people with Alzheimer's disease. This finding could provide the first reliable way of diagnosing the disease in a person who is still

alive. It might also lead to a better understanding of the disease and, ultimately, its cause.

Barbara Talamo of Tufts Medical School at Boston in Massachusetts and her colleagues compared autopsied tissue from the nasal epithelium of people with and without dementia. In the demented patients, they found abnormal accumulations of neurites: extensions of cytoplasm used by the cell to send and receive electrical signals.

The researchers labelled the neurites with monoclonal antibodies against a range of cellular components. They found that both the neurites and the nerve fibres of the olfactory neurons contained an abnormally wide variety of neurofilament proteins.

Neurofilaments form an important part of a cell's skeleton, especially in the nerve fibre. In normal olfactory cells, these cylindrical structures are composed of only one form of neurofilament protein: a medium-sized protein in a form called the phosphorylated form. However, the researchers found that in eight out of nine patients with Alzheimer's, the olfactory tissue also contained forms that should not have been there: the heavy and light forms, and phosphorylated forms of both the medium and heavy proteins. These patients all had substantial numbers of plaques and tangles, the characteristic features of Alzheimer's disease, in their brains. In addition, two antibodies that label the plaques and tangles also label the normal olfactory neurites.

Olfactory neurons are unusual in that the body generates them throughout its life; all other nerve cells are in place before birth. Talamo suggests that the immaturity of the olfactory cells may make them more sensitive to signals that induce abnormal growth. This model could account for the proliferation of neurites.

The nature of such signals is a matter of conjecture, but an external agent in the environment could, in theory, provide such a signal. Olfactory neurons are the only cells in the central nervous system that are exposed directly to atmospheric pollutants, for example.

By taking small samples of nasal epithelium from living people with and without dementia, scientists can look for the changes that Talamo has associated with Alzheimer's disease. If these changes do indeed turn out to be early events, the technique could enable doctors to detect the disease before the symptoms of dementia appear.

In addition, the accessibility of the nasal tissue compared with that of the brain will enable researchers to study the molecular basis of the disease in the laboratory. (Source: New Scientist, 11 March 1989)

Foetal tissue may not be needed for Parkinson's

The use of tissue from aborted human foetuses to treat Parkinson's and Alzheimer's disease may not be necessary. American and Swedish scientists described the first stages of a possible alternative treatment, which involves genetically altering the tissues from adult rats to repair their damaged brain cells, at a recent meeting of the Society for Neuroscience in Toronto.

The results have been so impressive that at least one researcher wants to extend the experiments to primates.

The technique, though promising, is controversial and poses many ethical problems. The alternative, reported at the meeting on neuroscience, involves implanting genetically-engineered skin cells taken from the patient.

One of the first researchers to explore the idea of using skin cells, four years ago, was Xandra Breakefield at Harvard Medical School. At the meeting, she revealed new research done in collaboration with Fred Gage and Ted Friedmann at the University of California in San Diego. The research could provide models for future work in primates and eventually for the treatment of Alzheimer's disease.

Scientists believe that Alzheimer's disease may be caused partly by the degeneration of cholinergic cells - cells that use the transmitter chemical, acetylcholine - in a part of the brain called the basal septum. The loss of these cells interrupts communication between the basal septum and higher parts of the brain. Communication between the two parts of the brain is essential to memory.

Breakefield, Gage and Friedmann first used retrovirus vectors to alter the genetic makeup of fibroblast cells taken from the skin of rats, so that these produced human nerve growth factor (NGF). This chemical stimulates the growth of some nerve-fibres in the brain and could be used to restore function in the nerves of people with Alzheimer's.

The researchers grafted cells that were producing NGF into the basal septum of rats where the connections between that part of the brain and the hippocampus, which has an important role in memory, had been cut.

They transplanted cells taken from a rat into its own basal septum to avoid the problem of rejection of the tissue by the rat. The hippocampus is a source of NGF. Without a supply of NGF, half of the cells of the basal septum would die.

After several weeks the researchers found that not only had the graft survived, but that none of the cells in the basal septum had died. (Source: New Scientist, 3 December 1988)

"Peter Pan" hormone helps genetic engineers

The recent identification of a substance that enables unspecialized embryonic cells to survive indefinitely in the laboratory should revolutionize methods for making transgenic animals. The substance, a growth factor, prevents the embryonic cells from maturing.

Cells that do not mature are invaluable to the genetic engineer because they retain their full developmental potential: once reimplanted into a young embryo, they can participate in forming any part of the animal. This characteristic makes them suitable vectors for carrying foreign genes into an embryo.

The growth factor will make it easier for researchers to maintain the cells in the laboratory while they insert foreign genes. They can then return the cells to embryos which, put back in the uterus of a living animal, develop with a high proportion of cells containing the foreign gene.

Scientists have known for a while that such a growth factor existed. They called it differentiation inhibitory activity, or DIA. Australian scientists were the first to identify the factor in embryonic cells from mice. Researchers

knew the size of the molecule, and some of its characteristics, but no-one knew the genetic structure of the factor. Without such information, it was impossible to manufacture the factor in bulk.

Nick Gough and his colleagues from the Walter and Eliza Hall Institute in Melbourne had been studying a hormone which inhibits the growth of leukaemic cells. Gough, together with Dave Gearing, cloned the gene for this substance, called leukaemia inhibitory factor (LIF), in both mice and humans, ahead of the Israeli and Japanese teams which had initially reported the existence of the factor.

The factor caused leukaemic cells from mice to abandon their uncontrolled growth and differentiate into a macrophage. When further research showed that LIF appeared to have no effect on the development of normal white blood cells, the researchers thought that this improved its potential for use in people with leukaemia.

Further research showed, however, that LIF seemed to have a clear effect only on one type of leukaemic mouse cell. Gough and his colleagues could find no normal function for the factor.

Then, the team made a discovery. Lindsay Williams, visiting Gough from the European Molecular Biology Laboratory in Heidelberg, West Germany, happened to be telling him about the properties of another factor. Differentiation inhibitory activity, DIA, had opposite actions to LIF. DIA prevented cells from going down the irreversible path of specialization.

As Williams described the characteristics of DIA, Gough grew increasingly intrigued. The physical characteristics of LIF and DIA were identical. When Williams tested LIF for its ability to prevent mouse embryonic cells from differentiating, it behaved exactly like DIA.

The two factors do appear to be identical.

What will this discovery mean for scientists who want to develop "transgenic" animals - ones carrying foreign genes, otherwise known as "transgenes"? So far, no-one has been able to culture embryonic stem cells from a species other than mice. The great excitement about LIF is that if pure LIF from mice will maintain embryonic stem cells of mice, maybe LIF from sheep will do the same for embryonic cells from sheep, and so on. If so, the commercial and scientific ramifications could be enormous. The Walter and Eliza Hall Institute and an Australian investment corporation, AMRAD, have taken out patents on LIF. (Extracted from New Scientist, 24-31 December 1988)

A mouse with a human immune system

A strain of mouse which has no effective immune system of its own has suddenly become a highly sought-after animal for experiments in human biology. Two research groups in California have shown that they could give the mouse parts of the human immune system.

The mice have an inherited condition called severe combined immunodeficiency or SCID. They are natural mutants, which scientists propagated because they hoped to learn about a similar genetic disease that afflicts humans.

The two groups of researchers used different techniques to transplant cells from the human immune system into the mice. To their surprise, the cells functioned.

At the moment, the demand for the SCID mouse far exceeds the supply. That should change when the Fox Chase Cancer Center in Philadelphia licences a company to mass-produce the mice for use in research laboratories. The center is also considering distributing the mice overseas. By the end of this year, the SCID mouse should be readily available to all the researchers who want it.

The mouse, complete with human immune system, promises to lead to a huge expansion in knowledge of how cells function and how diseases develop. The mouse model will also avoid some of the problems of using higher primates, such as the endangered chimpanzee, for research.

Leukaemias and hepatitis are two of the diseases that researchers will study with the aid of the mouse.

Scientists will also be able to use the SCID mouse to test therapies that, for ethical reasons, they could not test on humans. AIDS research will be one of the first beneficiaries. The two Californian research groups - one at the Medical Biology Institute and the other at Stanford - have now infected the altered SCID mice with HIV, the virus that causes AIDS. Both groups are now studying the progress of the disease and how the virus infects cells.

The potential for research has generated an unprecedented demand for the SCID mouse. Mel Bosma, an immunologist who discovered the mouse in 1983 at Fox Chase, said: "It was treated as just another immune-deficient mouse ... but it is quite special".

The team at Stanford has called its mouse SCID-hu: the "hu" stands for human. The project began because Joseph McCune, a specialist in infectious diseases and, until recently, a postdoctoral fellow in Irving Weissman's laboratory at Stanford, wanted to understand how HIV caused immune deficiency. He read that the SCID mice usually die of pneumonia caused by Pneumocystis carinii, the same infection that often afflicts people with AIDS.

McCune wondered whether, if he gave the mice parts of the human immune system, this would protect them from the pneumonia. Over a period of 18 months, researchers at Stanford have challenged many of the 200 mice in their colony with the organism that causes the pneumonia without any casualties.

The SCID mice do not reject the human tissue they receive because their own immune systems are so inadequate. The group at La Jolla injects mature human blood cells into the mice. The Stanford group transplants human foetal tissue: liver cells, thymus tissue and lymph nodes.

The foetal liver cells used by the Stanford group contain haematopoietic stem cells, which give rise to all the blood-forming and immune cells of the body. In adults, these stem cells are found in bone marrow. It is necessary to transplant foetal thymus tissue and lymph nodes as well, in order to provide an appropriate environment for the differentiation of immature lymphocytes into mature T or B lymphocytes.

The group at La Jolla has also shown that the SCID mice will produce human - not mouse - antibodies when injected with an infectious agent. The animals produced human antibodies when exposed to a tetanus toxoid. The implication is that it might be possible to use the mice to raise human antibodies

with which doctors could treat patients suffering from immunodeficiency.

Another finding was that if the donor of the white blood cells was infected with Epstein-Barr virus, the mice rapidly developed associated lymphomas (cancers of the lymphatic system). This provides an excellent animal model for the study of how the virus causes these tumours.

Because the Stanford model starts out with foetal tissue, it will allow the study of how cells differentiate into their mature forms and of the early development of disease. This is why the model may be especially useful for testing vaccines and drugs that may halt HIV infection.

Weissman says that the only limit on the uses of the mouse model for studying a whole range of congenital or acquired defects is the imagination and technical expertise of researchers. Transplantation of human liver tissue will allow the study of human hepatitis infection. It will also be possible to study the normal function of human liver cells, such as how they produce cholesterol. Another promising area of research will be the processes that lead to the tolerance, rather than the rejection, of foreign tissue, such as transplanted organs. Foetal tissue from diabetic women who miscarry could be implanted in SCID mice to unlock clues to the genetic component of diabetes. (Extracted from New Scientist, 14 January 1989)

Translocation could trigger childhood leukaemia

Canadian researchers have pinpointed a genetic defect that seems to underlie a form of childhood leukaemia. The researchers may have discovered a new form of cancer-causing gene, or oncogene.

Ian Dubé of the University of Toronto and his colleagues looked for chromosomal abnormalities in children with a form of acute lymphoblastic leukaemia (ALL) in which the T cells of the immune system become cancerous. ALL is the most common leukaemia among children, and between 5 and 10 per cent of the cases specifically affect T cells.

The researchers found physical alterations in two chromosomes in the leukaemic cells of all 10 patients that they studied. Part of chromosome 10 had been exchanged with a portion of chromosome 14. Geneticists call such a mutation a translocation, and use it as a signpost to the location of an oncogene that they think may be present. Researchers suspect that in many cases, an oncogene lies at the "breakpoint" - the area where the segment of chromosome breaks from the parent chromosome to move to another chromosome. The translocation may activate a previously harmless "proto-oncogene" - the precursor of the cancer-causing gene - by moving it away from neighbouring stretches of DNA that normally control the activity of the gene and placing it next to a gene that is active all the time.

Support for this notion comes from earlier work by Carlo Croce of the Wistar Institute in Philadelphia, and colleagues, which demonstrated that chromosomal translocations appear in several types of cancers. A translocation between chromosomes 8 and 14 is a feature of Burkitt's lymphoma, for instance; and in chronic myelogenous leukaemia, chromosomes 9 and 22 have exchanged pieces of DNA in the cells that are cancerous. In both of these cancers, the break in one chromosome is within an oncogene and the other break is in a gene that is active specifically in the type of cell that becomes cancerous.

Dubé found that, in the form of ALL that affects the T cells, the breakpoint in chromosome 14 is in a gene that is active in all T cells. The oncogene may therefore be at the breakpoint in chromosome 10, rather than chromosome 14. Dubé's team is now characterizing the DNA at this point to find the proposed oncogene. It may turn out to be a new oncogene that is specific to human T cells. Its discovery may help scientists to study how normal T cells regulate their growth and how mutations of the oncogene give rise to cancer. (Source: New Scientist, 25 February 1989)

Early embryo sex test forewarns of disease

Researchers in London have discovered a harmless way to identify the sex of very young human embryos. This achievement proves for the first time that it is feasible to diagnose genetic diseases carried on the X chromosome in embryos produced in the laboratory through in vitro fertilization (IVF). This would enable doctors to introduce into a woman's uterus only those embryos free of a specific genetic defect. Such an approach - known as pre-implantation diagnosis - could enable couples to know that they are carriers of severe genetic disorders to enter into a pregnancy knowing that the foetus has not inherited the disease.

Andrew Handyside and his colleagues at the Hammersmith Hospital in London, with others at the Clinical Research Centre in Harrow and at University College, London, perfected the delicate task of removing a single cell from 30 embryos three days after fertilization. At this stage, the embryos consist of a cluster of between six and 10 cells.

The procedure apparently left the embryos unharmed, as a normal proportion of the embryos (37 per cent) went on to develop in culture to the blastocyst stage - when embryos in vivo implant in the wall of the uterus. No one knows why most embryos in culture stop developing before this stage - it could reflect a deficiency of the culture medium, or a natural failure rate.

Having removed a single cell from each embryo, the researchers then determined its sex by using a relatively new technique based on the polymerase chain reaction. It amplifies a repeated sequence of DNA found only on the Y chromosome - genetic material which is unique to male humans.

When Handyside and his colleagues cut up the cell's DNA with enzymes into fragments of varying size and separated the fragments on a gel, they could see the band created by the fragments of the amplified segment of the Y chromosome after staining the DNA with a standard dye. The simplicity of the approach speeds up the test: there is no need to add a probe labelled with a radioactive isotope, for example, which would add 12 hours to the procedure. (Extracted from New Scientist, 25 February 1989)

One gene makes tumours resistant to drugs

One gene may account for the resistance of many cancers to chemical treatment. Certain tumours of the colon, kidney, liver and adrenal gland possess a highly active form of a "multidrug resistance gene" (MDR1) long implicated in the resistance of some cancers to drugs.

The MDR1 gene codes for a protein p-glycoprotein found in the cell membrane of many

normal cells. Scientists believe that the protein protects healthy cells by pumping out toxins encountered in nature.

Victor Ling of the Ontario Cancer Institute in Toronto believes that the presence of the functioning MDR1 gene in cancerous cells could be linked to drug resistance. One possibility is that when a normal cell from the kidney or liver turns cancerous, the p-glycoprotein continues to work: it fails to distinguish between toxins and various drugs for treating cancer. As a result, it pumps out the drugs as well as the toxins.

Until recently, researchers were uncertain whether the pump and its MDR1 gene exist in every type of cancer cell, or whether different kinds of tumours have different pumps for resisting toxins. The current study, published by a team of 14 scientists from the institute, is the first to show that the p-glycoprotein pump is common in many types of cancers.

The researchers tested samples from more than 400 patients for elevated levels of messenger RNA. They found high levels of messenger RNA in tumours of the colon, kidney, adrenal gland and liver. These tumours are resistant to drugs from the start, and they derive from tissues where the p-glycoprotein is naturally present. The scientists also measured elevated mRNA from MDR1 in carcinoid tumours, cells within the epithelial lining, certain tumours of the lung and pancreas, and one type of leukaemia.

Samples from other cancers, including cancer of the breast which had acquired resistance to drugs, also showed raised levels of mRNA from the gene. This finding helps to explain the baffling resistance that some tumours develop to previously successful treatments. In these cases, something may switch on the dormant MDR1 gene. (Source: New Scientist, 18 March 1989)

A small step in cystic fibrosis

Cystic fibrosis (CF) is the most common fatal genetic disease in the US, notes the Stanford University Medical Center (Stanford, CA). About one baby in 1,600 is born with the disease. CF patients, who have abnormally thick body secretions that plug the body's organs, generally die of respiratory failure, often by the age of 30. While the cause of the disease is unknown, studies have implicated faulty chloride channels in cell membranes. But scientists have had trouble studying those defects because they show up in cells that are difficult to maintain in a laboratory. Now Stanford researchers, led by Phyllis Gardner, assistant professor of medicine, have discovered that the defects also show up in white blood cells, which are easy to get from a patient's blood sample. Besides being simpler to study, those cells can serve as a pre-natal test or as a marker to indicate who might be a CF carrier and thus at risk for bearing children with CF. Stanford also says that the existence of the defect in white blood cells may point to a link between the disease and the immune system, backing up previous evidence. (Source: Chemical Week, 22 February 1989)

Structure of mutant human oncogene protein determined

The protein encoded by a mutant human oncogene differs only slightly in structure from the native protein that initiates normal cell division, a finding that may complicate efforts to develop inhibitors of the mutant protein according to chemists at the University of California, Berkeley.

Sung-Hou Kim, a Berkeley chemistry professor and senior scientist at Lawrence Berkeley Laboratory, last year reported the X-ray structure of the protein encoded by the normal c-Ha-ras gene, a protein believed to signal cells to start or stop dividing through its interaction with guanosine triphosphate (GTP).

Kim has now determined the structure of the protein encoded by a transforming c-Ha-ras oncogene in which a valine codon replaces the normal glycine codon at position 12 in the gene. The differences in the structures of the mutant and normal proteins are located primarily in a loop that interacts with the β phosphate of a bound guanosine diphosphate (GDP) molecule.

Working with Kim at Berkeley were graduate students Liang Tong and Michael V. Milburn, post-doctoral fellow Abraham M. de Vos, and laboratory chemist Jarmila Jancarik. Kim collaborated in the research with Suysumu Nishimura and Sigeru Noguchi at the National Cancer Centre Research Institute, Tokyo, and Eiko Ohtsuka and Kazunobu Miura at Hokkaido University, Sapporo. The research was supported by the National Institutes of Health; Department of Energy; Japanese Ministry of Health and Welfare; and Merck, Sharp & Dohme.

In a healthy cell, the normal ras protein binds with GTP and transmits signals from the cell membrane to the cell interior that initiate a cascade of reactions that cause the cell to divide, Kim explains. This ras protein exhibits GTPase activity, and in the normal course of events, the protein cleaves a phosphate ion from the bound GTP to produce GDP, which signals the cell to stop dividing.

The mutant ras protein, which has been found in almost all pancreas tumours and about half of colon tumours as well as tumours from the breast, bladder, and lung, appears to have a significantly reduced GTPase activity. Kim says that the rate of conversion of GTP to GDP in the mutant protein is less than 5 per cent of what it is in the normal protein.

The recently reported research suggests why this might be so. The ras protein contains six β-strands, four α-helices, and nine connecting loops. The protein consists of two structural domains - the amino-terminal domain, containing the first 75 amino acid residues (including the first three β-strands and one α-helix), which binds phosphate; and the carboxy-terminal domain (including the last three β-strands and three α-helices), which recognizes guanine. (Extracted with permission from Chemical and Engineering News, pp. 31-34, 16 January 1989. Copyright 1989 by the American Chemical Society)

Research on animal genes

Genetic clues to the development of sex

The two sexes develop in a fascinating variety of ways in different species. In mammals, the primary step seems to be the sex chromosomes, and biologists have recently identified a gene on the Y chromosome that some researchers think determines male development. In the absence of that gene, development typically proceeds in a female direction.

The mammalian pattern is far from universal, however. In modern reptiles, for instance, some species have clear differences in chromosomes between the sexes, while in others, the temperature at which the egg incubates determines the embryo's sex.

Researchers believe that a study of the genes involved in each process of sex determination might indicate something about the evolution of such processes. James Bull and his colleagues at the University of Texas in Austin looked at reptilian genes using a copy, or clone, of the mammalian gene believed to determine male development. The gene is called the testis determining factor (TDF), or, as it is a "zinc finger" protein, ZFY.

If the structure of DNA in the cloned gene is very similar to sequences in the DNA of other species, then the cloned gene will match up, or hybridize, with them. Somewhat surprisingly, all the species that the researchers studied - species of lizards, snakes, turtles and crocodilians - had DNA that hybridized with ZFY.

This genetic similarity among the species, the researchers believe, suggests that the sequences of DNA have persisted through evolution. Interestingly, the team found no difference in patterns of hybridization between species having each type of sex determination.

In reptiles, unlike mammals, DNA from both males and females will hybridize with ZFY. This finding suggests, say Bull and his colleagues, that the reptilian genes are located on the autosomes - which are common to both sexes - and not on the sex chromosomes. So, if these genes do have a major role in determining sex in reptiles, the mechanism differs from that of mammals.

Yet there are some similarities hidden in the diversity shown by animals. One species of nematode worm, Caenorhabditis elegans, for example, appears to have a mechanism for differentiating the sexes that is similar, in some ways, to the mammalian type. C. elegans, has two sexes, distinguished by sex chromosomes: male (XO) and hermaphrodite (XX).

In humans, the possession of a Y chromosome usually guarantees that a foetus develops as a male. A year ago, scientists in the US identified a gene on the Y chromosome of a number of mammals that might be responsible for male development.

Andrew Sinclair, at La Trobe University in Victoria, Australia, and colleagues in the US and Britain have found that marsupial mammals such as kangaroos have the ZFY gene, just as placental mammals do. But, according to the new work in marsupials, the gene is not on the sex chromosomes at all: instead, it is on the autosomes, the set of chromosomes shared by both sexes.

Sinclair and his colleagues used a genetic probe to identify matching sequences of DNA from several species of marsupials. The probe matched stretches of DNA taken from three species of kangaroos and wallabies: but in all three the matching sequence was present in both males and females. The researchers found no such sequence on either of the sex chromosomes.

Yet marsupials, like placental mammals, depend upon something on the Y chromosome to determine the development of testes. If an equivalent to ZFY is not on either sex chromosome, then this means either that ZFY is not what determines the development of testes at all, or that other, unknown, genes are responsible in marsupials. The researchers favour the second possibility; the evidence is strong, they argue, that ZFY is the gene involved in humans and other placental mammals.

In Britain, Jonathan Hodgkin of the Medical Research Council, Laboratory of Molecular Biology in Cambridge suggests one explanation: he believes that the marsupial gene identified by the gene probe may not be equivalent to ZFY at all. Placental mammals also have a closely related gene on the X chromosome, called ZFX: Hodgkin argues that it may be the ZFX gene that is similar to the marsupial gene.

One puzzle for biologists is how the differences evolved. Marsupials diverged in evolution from placental mammals more than 130 million years ago. David Page, of the Whithead Institute in Boston, Massachusetts, who first identified ZFY in humans, has also found similar sequences in birds; these, too, are not on the sex chromosomes. So, Sinclair and his colleagues argue, the ZFY gene acquired its testis-determining role and moved to the Y chromosome only after placental mammals diverged from marsupials. (Extracted from New Scientist, 17 December 1988 and 25 February 1989)

Technique reduces time needed for gene splicing

Researchers have developed a technique, positive and negative selection, to cut half the time needed for animal gene splicing. The technique was developed by University of Utah biology professor M. R. Capecchi and colleagues S. L. Mansour and K. R. Thomas. Current methods for making genetic alterations involved random placement of the synthetic gene material. Currently, the PNS method works only on embryo cells and targets some genes better than others. Refinements are being made to the technique. (Extracted from Wall Street Journal, 25 November 1988)

RGF refined from pigs

Calpis Food Industry (Japan) has successfully refined a glycoprotein hormone called high-purity renal growth factor (RGF) from the pituitary gland of a pig. It was working jointly with a research group from Tokyo Women's Medical College. RGF stimulates kidney cells and is therefore regarded as a promising therapy for renal insufficiency and other diseases. Calpis and Genentech (US) have signed an agreement whereby the latter will further develop RGF into an actual product. (Extracted from Japan Economic Journal, 26 November 1988)

Silkworm becomes the moth of invention

Researchers in the French city of Lyons are waiting anxiously for the moment when a batch of silkworm larvae emerges as moths. When the moths mate, their offspring will be the subject of intense scrutiny among academics and biotechnology companies.

The scientists want to know whether the new generation of silkworms will carry the foreign genes injected into the parent insects while these were still embryos. The eventual aim is to propagate generations of silkworms which would produce valuable proteins such as interferon or insulin in their silk.

There is much commercial interest in the project because the proteins would be easy to purify. At the moment, the most expensive process in biotechnology is purifying the required proteins. Pierre Coubel, at the Claude Bernard University in Lyons, says: "The silkworm is one of the best producers of protein in the world. It is even more efficient than industrial fermentation plants".

Silkworms produce vast quantities of silk protein because of the promoters. The promoter sequences in the genes for silk proteins cause the worm to produce large amounts of the five proteins in silk from the information held in the cell's single copy of each gene. Couble and his colleagues wanted to see if they could make these promoter sequences work with other genes, and promote the same massive production of the required substance.

The team carried out its initial work on the fruit fly, Drosophila. The cells in the salivary glands of these flies are large: it is easy to inject them with material using minute glass needles. Couble expected the silk promoter to work in the fruit fly's glands because the silk glands of the silkworm are modified salivary glands.

Another feature of the fruit fly is that its cells naturally contain a sequence of DNA, known as the P-element, which cuts into its genome and inserts chunks of DNA. Scientists can use the P-element to insert foreign DNA. At the start of their work, Couble had such a sequence, called a transposon, which worked only in fruit flies. He now has a transposon for silkworms.

The team injected the salivary glands of the fly with the promoters from the silkworm, plus a bacterial gene which codes for an enzyme called beta-galactosidase. By using a test for the product of the enzyme, the researchers showed that the enzyme was present in the fly's salivary gland, indicating that the silk promoter will indeed work with a foreign gene.

The team then went on to perfect a method for microinjecting the embryos of silkworms. The scientists injected the silkworm's transposon into the embryo to clip the foreign sequence of DNA coding for beta-galactosidase into the silkworm's genome. They did this before the cytoplasm of the egg began to divide into separate cells.

One drawbak with microinjection into cells is that only some of the DNA will be incorporated into the genome. It is also hard to tell whether the DNA expressed in an injected insect has been stably incorporated into its genome or not. But foreign genes expressed by the offspring of injected insects must be stably incorporated into the genome: hence the anxious wait for offspring of the moths that Couble injected as embryos.

The silkworms will not secrete the products of the injected genes in their silk, however. Couble and his colleagues have deliberately used genes that code for proteins that cells cannot secrete. This methods allows the researchers to check whether all the cells in the insect are expressing the foreign gene, by staining slices of the insect. The researchers need to be sure that all the nuclei that form the insect embryo take up the foreign gene, otherwise some of the silkworms in subsequent generations may not produce the foreign protein. (Source: New Scientist, 11 March 1989)

Hawaii Biotechnology Group develops new Mediterranean fruit fly strain

Hawaii Biotechnology Group, Inc. has filed a patent application for a new strain of Mediterranean fruit fly, Ceratitis capitata, which can be used to control and eradicate this pest.

The new strain produces healthy winged males and flightless females, explains discoverer Dr. Stephen Saul, a University of Hawaii research and consultant to HBG. The new approach could revolutionize release control of the medfly, oriental fruit fly, melon fly and similar insect pests through sterile release programmes.

The tiny fly is a major agricultural pest throughout the tropical and subtropical world, attacking more than 150 varieties of cultivated fruit and vegetable crops. It is endemic to Europe, the Middle East, South Africa, Central and South America, and Hawaii, but not - so far - to North America. A handful of medflies discovered in Southern California insect traps in 1981 sparked a successful $100 million eradication effort.

Eradication programmes for medflies and other fruit flies typically employ massive spraying of a baited insecticide, usually malathion, to destroy the target population across broad agricultural and residential areas. Widespread insecticide spraying programmes can be effective, but they also raise serious environmental questions. And, as the State of California discovered, spraying over residential areas is at least as effective in producing public protests and lawsuits as it is in controlling insect pests.

The alternative to spraying is the Sterile Insect Release Method (SIRM), used successfully in California, Texas, Central America and other locations around the world. Millions of sterilized flies are released to mate with the wild population, which then produce no offspring. Effective in the long term, SIRM produces a short-term agricultural disaster that severely limits its use.

Dr. Saul's new fly is the first effective genetic sexing system in the medfly. Hawaii Biotech has been working since 1986 on genetic sexing using purine-metabolizing genes from Drosophila and Ceratitis to transform a rosy-eyed, purine-sensitive medfly mutant.

Funded by a part of Hawaii Biotech's $1.2 million R&D limited partnership, Dr. Saul developed a medfly strain which produces only v-wing$^+$ males, flies with normal wings which can fly, and v-wing females with stubby wings which cannot fly. The only specific culture requirement is rearing at 30°C or higher to maximize the stubby-winged expression, although tests are under way to see if lower temperatures can produce full expression. The mixed male and female population is then sterilized, usually by exposure to radioactive cobalt.

When released, the sterile males will be able to disperse immediately to mate with wild females. The flightless sterile females will not be able to leave the release site, removing both objections to SIRM control programmes.

The new strain, descended from medflies imported from Israel, is expected to remain in quarantine until early this year. Hawaii, which has suffered from repeated introductions of exotic species, has some of the most stringent plant, animal, and insect quarantine regulations in the United States.

The USDA, ultimately responsible for growing and releasing the sterile flies, must also be satisfied that the new strain performs as advertised. The first hurdle is flyability - can the sterile males actually fly far enough and long enough to find and mate with wild females? Another question is the ability of laboratory-raised flies to mate in the wild. There are also culture questions.

The most likely site for outdoor testing is the island of Kauai, the most isolated of the major

islands of Hawaii. If the tests are successful, Hawaii Biotech hopes to introduce the new fly in Central ALmerica through a control programme administered by the USDA for the United Nations Food and Agriculture Organization. A proposed expansion of this programme (dubbed CAPMed) involves a five-year $250 million programme aimed at pushing the medfly out of Central America as far south as the Isthmus of Panama using sterile release. (Source: Genetic Engineering News, February 1989)

Mutant fruit flies hold clues to aging

Dr. Glenn C. Bewley, North Carolina State University (Raleigh) professior of genetics, is experimenting with fruit flies to determine the role that superoxide dismutase (SOD) and catalase play in the aging process and in lifespan determination. These anti-oxidant or "scavenging" enzymes could slow the rate of aging by breaking down oxygen free radicals.

Dr. Bewley constructed strains of mutant flies that were acatalesemic. While normal fruit flies live about 60 days, those without catalase activity had life spans of 12 to 20 days. He now plans to determine if acatalesemic fruit flies have higher mutation rates than normal fruit flies. He will use the mutant flies to determine the rate of damage to genetic material by oxygen free radicals and to learn the extent to which anti-oxidant enzymes protect DNA from oxidative damage.

The scientist will also create mutant flies without SOD activity and another strain lacking SOD and catalase activity. He predicts that fruit flies lacking both enzymes will be very susceptible to DNA damage and will not live very long. (Source: Genetic Engineering News, February 1989)

Research on plant genes

Simple weed could hold key to genetics

A weed with one of the simplest set of genes of any flowering plant is about to prove its worth as a potential tool for plant scientists who want to engineer the genetics of crops. They hope that the humble Arabidopsis, or thale cress, will become the next Drosophila or Escherichia coli - two organisms which have achieved fame by helping scientists to solve some of the greatest problems in genetics.

Researchers at the Institute of Plant Science Research and the Sainsbury Laboratory in Norwich are hoping that Arabidopsis will help them to discover new genes that will make crops resistant to pests. The hope is that crops with resistance genes built in will need little if any chemical pesticides to protect them from attack.

The weed, which grows about 5 centimetres high, is causing interest because it has a relatively simple genetic structure. It has about a tenth of the DNA contained within the cells of other flowering plants, such as tomato or tobacco plants, and a hundredth of the DNA contained within a single human cell.

Geneticists hope that such a simple genetic structure will make it easy for them to distinguish the important genes from the "junk" DNA that has no apparent role to play in an organism's ability to fight disease.

Mike Daniels, the head of the Sainsbury Laboratory, is hoping that Arabidopsis will be able to prove a better guinea pig than the more complex plants he has used in the past. Daniels is beginning an experiment this year to test his theory.

He will first soak the seeds of Arabidopsis in a chemical that will cause mutations in the genes of the plant. The weed has extremely small seeds, 0.5 millimetres long, which means that a teaspoon can hold about 10,000 seeds. The very large number of seeds that the plant produces is also an advantage in screening its progeny for new resistance traits.

After soaking, the seeds will then be allowed to grow and self-pollinate. In the subsequent generation, therefore, about a quarter of the mutations that have occurred will appear as physical traits of the plant. This follows the usual rules of Mendelian inheritance, which state that a recessive mutation will appear in about 25 per cent of the first generation.

The next step is to see whether any of these mutations increases the plant's ability to fend off an attack by a plant pest, such as a bacterial or fungal infection.

If there are indivual plants that appear resistant, the researchers will begin the difficult task of trying to locate and isolate the gene responsible. The next step is to clone the gene so that it can eventually be transferred into commercially important crops to pass on resistance.

The amount of DNA in Arabidopsis is so small that it is feasible for plant geneticists to locate the gene by a technique they call "chromosome walking". This technique allows geneticists to map the piece of DNA that contains the gene by gradually building up a jigsaw of fragments lying between two known points, or genetic markers.

The researchers will know when they have "walked over" the gene that they are searching for by inserting the individual fragment in question into a plant that does not possess that trait. If the plant then becomes resistant to the pest, the scientists have found what they are looking for. (Source: New Scientist, 4 February 1989)

Artificial seeds

Artificial seeds have been produced from normal plant cells by researchers at the University of Guelph. The technique could save endangered species, and could allow international propagation of plants without international transport of cuttings. Perhaps 100,000 identical seeds could be produced from a single plant. The artificial seeds can be dried out just like normal seeds, without affecting their ability to germinate. The seeds are produced by placing a small amount of plant tissue in a culture containing 2,4-dichlorophenoxyacetic acid, which is a derivative of auxin. This medium causes some cells to start to develop into embryos. A combination of nutrients slows down the metabolism so the embryos are resistant to dessication. The seeds could also be coated to further protect them. (Extracted from New Scientist, 18 February 1989)

Plant scientists breakthrough

Researchers at the Swedish University of Agricultural Sciences and Du Pont have described the structure of the active site of the key plant enzyme, Rubisco. A better understanding of this enzyme's activity could lead to more efficient, higher yielding crops, according to Dr. Ron Fraser, head of Littlehampton AFRC Institute of Horticultural Research.

The enzyme, which is the most abundant protein on Earth, is responsible for catalyzing two competing reactions. It catalyzes the carboxylation

step in the Calvin cycle which ultimately converts carbon dioxide to sugars using solar energy trapped during photosynthesis. It also catalyzes the competing photorespiration reaction during which a considerable amount of stored energy is converted to heat thus limiting crop yields. Plant scientists are hoping to modify the latter activity to improve the fixation efficiency.

By determining the crystal structure of the enzyme's active site, the researchers are one step closer to determining how the enzyme works. In higher plants the enzyme spends about two thirds of its time catalyzing carboxylation and the rest photorespiration whereas in lower photosynthetic organisms the carbon fixation activity is less efficient.

Dr. Alfred Keys, at the Institute of Arable Crop Research, Rothamsted, explains that one goal of plant reseachers is to determine whether nature's evolutionary advances in the enzyme's efficiency can be further improved. In the longer term scientists may be able to introduce a modified, more efficient enzyme into other plants.

Professor David Hall, of Kings College, London, cautions that to date all attempts to improve carboxylation at the expense of photorespiration have failed. But if the process can be copied chemically then it may be possible to utilize carbon dioxide better. Moreover, it may even provide a solution to the problems of the so-called greenhouse effect. (Source: European Chemical News, 30 January 1989)

Recombinant melanin expressed in plants

A proprietary gene expression system that acts quickly and temporarily to produce recombinant products in plant tissues - Biosource Genetics Corporation's (Vacaville, California) Genevare^{R} - produces melanin for a "natural" sunscreen. Based on a plant RNA virus vector, the system inserts recombinant RNA directly into the plant's cytoplasm. Once inserted, the vector begins expressing the recombinant product in a matter of days - much faster than other transformation methods that target the cell nucleus.

Unlike PABA (para-amino-benzoic acid, now the sunscreen of choice), melanin completely blocks not only UV-A and UV-B ultraviolet radiation, but also the highly mutagenic UV-C (of which none reaches the Earth now, thanks to the ozone layer).

The vector is constructed from viral replication genes plus selected promoters. Once in the plant cells the vector multiplies by cell-cell transmission.

Neither stable over time nor sexually transmitted, the Biosource vector disappears after a few weeks. But that is enough time to "crank out a lot" of melanin.

Biosource scientists are experimenting with various production methods. They have had success with bioreactor cultures, generally using tobacco plant cells grown in airlift reactors (76 litres working volume). In one system, melanin is secreted into the medium; researchers are adapting that system to continuous flow culture.

Melanin from plants will be a more convenient and less expensive alternative to current commercial sources, which are now extracted from octopus, squid, and other cephalopods. Melanin from Sepia officinalis now costs about $74/gram.

The vector leads the way for augmenting production of valuable compounds already made by plants - for example, increasing the production of the chemotherapeutic agent vincristine in periwinkles.

Besides the melanin-gene vector, Biosource Genetics is developing another version of the vector that will function as a gametocide. Plant breeders currently inhibit pollen production with chemical gametocides, which make it easier to produce hybrid seeds. But whereas chemical gametocides sterilize the entire plant, the recombinant gametocide envisioned would sterilize only the pollen by inducing cytoplasmic male sterility.

Other applications in developent at Biosource include using plant bioreactor cultures to produce carbohydrates for cosmetic uses and to produce stereoselective enzymes. (Source: Bio/Technology, Vol. 7, January 1989)

Herbicide tolerance engineered into cotton

Monsanto scientists have genetically engineered cotton for tolerance to the company's non-selective Roundup herbicide. Calling such tolerance a trait of major commercial significance, Monsanto says it anticipates commercialization of genetically engineered cotton with Roundup herbicide tolerance as early as the mid-1990s. The cotton plants were produced using a gene transfer system mediated by Agrobacterium tumefaciens. The agrobacterium has the natural ability to transfer some its own DNA into plant cells, but the result is usually a type of injury known as crown gall. Monsanto researchers developed a method to stop the micro-organism from causing crown gall but keeping its ability to insert DNA into plant cells. Altered plant cells were then regenerated into healthy cotton plants using tissue culture. Monsanto recently announced success in genetically engineering soybeans for Roundup herbicide tolerance (Reprinted with permission from Chemical and Engineering News, p. 21, 28 November 1988. Copyright 1988 by the American Chemical Society)

Plants that perfect a trick of the light

A researcher in the US has discovered why plants have two slightly different mechanisms for photosynthesis. When plants photosynthesize, electrons are taken from water and given sufficient energy to reduce carbon dioxide to carbohydrate. In order to do this, two systems that absorb slightly different wavelengths of light work in series. The systems, called PSI and PSII, use the light to convert the carbon dioxide to carbohydrate.

Researchers have found that plants redistribute energy from one photosystem to another. The conversion to carbohydrate in PSI occurs more rapidly than that in PSII if light of wavelengths greater than 680 nanometres - 680 millionths of a millimetre - shines onto PSI. This wavelength is in the far red spectrum. After 10 to 15 minutes, the energy from the absorbed light is redistributed between the two photosystems and PSII begins to pick up at the expense of PSI. One of the ways that the plant achieves this is by moving chlorophyll molecules between PSI and PSII.

After this redistribution the plant is said to be in state I. State II - the reverse pattern -

occurs when PSII begins to work faster than PSI and the plant reorganizes to give more of the light energy to PSI.

Until now, scientists had not known why plants needed to switch between the two states in nature. They thought that plants operated in state I only under artificial conditions, such as under infrared light or in the presence of certain chemicals.

Hugh McTavish, of Brown University in Rhode Island, studied two species in the outdoors - tree of heaven (Ailanthus altissima and colts foot (Chenopodium album), in order to discover why plants need to change states in this way.

He picked leaves of each plant, ground them in a solution of sorbitol and then filtered the mixture to leave a suspension of chloroplasts. He put the suspension in capillary tubes and froze it in liquid nitrogen. This took about one minute from start to finish - too short a period for the cells to switch from one state to the other.

McTavish found that if he shone visible light onto the suspensions they began to fluoresce a deep red colour. He found that the fluorescence of PSII peaked at wavelengths of 695 nanometres, and that of PSI peaked at 730 nanometres. The level of fluorescence depended on the amount of light each suspension received.

By monitoring changes in the ratio of fluorescence at 695 nanometres and 730 nanometres, McTavish was able to tell when the plant cells changed state.

McTavish showed that in the morning, when the two species were in full sunlight, they were both in state II. In the afternoon they were both under shade, and so received mostly green light. Under these conditions, he found that the colt's foot was in state I and the tree of heaven was in an intermediate state between I and II. According to McTavish, transitions from one state to the other enable plants to photosynthesize with maximum efficiency in both white and green light. (Source: New Scientist, 3 December 1988)

Mutant petunias join the wild bunch in Germany

The authorities in the Federal Republic of Germany have approved for the first time an outdoor experiment with genetically engineered organisms. The FRG committee on recombinant DNA technology cleared the Max Planck Institute for Plant Breeding in Cologne to release 37,000 genetically modified petunias.

There is no law in the FRG governing the release of genetically modified organisms, but scientists are forced to request permission from the rDNA committee if they wish to undertake such experiments. The petunias are the first organisms containing recombinant DNA that the committee has reviewed for approval. The FRG Drug Licensing Authority must ratify the decision before the experiment proceeds, however.

Heinz Saedler and colleagues will plant the petunias on a plot of 5,000 square metres at the institute. The experiment is designed to observe and capture "jumping genes", segments of DNA that can move about within the genome of the petunias. They occur in all organisms, but are difficult to isolate except in maize, where they have been well studied.

The team in Cologne wants to see whether jumping genes in maize resemble those in distantly related plants, such as the petunia. First, the team will insert A-1, a conventional gene from maize, into the genes of white petunias. The A-1 gene codes for an enzyme which makes a pigment that turns flowers pink.

A jumping gene from the petunia could disrupt the A-1 gene, which will no longer function. This will cause a white spot to appear amid the pink. Scientists know the sequence of DNA that makes up the A-1 gene, and can construct strands of DNA that will bind strongly to it.

This permits scientists to locate the gene easily within the petunia's genes. By isolating the A-1 gene within a white spot, they will be able to extract the petunia's jumping gene as well.

Because jumping genes disrupt the activity of genetic material, they give clues to the function of their host gene. The probability of a gene jumping into the A-1 gene in the petunias is low. One in 5,000 to 10,000 plants will develop white spots. This is why the team must plant so many flowers. (Source: New Scientist, 11 March 1989)

PGS develops plant peptide producers

Plant Genetic Systems (PGS), the Belgian agrobiotechnology company, has genetically engineered plants so they can produce high value pharmaceutical peptides. With the technique, developed in collaboration with the University of Ghent, economically important peptides can be produced and stored in a stable form within specific plant organs.

According to Walter De Logi, PGS managing director, peptides are produced at high levels, and can be extracted by a simple process. Products that can be made include drugs such as blood factors and growth hormones. (Source: European Chemical News, 27 February 1989)

UNC scientists hybridize seaweed

Dr. Donald F. Kapraun and D. Wilson Freshwater, marine botany researchers at University of North Carolina (Wilmington), have used genetic engineering techniques to hybridize a seaweed known as green nori that does not reproduce sexually, a staple in Japanese diets. Production of green nori currently relies on harvesting wild plants. Because this variety of seaweed has no egg and sperm, it is not possible to produce hybrids in a normal way. The scientists used parasexual hybridization to combine genotypes.

According to Dr. Kapraun, this is the first time genetic characteristics have been transferred in any seaweed by producing fusion cells with hybrid nuclei that could regenerate hybrid plants. The next step is development of a genetically superior variety of green nori, using the researchers' collection of cloned seaweeds gathered from throughout the tropics of North, Central and South America. (Source: Genetic Engineering News, February 1989)

Research on yeast and fungus genes

Research on ligninases takes big step forward

Efforts to harness for practical purposes the lignin-degrading enzymes of the white rot fungus

Phanerochaete chrysosporium have been brought somewhat closer to reality as a result of recently reported research from scientists at Oregon Graduate Center.

Michael H. Gold, professor and chairman of the Beaverton-based graduate centre's Department of Chemical and Biological Sciences, and co-workers have made major contributions toward understanding the biodegradation of lignin, which is the second most abundant natural polymer. Lignin is a random phenylpropanoid matrix that makes up 20 to 30 per cent of woody plants and retards microbial depolymerization of cellulose.

Two extracellular enzymes produced by P. chrysosporium, lignin peroxidase and manganese peroxidase, are responsible for the breakdown of lignin. Lignin peroxidase (LiP) was discovered independently in 1983 in Gold's laboratory and in the laboratory of T. Kent Kirk at the US Forest Products Laboratory in Madison, Wis. Gold's group discovered manganese peroxidase (MnP) the following year.

With Margaret Alic, Janet R. Kornegay, and David G. Pribnow, Gold has now developed the first DNA transformation system for P. chrysosporium. The system will facilitate studies on the regulation and expression of the genes that encode LiP and MnP as well as genetic approaches to structure-function studies of the enzymes.

Additionally, Gold, Pribnow and Mary B. Mayfield, Valerie J. Nipper, and Julie A. Brown have characterized for the first time a cDNA (that is, a deoxyribonucleic acid copy of a messenger ribonucleic acid) that encodes MnP. Combined with the P. chrysosporium transformation system, as well as research by other groups the results of the research on MnP gene should allow the Oregon Graduate Center scientists to produce large amounts of recombinant LiP and MnP in the near future.

LiP and MnP, or modified organisms that produce these enzymes themselves, could find use in a number of bioprocessing applications. There are a number of points in the production of paper, for example, where the enzymes might be used in place of traditional chemistry. Also, numerous possibilities exist for the use of these enzymes as non-specific oxidative reagents for degrading aromatic environmental pollutants such as chlorophenols and dyes. (Extracted with permission from Chemical and Engineering News, p. 29, 27 March 1989. Copyright 1989 by the American Chemical Society)

New enzymes the old-fashioned way: find them

Traditional microbial screening programmes continue to be important in the industrial development of novel enzymes as evidenced by presentations at the Taniguchi Foundation's Seventh International Symposium on the Life Sciences. One highlight - a new fungal peroxidase - that might brighten the laboratories of biologists doing assays using hydrogen peroxide coupled reactions as detectors, was described by Teruo Amachi (Suntory Ltd., Osaka, Japan)

The ability of hydrogen peroxide oxidoreductases to couple hydrogen peroxide to a variety of substrates has been exploited in diagnostic and research laboratories in applications ranging from enzyme-linked immunosorbent assays (ELISAs), to nucleic acid hybridization, to tracing neuronal connections. These assays most frequently employ the peroxidase isolated from horseradish roots (HRP). But HRP's activity with some useful substrates is less than optimal, and most commercially available enzymes contain a number of isozymes.

The Suntory scientists screened soil fungi and found a previously undescribed taxon of the Hyphomycetes (Arthomyces ramosus) that secreted large amounts of a very active peroxidase, which they have termed ARP. ARP's activity resides in a single-chain, heme-containing glycoprotein of 41 kD (as estimated from sedimentation equilibrium), with about 5 per cent carbohydrate content and one molecule of heme. The researchers presently purify the enzyme from 2,000-litre fungal cultures, under conditions where the cells secrete 100 units/ml. Protein from the final gel-filtration is readily crystallized from a 60 per cent saturated ammonium sulphate solution.

With the most common clinically used hydrogen donor substrate (4-aminoantipyrine), the Vmax of ARP is three times that of the HRP isozyme mixture. And with the chemiluminescent substrate luminol, its Vmax is 500 times greater. The Suntory group has used this differential to design glucose and cholesterol assays that are notably more sensitive than corresponding assays using HRP. It should be possible to develop enhanced-sensitivity ELISAs based on this "chemiluminescent potential". It will also be interesting to determine how the new enzyme compares to HRP in the oxidation of tetramethyl benzidine, the chromogen of choice in molecular biological applications. (Source: Bio/Technology, Vol. 7, January 1989)

Research on bacterial genes

Full sequence for E. coli

Japan's Ministry of Education, Culture and Science (MESC) will announce its backing for a project to sequence the entire genome of the bacterium Escherichia coli. With luck, E. coli's estimated 4,700 kilobase pairs, one thousandth the number of the human genome, could be sequenced in five years. Funding for the project will remain uncertain until the Diet passes the 1989 budget, delayed by political quarrels over the Recruit bribery scandal. But given the scale of MESC's "priority areas of research" fund, it seems likely that more than a million dollars a year will be provided for an initial three years.

The project is led by Takashi Yura of Kyoto University and Katsumi Isono of Kobe University and builds on a physical map of the E. coli chromosome put together from 3,400 clones. Researchers from Kyoto, Kobe, Osaka and Tokyo universities will make up the core of the project, but international collaboration should become possible once a clone bank has been established at the National Institute of Genetics at Mishima.

E. coli has already been extensively studied. More than 1,000 genes have been mapped and about 450 kilobase pairs have been sequenced by researchers around the world. Isono says he hopes his laboratory alone will be able to manage 200-500 kilobases a year. He adds a note of caution, however, because in sequencing projects, "90 per cent of the work is done in 50 per cent of the time", with unbridgeable gaps remaining.

If unsuccessful, the complete E. coli sequence will be the first for an independently living organism. (Source: Nature, Vol. 338, 23 March 1989)

Ancient bacteria resistant to some antibiotics

Bacteria taken from the frozen bodies of 19th-century explorers are resistant to certain types of antibiotics. Antibiotics came into general use 40 years ago, so the discovery challenges the view that only the widespread use and abuse of antibiotics has built up resistance to them.

Kay Kowalevska-Grochowska and colleagues from the University of Alberta Hospital at Edmonton in Canada, isolated six strains of bacteria of the genus Clostridium from the bodies of William Braine and John Hartnell, members of the Franklin expedition to the Arctic in 1845. Kowalevska-Grochowska grew the bacteria, which are part of the normal flora present in people's intestines, and tested the microbes' resistance to various antibiotics. Chloramphenicol, metronidazole and penicillin were active against the six strains. But, surprisingly, the 140 year-old bacteria were resistant to two other antibiotics, cefoxitin and clindamycin. Cefoxitin is used widely for many infections including peritonitis and gonorrhoea.

The researchers speculate that resistance to clindamycin and cefoxitin arose because the explorers came into contact with the micro-organisms that naturally produce these antibiotics. Another possibility is that a random mutation in the chromosomes of the six strains of Clostridium bacteria may have rendered them resistant.

John Franklin left England with 129 men in 1845, to search for the Northwest Passage. All of the party died within three years. Owen Beattie, of the University of Alberta, led an expedition to the Arctic to try to discover why they died.

Beattie found the Clostridium bacteria only in the two men's bowels, indicating that the bacteria were not present as a result of contamination. The researchers are now trying to determine the mechanism of resistance. One theory is that the gene for resistance to lead and the genes for resistance to cefoxitin and clindamycin may be on the same segment of DNA in the bacteria. (Source: New Scientist, 11 February 1989)

Protease discovered

A protease has been discovered that can withstand temperatures above 40° C by Dr. T. Gusek of Cornell University. The enzyme, isolated from a strain of bacterium, thermomonospora fusca, can break down plant and animal proteins at temperatures up to 85° C. It works 13 times faster at 80° C than subtilisin, a protease currently being used in detergents. Protein molecules, found in stain-causing substances such as blood, grass and wine, are made of protein molecules which, when they meet fabric, unravel. This exposes reactive chemicals which cling to the fabric. Most detergents find it difficult to remove these molecules. A protease, when added to the detergent, attacks those bonds along the protein's molecular chain, breaking them into fragments which can more easily be attacked by a detergent.

The new strain of protease, dubbed YX, can be used to make protein hydrolysates, liquid foods administered to post-operative patients through tubes. Thermomonospora fusca secretes very minute quantities of protease. Scientists plan to tinker with the genes of another soil bacterium species used to make antibiotics. The gene that codes for YX protease in Thermomonospora will be taken and put into DNA molecules, called plasmids, from the other microbe. When these plasmids are returned to their original owners, they may produce large amounts of the enzyme. (Extracted from The Economist, 10 March 1989)

Genetically engineered bacteria against wheat take-all disease

Monsanto has genetically engineered bacteria to prevent wheat take-all disease, a fungal disease for which there is no remedy and no resistant varieties. The fungus invades wheat roots. The Pseudomonas bacterium naturally makes a compound related to the antifungal phenazine. Monsanto researchers have added two genes to allow tracking of the bacterium in the soil at a Clemson University test site. The bacteria did not actually have fungicidal activity. Preliminary tests were intended to determine if the bacteria exchanged genetic information with any wild-type bacteria in the soil. No transfer was detected. All the bacteria stayed within 7 inches of where they were placed. The next set of experiments will determine if the altered Pseudomonas, when coated on wheat seeds, might prevent infection by the fungus. (Extracted from Science News, 5 November 1988)

Photosynthesizing, nitrogen-fixing bacterium discovered

Scientists at Cornell University's Boyce Thompson Institute for Plant Research (BTI) in Ithaca, NY have discovered a bacterium that can fix nitrogen for use by plants without depending on the plants for energy.

The organism, named Photorhizobium thompsonum, is the first known symbiotic bacterium that is both phtosynthetic and nitrogen-fixing. The researchers believe that by studying this bacterium genetic engineers could develop methods to incorporate nitrogen-fixation capabilities into crop plants that now lack them. Expanding plants' ability to fix nitrogen from the air would greatly decrease the need for chemical fertilizers.

In addition, the new bacterium could lead to the development of crops with greater yield. It has been widely known that some bacteria (rhizobia) form symbiotic relationships with legumes such as soybeans, peanuts and alfalfa. However, rhizobia usually require energy from the plant to perform nitrogen fixation.

If plants could be developed that no longer need to give up some of their energy to the bacteria in exchange for nitrogen (in some cases, up to 12 pounds of "energy materials" for one pound of nitrogen), that effort could translate into increased yields.

Leguminous plants attract nitrogen-fixing micro-organisms that are held in root nodules, allowing them to thrive in soil with little available nitrogen. The rarer growth of nitrogen-fixing nodules on plant stems has been a subject of intense study at BTI. Stem nodules do not normally appear on agriculturally important crops (e.g. corn), but do occur on some plants living in flooded conditions, particularly weedy plants of the genera Aeschynomene and Sesbania. Stem nodulation is believed to aid plants when water cuts off most of the oxygen and nitrogen needed by root nodules.

With the discovery of P. thompsonum, researchers can now try to find out how the bacterium forms nodules on plant stems instead of

the roots. In time, the scientists might be able to transplant these bacteria onto other plants.

The BTI scientists discovered the new bacterium while attempting to save Aeschynomene indica plants without nodules that were suffering from nitrogen-deficiency. Rather than destroy the dying plants, they transplanted them into sand from another greenhouse and flooded the roots with water. Within two weeks, nitrogen-fixing nodules appeared on the stems.

A subsequent series of tests showed that the nodules were caused not by a previously identified nitrogen-fixing bacterium in the sand, but by a completely new and different form that fixes nitrogen and conducts photosynthesis. The plant physiologists traced the sand to Virginia. Then they learned that another Aeschynomene species, A. virginica, is native to fresh and brackish tidal waters from New Jersey to southern Virginia.

Bacteria that produce nodules in A. virginica may have been present in small amounts of soil, which mix with sand during mining, and may be "promiscuous" enough to form nodules on other Aeschynomene species.

The scientists speculate that P. thompsonum may represent a primitive evolutionary form that could give hints of how nitrogen-fixing bacteria evolved and how the nitrogen-fixing nodulation in plants began. (Source: Genetic Engineering News, February 1989)

Research on viral genes

Probing the weak points in a retrovirus's defence

A new technique is helping scientists to understand how retroviruses splice their own genes into the genetic material of target cells. Patrick Brown at Stanford University in California, and his colleagues are studying the way in which viruses "integrate" into the chromosomes of host cells in the test tube. This work may speed the quest for ways of treating or preventing retroviral infections.

Retroviruses carry out a series of precisely choreographed steps once they enter the host cell. The genetic material of retroviruses is RNA, so the virus must convert its RNA to DNA to be able to infiltrate the DNA of the host cell. The viral DNA is then "stitched" into the DNA of the infected cells. These cells then replicate the viral genes along with their own DNA. If the "stitching" or integration of viral DNA into host DNA is blocked, the retrovirus cannot replicate.

Brown and his colleagues are looking at each step in the process of integration using a leukaemia virus from mice. They hope to find a potential target for drugs that can block the viral attack. All retroviruses appear to use the same method for integration.

Brown infects cells with the leukaemia virus, then extracts DNA which the virus has converted from RNA, but which remains unintegrated, from the cells. He also removes the enzymatic machinery required for subsequent integration. Using this method, Brown and his colleagues have identified the transformations that the viral genetic material undergoes as it is integrated. They have also identified some of the enzymes involved. Brown thinks that certain steps are more promising than others as targets for viral inhibitors.

He suspects that the process may be particularly vulnerable when one end of the viral DNA is cleaved. It could also be vulnerable later, when the target DNA is broken and viral and target DNA are joined. The researchers now want to investigate these steps, and the enzymes that are involved, in detail.

Brown's work may also help in developing effective methods for introducing new pieces of genetic information into cells. This technology is crucial for gene therapy, replacing defective genes with healthy ones. (Source: New Scientist, 25 March 1989)

Hepatitis virus may trigger gene for liver cancer

Researchers in France have found what they believe is the molecular mechanism that explains why certain viral infections of hepatitis B can lead to the development of cancer in the liver.

Tsuey-ying Hsu, Pierre Tiollais and colleagues from the Pasteur Institute in Paris have now found a possible explanation for the epidemiological evidence that links the virus for hepatitis B with liver cancer. They suggest that the virus can become integrated into the genetic material of the host at a position near to a dormant oncogene - a gene that can cause cancer. The integration of the viral material near to the oncogene results in the activation of the oncogene and the onset of cancer.

The researchers came to their conclusion after they had studied woodchucks that were infected with a virus that is indistinguishable from the human hepatitis B virus. The woodchuck virus shares identical sequences of nucleotides with the human virus. The animal is a good model of what happens in humans because infection with the virus can also lead to the development of liver cancer.

The team from the Pasteur Institute studied tumours from a number of animals that had developed cancer as a result of infection with woodchuck hepatitis virus. The researchers were particularly interested in the over-expression of a known oncogene, called the c-myc. In two out of three animals that were found to have an over-expression of the c-myc gene, the researchers could identify the integration of a viral material next to the oncogene.

The scientists suggest that the insertion of the viral material next to c-myc has activated the gene by disturbing the normal mechanism of control that keeps the gene dormant.

This research is the first to point to a mechanism for viral infection leading to liver cancer, although similar mechanisms are suggested for certain types of blood cancer. (Source: New Scientist, 3 December 1988)

How DNA viruses may cause cancer

Three viruses in particular, all of which have DNA as their genetic material, have been linked to common cancers: hepatitis B virus to liver cancer, Epstein-Barr virus to lymphomas and nasopharyngeal cancer, and certain strains of human papilloma virus to cervical and other genital cancers.

Many of the principal researchers who have been investigating the links between the DNA viruses and cancer gathered in San Diego to describe their recent findings at a conference on the role of DNA viruses in human tumours. Their presentations

showed that they are beginning to learn how these viruses help make cells malignant, although in no case is the viral action completely understood. What was clear, however, is that efforts to use vaccination to prevent the viral infections - and presumably the cancers with which they are linked - can proceed in the absence of a full understanding of the viral mechanisms of action.

The hepatitis B virus provides a case in point. As many as 300 million people, most of them concentrated in South-East Asia and especially in southern China, have become long-term carriers of this virus. A 10-year epidemiological study conducted in Taiwan by Palmer Beasley and his colleagues has shown that the carriers' risk of getting liver cancer is at least 100 times greater than that of non-carriers. For comparison, Beasley notes that cigarette smoking increases the risk of getting lung cancer about 20-fold. "It's absolutely clear that hepatitis B virus is the major cause of hepatocarcinoma", he concludes.

Effective vaccines to protect against hepatitis B virus infections have been available since the early 1980s. The major route of the virus transmission is from a carrier mother to her infant children at birth.

Several Asian countries, including Taiwan, Indonesia, Thailand, and China, have already embarked on infant vaccination programmes. Many years will be required to establish that vaccination reduces the toll taken by liver cancer in those countries. But all available evidence indicates that it will.

A vaccine to protect against Epstein-Barr virus infections may also be available soon, according to M. A. Epstein of Oxford University. The Epstein group has shown that a vaccine containing gp340, a large surface glycoprotein from the virus, works in cottontop tamarins.

Ordinarily these monkeys develop a malignant lymphoma within weeks of being infected with Epstein-Barr virus. The animals do not get sick, however, if they are first vaccinated with the gp340 preparation.

Epstein has approval from the appropriate committees in the United Kingdom to begin preliminary clinical trials of the gp340 vaccine in human volunteers to see whether it will elicit appropriate immune responses without producing unacceptable toxicity. If the vaccine passes muster in this trial, then a more extensive study will be undertaken to determine whether it will protect humans against Epstein-Barr virus.

Most of the presentations at the tumour virus conference focused, however, on efforts to understand how the viruses put the cells they infect on the path to malignancy, rather than on efforts to prevent those infections. The hope is that a better understanding of how the viruses induce cancers will pay off in a better understanding of the origins of cancer in general.

Recent results suggest that the Epstein-Barr and human papilloma viruses carry genes that immortalize infected cells and cause them to divide continuously. A variety of evidence points to two genes, designated E6 and E7, as the likely transforming genes of the cancer-associated papilloma viruses. Both genes are consistently found in the DNA of cervical cancer cells, for example, and are active there.

Peter Howley of the National Cancer Institute (NCI) in Bethesda, Maryland, have found that the E7 protein forms stable complexes with a cellular protein, the product of the retinoblastoma (RB) gene. The E7 protein resembles transforming proteins from two other viruses, adenovirus and simian virus 40, that also bind to the RB protein.

Because the RB gene is missing or inactivated in certain cancers, including retinoblastoma tumours of the eye, researchers think that the RB protein normally acts to inhibit cell growth. By binding to the RB product, E7 and the other transforming proteins may prevent it from acting, thereby allowing cells to grow out of control. At present, there is little information about the E6 gene's contribution to cell transformation.

The Epstein-Barr virus also appears to carry transforming genes. In addition, William Sugden of the University of Wisconsin in Madison has used a genetic approach to show that another gene, designated EBNA-2 (for Epstein-Barr virus nuclear antigen 2), immortalizes cells. The EBNA-2 product may work at least partly by stimulating the expression of other viral and cellular genes, including the LMP gene. (Extracted with permission from Science, Vol. 243, p. 1012-1013, J. L. Marx. Copyright 1989 by the AAAS)

Viral proteins could offer new herpes vaccine

Researchers in Cambridge have sequenced the giant herpes virus, cytomegalovirus. The virus has nearly a quarter of a million base pairs - twice the number of base pairs as the Epstein-Barr virus, which was previously the longest unbroken length of DNA that researchers had sequenced. The work could also pave the way for a new vaccine for herpes.

Bart Barrell, a molecular biologist at the Laboratory for Molecular Biology at the University of Cambridge, led the 10-year project to sequence the virus. He said that he was puzzled by the complexity of the virus. "It's packed with genes. A typical virus has only a dozen or so, but this has 200, each coding for a different protein. We have no idea yet what most of the proteins are for, but there seems to be some mimicry of host immune-cell proteins", he said.

Such a large reservoir of proteins may allow the virus to undergo chameleon-like changes to its envelope which may allow it to evade the host's immune system. This might explain why it can lie dormant in some people for years and suddenly flare up again, Barrell suggested.

Scientists at the Laboratory for Molecular Biology have identified two key proteins which may prove useful in a synthetic vaccine against the virus.

In the laboratory, these proteins, both glycoproteins from the envelope of the virus, induced mouse cells exposed to the virus to produce neutralizing antibodies which killed the virus. Scotgen, a biotechnology company based in Aberdeen, has now produced mouse myeloma cells that make large quantities of the proteins. The Merieux Institute at Lyons in France intends to use the proteins to try to develop a vaccine. (Source: New Scientist, 4 February 1989)

Rhinovirus receptor same as ICAM-1

The site at which human cells are attacked by cold viruses has been thoroughly analyzed by researchers at Molecular Therapeutics (W Haven, CT) and Harvard Medical School. The Molecular Therapeutics team found that the receptor through which the hundred-odd rhinoviruses that cause the

common cold invade is the same as ICAM-1 (intercellular adhesion molecule), a previously identified receptor involved in the mobilization of immune system cells. The Harvard Medical School team was examining ICAM-1 and found that it is the same at the main rhinovirus receptor. Merck Sharp & Dohme Research Laboratories researchers said three years ago that almost 90 per cent of common cold rhinoviruses attack cells through one receptor. Previously it was believed that there might be a different receptor for each rhinovirus. The knowledge that the viruses actually attack a single receptor may help researchers develop drugs to treat the common cold. (Extracted from New York Times News, 10 March 1989)

Multiple sclerosis - catching the virus

Viruses are like trouble: the more you look for, the more you find. As the techniques for ferreting them out improve, they are implicated in more and more unpleasantness. Now American and Swedish scientists have brought forth evidence that a relative of HIV, called HTLV-1, may be involved in multiple sclerosis (MS).

The case is not proven, but there are some convincing lines of argument.

A team led by Dr. Premkumar Reddy at the Wistar Institute in Philadelphia, working with Dr. Magnhild Sandberg-Wolheim at Lund University in Sweden, found HTLV-1 infecting white blood cells in all of a group of six MS patients they examined. In a control group of 20 healthy people, the virus was found in only one.

The virus was found by polymerase chain reaction, which "amplifies" genes by making millions of copies of the desired genetic sequence.

The idea that multiple sclerosis may be caused by a virus is not new. HTLV-1 is the 20th candidate in the past 40 years, none of which has stood the test of time. The other viruses, however, were all found in other parts of the body as well as in the cells of the immune system. It is an attack by the immune system on the myelin sheaths around nerves that is thought to cause MS symptoms. Other research has pointed to HTLV-1 as the cause of Tropical Spastic Paraparesis, a disease that has been called the "MS of the tropics" because of its similar symptoms.

Dr. Reddy now plans to create transgenic mice - mice that have some of the genes of HTLV-1 - and see if they show symptoms anything like those of multiple sclerosis. There is already some evidence that HTLV viruses may cause brain and nervous-system disorders in mice by disturbing the mechanisms that switch genes on and off.

If such experiments provide further evidence that HTLV-1 is a cause of MS, there are weapons that might be used to combat it almost immediately. Because HTLV-1 is similar to HIV, drugs used to slow the progress of AIDS - AZT and its successors - might also be used in severe cases of MS. The techniques developed to investigate HIV, and much of what has been learnt from them, could be applied to MS. Vaccines of the several types being developed for HIV could be developed for HTLV-1.

It might also prove possible to protect people against MS, and to make some patients better, by using a vaccine already developed to protect people from HTLV-1. This vaccine is being used in Japan to avert adult T-cell leukaemia, which is caused by HTLV-1; it needs no further trials. It would probably be used first to try to stimulate immunity in MS patients whose disease is in remission. If MS is caused by HTLV-1, then remissions may be due to successful come-backs by a patient's immune system. A vaccine could stimulate the immune system to attack more strongly.

Dr. Reddy emphasizes that there is still no direct evidence that HTLV-1 is a cause of MS. He thinks it is unlikely to be the only cause. He also stresses that HTLV-1's similarity to HIV should not be misinterpreted: nobody should think that AIDS and MS are related, or that MS spreads in the same way as AIDS. Exhaustive research has shown no evidence at all of MS spreading from person to person by any infection. (Source: The Economist, 18 March 1989)

Breakthrough on the common cold

Scientists at a Miles Inc. research centre have identified a protein that serves as a receptor for viruses that cause the common cold. Miles scientists named intracellular adhesion molecule-a (ICAM-1) as the receptor protein for human rhinoviruses. Rhinoviruses are the primary cause of the common cold.

Rhinoviruses invade the body and attach to a protein molecule on the surface of cells, causing a common cold infection. ICAM-1 is a previously identified protein molecule that, researchers have now discovered, is the receptor, or site of attachment, on the cell surface.

To identify the receptor for the cold virus, the scientists, led by Jeffrey Greve, Michael Kamarck and Alan McClelland, used monoclonal antibodies to first isolate, then purify the protein molecule, which was then shown to attach to the rhinovirus in vitro. The structure of the resultant purified protein turned out to match that of ICAM-1, bringing researchers a major step forward to unlocking the secrets of the common cold.

The average person suffers from more than 100 colds in a lifetime. Colds result in more lost work days than any other viral infection and can lead to more serious conditions such as bronchitis and asthma.

The discovery of the receptor protein was made by scientists from Molecular Therapeutics Inc., a research group at the Miles Research Center in West Haven, Conn. The centre focuses on research in molecular biology aimed at developing new therapeutics and diagnostics as well as research in arthritis and autoimmune diseases. (Source: Chemical Marketing Reporter, 13 March 1989)

Antibody-like molecule made to fight AIDS

Scientists at Genentech, the National Cancer Institute, and Harvard Medical School hve produced an antibody-like molecule that contains the receptor for human immunodeficiency virus (HIV-1). The properties of the molecule "make it a good candidate for therapeutic use" against HIV-1, according to Daniel J. Capon, who directed the research at Genentech.

The infectivity and pathogenicity of HIV-1 are critically dependent on binding of gp120, the viral envelope protein, to CD4, a protein on the surface of T lymphocytes susceptible to HIV-1.

Dubbed "immunoadhesins" by the scientists, the newly reported molecules represent what appears to be at least a partially successful effort to combine

the anti-HIV-1 activity of soluble CD4 with desirable properties of antibodies.

A feature that has made soluble CD4 attractive as a therapeutic is that it is unlikely that HIV-1, which appears to elude the human immune system through a highly variable envelope, can afford to vary the region of gp120 that recognizes and binds to CD4. Thus, CD4 should be effective against all of the many strains of the virus. However, a problem with soluble CD4 is that it is cleared from the body fairly rapidly.

Soluble CD4 is already undergoing Phase I clinical trials in AIDS patients. No results from those tests have yet been reported.

To produce the immunoadhesins, the Genentech scientists spliced together DNA sequences that encode the CD4 protein and the constant domain of a human immunoglobulin molecule. Two immunoadhesins are active against HIV-1 in vitro, and one has a half-life in rabbits nearly 200 times longer than that of soluble CD4.

Whether the immunoadhesins stimulate an active immune response against HIV-1 and virus-infected cells has not yet been determined and is the subject of on-going research. (Extracted with permission from Chemical and Engineering News, 13 February 1989, p. 7, by Rudy Baum. Copyright 1989 by the American Chemical Society.

HIV-1's reverse transcriptase is error prone

Efforts to develop a vaccine against AIDS have been complicated by the ability of human immunodeficiency virus type 1 (HIV-1) to mutate rapidly and escape the host's immune defenses. Two independent research groups have now found evidence to suggest that the virus' hypermutability is due to a high error rate in reverse transcription in vitro. HIV-1's reverse transcriptase (RT) strings together nucleotides to make a DNA copy of the viral RNA genome - an early step in the subversion of cells invaded by the virus. The enzyme is "exceptionally inaccurate", according to Thomas A. Kunkel and co-workers at the National Institute of Environmental Health Sciences in Research Triangle Park, N.C. In their assays, RT incorporated the wrong nucleotide once in every 1,700 nucleotides detected. Bradley D. Preston of Rutgers University and two co-workers performed similar assays and found that HIV-1's RT introduced base-substitution errors in DNA at estimated frequencies of 1 in 2,000 to 1 in 4,000. By comparison, other isolated polymerases are at least 10 times more accurate. (Reprinted with permission from Chemical and Engineering News, 28 November 1988, p. 21. Copyright 1988 by the American Chemical Society)

AIDS enzyme described

AIDS research received an important boost when scientists at Merck Sharp and Dohme in the USA announced the first description of an enzyme of the HIV virus.

Scientists from the Rahway, New Jersey based company gave a detailed description of HIV protease, an enzyme essential to the reproduction of the virus.

Scientists are now cautiously optimistic that an inhibitor to the enzyme can be found and that an effective AIDS drug can be developed.

Pharmaceutical firms have recognized the importance of protease in the HIV virus. Protease clips apart two proteins in the reproduction process of the virus. If these proteins are not separated, the virus cannot reproduce. The X-rays of the protease structure show the exact location on the enzyme where the cutting occurs. Scientists hope to be able to design drugs that would fit into these parts.

Similar technology has been used in developing inhibitors of renin, for antihypertension drugs. But potential AIDS drugs still face many difficulties. The main obstacle is the size of the protease inhibitors. At the moment, in vitro inhibitors are all too big to enter HIV-infected cells. (Extracted from Chemistry and Industry, 6 March 1989)

AIDS resists AZT

Some strains of the HIV virus have displayed reduced sensitivity to the only licensed AIDS drug, AZT, marketed as Retrovir by Wellcome. Although the company says that no changes in the clinical efficacy of the drug have been observed, Wellcome last month sent out letters to doctors, advising them of the discovery of resistant strains of the virus.

The discovery has been made by scientists at Burroughs-Wellcome and the University of California. So far, the strains have only been found in samples from 11 people, seriously ill with AIDS.

Experts at Wellcome say that related drugs, such as Hoffman-La Roche's DDC and Bristol-Meyers' DDA and DDI, could still be effective against AZT-resistant strains. The use of a "cocktail" of drugs in AIDS treatment could be stimulated by the discovery of these strains.

The quest for new and better AIDS drugs is not likely to be influenced by the discovery of AZT-resistant strains. One promising development, CD4 antibodies, works on a completely different part of the virus.

A potentially less toxic version of Wellcome's Retrovir has been developed by scientists at Tulane University in New Orleans. Dipyridyl-AZT, as it is called, was less toxic to bone marrow cells in vitro, but has not yet been tested in animals or human patients. (Extracted from Chemistry and Industry, 3 April 1989)

Tree compounds may strip the HIV virus of its powers

Several compounds which interfere with the addition of sugar molecules to the outer coat of the human immunodeficiency virus are showing promise as potential drugs against AIDS. Tests in patients may begin shortly.

All three substances come from plants. Biochemists have also been modifying the three parent compounds, to try to improve their activity against the virus. Drugs with greater activity can be used in smaller quantities, which means they are less likely to be toxic.

The first of the three compounds is castanospermine, which is found in the seeds of the Moreton Bay chestnut, Castanospernum australe. Scientists at King's College in London isolated this substance in 1981. The other two compounds are deoxynojirimycin (DNJ), extracted from the root of the black mulberry tree, Morus nigra, and DMDP (short for 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine), which is found in a tropical legume.

All three compounds are alkaloids and have chemical groups which resemble sugars. Castanospermine and DNJ have groups similar to glucose; part of DMDP resembles fructose. The compounds interfere with the synthesis of sugar chains.

When scientists first discovered this property, they had high hopes that it might eventually lead to a cure for viral illnesses such as the common cold, influenza and herpes. Then, in 1987, three separate laboratories working with castanospermine discovered at about the same time that the compound was active against HIV. One of the groups was at Kew Gardens, working with researchers at St. Mary's Hospital, Paddington. The others were in the USA and the Netherlands. The team in London also discovered that DNJ and DMDP had activity against HIV.

Although nobody really knows how these substances have their effect, they all act by inhibiting the enzymes, known as glycosidases, responsible for trimming the sugar chains on the glycoproteins. Experiments at St. Mary's have shown that castanospermine and the related alkaloids act not by stopping the production of the virus but by rendering it non-infectious.

Of the three compounds tested at St. Mary's, initial research found that castanospermine was the most active against HIV. Unfortunately, a very high concentration of the substance is required to have any effect on the virus, which increases the likelihood that it will be toxic as a drug. Furthermore, there is no known source of the compound other than Castanospermum australe and a South American tree of the Alexa species. It is also extremely difficult to synthesize castanospermine.

A modified version of castanospermine may have more potential, however. Representatives of the pharmaceuticals company Merrell Dow, of Cincinnati, Ohio, reported recently in the US that 6-butyryl-castanospermine is 10 to 20 times more active against HIV than castanospermine itself. Possibly, the modified compound is broken down into castanospermine within the cell.

Unlike castanospermine, DNJ is relatively easy to synthesize. Fellows suggested to collaborators at Oxford University that they might try modifying the compound chemically to see if this increased its activity. (Source: New Scientist, 26 November 1988)

Mouse models for AIDS study developed

Despite impressive gains in understanding acquired immune deficiency syndrome (AIDS) and the human immunodeficiency virus (HIV) that causes it, research on AIDS has been hampered by the lack of suitable animal models. Only two animal species - humans and chimpanzees - are susceptible to HIV infection and, apparently, only humans develop disease as a result of the infection.

In the past few weeks, however, significant steps in developing mouse models for studying AIDS have been reported by researchers at the National Institute for Allergy and Infectious Diseases and at Stanford University where Malcolm A. Martin, John M. Leonard, David S. Pezen, and colleagues created what are known as transgenic mice that contain intact copies of HIV proviral DNA. The transgenic mice are created by micro-injection of viral DNA copies into single-celled mouse embryos, which are then implanted in females. Of the 64 micro-injected ova carried to term, 12 carried full-length HIV proviruses in their chromosomal DNA. All of these "founder" animals were healthy throughout their lives.

When mated with non-transgenic males, one of the founder mice - designated No. 13 - produced offspring, 45 per cent of which developed a fatal syndrome with symptoms that resembled some symptoms associated with human AIDS. In particular, skin abnormalities and pulmonary lesions in the mice appear similar to unexplained problems suffered by AIDS patients. Infectious HIV particles were recovered from these animals.

The offspring of two other founder animals showed increased mortality rates but not the characteristic disease syndrome, and virus could not be isolated from them.

All but three of the transgenic mice were inadvertently destroyed in an accident in early December when the power to the laboratory was cut off during routine maintenance. The accident has set back the research about six months, Pezen says.

At Stanford, Joseph M. McCune and co-workers injected HIV into mice with human foetal thymic or lymph node implants. The chimeric mice, which were first described earlier this year in a report from McCune's group, produce a transient wave of human T and B lymphocytes and antibodies, producing an immunological environment similar to that experienced by HIV in humans.

Viral replication spread through the human lymphoid organs in the chimeric mice injected with HIV. This will allow study of the progress of an HIV infection at both the cellular and molecular levels.

The two murine models are complementary. The NIAID mice do not produce the CD4 T lymphocytes susceptible to HIV infection, so the direct effects of viral proteins and particles can be studied in the absence of continued reinfection of immune cells. By contrast, the Stanford mice contain the human tissues that appear to be most susceptible to HIV infection, so the process of infection and initiation of disease can be followed in them. (Reprinted with permission from Chemical and Engineering News, 2 January 1989, p. 8. Copyright 1989 by the American Chemical Society)

Drug may suppress AIDS virus in animals

3'-Fluoro-3'-deoxythymidine (FDT) is one of many nucleoside analogs being studied as weapons against human immunodeficiency virus (HIV), which causes AIDS. According to researcher Bo Oberg of Medivir, a new company being set up in Stockholm to develop antiviral agents, FDT is showing promise. He finds that in initial trials on monkeys infected with simian immunodeficiency virus (SIV), a close relative of HIV, the drug is some four times more effective in delaying the appearance of SIV antigens in the blood as zidovudine (3'-azido-3'-deoxy-thymidine, or AZT). Moreover, Oberg suggests that FDT should cause fewer side effects than AZT or other agents being tested against the AIDS virus. Medivir is seeking financial backing for its research programme. (Reprinted with permission from Chemical and Engineering News, 19 December 1988, p. 23. Copyright 1988 by the American Chemical Society)

CD4 effective in treating SIV in monkeys

Soluble human CD4 is effective in treating rhesus monkeys with simian immunodeficiency virus, according to researchers at the New England Regional

Primate Center and Biogen. Both SIV and HIV (the AIDS virus in humans) bond to CD4 so that they can enter target cells. Researchers found it difficult to isolate the SIV from the monkeys during treatment with soluble CD4, probably because the virus was not replicating. It did not disappear, however, and could again be isolated after treatment was halted. (Extracted from New Scientist, 28 January 1989)

Cats and cows have their own versions of AIDS, too

Scientists can glean a great deal of insight into HIV from studying animals which harbour other lentiviruses causing similar life-long infections in their hosts. One example is the virus that Matthew Gonda and his colleagues at the Frederick Cancer Research Facility isolated from cattle with a wasting syndrome. Both the bovine disease and the virus which causes it are comparable to AIDS and HIV respectively. Following infection and the development of antibodies, the lymph nodes of the animals become enlarged. Progressive weakness and neurological degeneration follow.

Researchers have called the virus bovine immunodeficiency virus or BIV. The extent of its spread among cattle in the US and elsewhere is not known. Gonda and his colleagues are studying the virus, which appears to have similar structural and molecular properties to its human counterpart. Researchers are also developing tests to assess the prevalence of BIV.

The domestic cat is also host to several retroviruses. Those most relevant to AIDS research are feline immunodeficiency virus (FIV), which is a lentivirus, and feline leukaemia virus (FeLV), a C-type virus.

Niels Pedersen, of the University of California at Davis, isolated FIV in 1987 from a colony of domestic cats. These had suffered periodic outbreaks of disease since 1982. The cats had no antibodies to FeLV. The disease, which was infectious, was characterized by diarrhoea, anaemia, loss of weight, mouth infections, and neurological and immunological abnormalities.

Researchers are studying the virus; so far, its proteins do not appear to be related to those of HIV, nor does it grow in human cells in culture. There is no evidence of transmission of this virus from cats to humans or vice versa.

FeLV has a longer history with a success story which may prove valuable in the search for a vaccine against HIV. First isolated from domestic cats in Glasgow more than 20 years ago, FeLV resembles HIV in the way that it causes disease. Among other things, FeLV causes lymphoma and lymphosarcoma (cancers affecting the lymphatic system), anaemia and malfunctions of the immune system. The good news for the cat and, perhaps, for the future of vaccines against retroviral diseases is that researchers have produced two vaccines against FeLV. One of these is better at inducing a protective immune response in cats than the other.

The more successful vaccine has been developed by the same team, led by Bill and Os Jarrett at the University of Glasgow, that originally isolated FeLV in 1964. Their vaccine uses an immunostimulatory complex (ISCOM) to present viral membrane proteins to the immune system in an array. The matrix that binds the proteins together can also function as an adjuvant - in other words, it can enhance the ability of the protein to stimulate the immune system.

This vaccine, which is now in production, has a success rate of more than 80 per cent in protecting cats from leukaemia, providing they have no antibodies to FeLV at the time of vaccination. Using the vaccine on cats that have antibodies to FeLV, and so are already infected, can also boost the level of antibodies capable of neutralizing the virus. Researchers at the Jarrett's laboratory are currently trying to use the same technology to produce a vaccine against HIV. (Source: New Scientist, 25 March 1989)

Vaccines confirm seal virus

Researchers in the Netherlands have confirmed the link between the disease that killed thousands of common seals off European coasts last year and a virus found in the sick seals. The results offer what the researchers call "final proof" that the suspected morbillivirus, now known as phocine distemper virus (PDV), is the direct cause of the epidemic. They also demonstrate that vaccines for canine distemper (CDV) can protect seals from PDV, confirming that the new morbillivirus is closely related to CDV.

The researchers, led by Albert Osterhaus at the National Institute of Public Health and Environmental Protection at Bilthoven, inoculated six healthy common seals, previously isolated from contact with other animals, with vaccines against CDV. They also inoculated two more healthy seals with a "sham" vaccine. Next, they put all eight seals in a closed environment and infected them with material from diseased seals. Both of the seals that received the sham vaccine became ill with the virus and died. However, the six immunized animals remained healthy. (Source: New Scientist, 14 January 1989)

Shapely molecules for foot-and-mouth

Researchers in Britain have determined the shape of the virus that causes foot-and-mouth disease (FMDV). Their results indicate that the virus has a novel way of protecting itself from the immune system. The discovery could also help scientists to determine a better vaccine to the disease.

Foot-and-mouth disease still kills large numbers of pigs and cattle throughout the world, even though an effective vaccine has been on the market for more than 40 years. In areas where the disease is endemic, vaccination is the only way of controlling the disease. The disease persists partly because the present vaccine, which contains dead virus, needs to be kept refrigerated. However, refrigeration is not always possible in remote areas. In some countries, including Britain, farmers control the disease by slaughtering animals.

Work by Ravindra Acharya and colleagues at the laboratory of molecular biophysics at Oxford may lead to a stable vaccine. The researchers crystallized the virus and then bombarded it with X-rays, which are deflected by molecules in the virus. The researchers then built up a picture of the virus by analysing the pattern formed by the scattered X-rays.

FMDV belongs to the family of the picornaviruses, which includes the viruses that cause poliomyelitis and the common cold. They consist of a single strand of RNA surrounded by several copies of four proteins, VP1 to VP4. The researchers expected FMDV, like the other picornaviruses so far studied, to have a depression on its surface. This depression enables

picornaviruses to bind to a receptor molecule on the surface of the cell it infects. The depression prevents large molecules of antibody produced by the host's defences blocking the binding site.

Instead, the researchers found that FMDV has no depressions on its surface.

FMDV seems to have devised another way of protecting its binding sites from antibodies. The researchers found that the virus has tiny "bubbles" wherever VP1 occurs on its surface. VP1 has a short loop, the length of a chain of 20 amino acids.

These loops, the researchers believe, contain the binding site as well as disguising it from the host's antibodies. They show up as fuzzy patches in X-ray pictures because they contain variable regions. The loops protect the virus by concealing the receptor binding site. According to the researchers, the variability of the loops "camouflage the small constant region within a sea of constant variability".

The host's immune system recognizes protein molecules by their shape. The immune system mounts an attack on invading organisms by producing antibodies whose shape depends on the protein coats of the organisms. Although scientists know one peptide, a sequence of amino acids, that could induce cells to produce high levels of antibody against FMDV, they do not know the shape of the peptide. If they knew its shape they could produce a more effective vaccine. (Source: New Scientist, 18 March 1989)

Viral enhancing factor discovered

A protein fragment that can help a virus penetrate the stomach membranes of an insect has been discovered by researchers at Cornell University's Boyce Thompson Institute for Plant Research. The fragment was obtained from the Trichoplusiani granulosis virus (TnGV), which is common among insects. When used in conjunction with the virus, the protein fragment or "viral enhancing factor" can increase the potency of the virus against the cabbage looper larvae by 25 to 100 times. (Extracted from Chemical Week, 29 March 1989)

Research instrumentation

Fluorescent DNA sequencer

Hitachi Ltd. is marketing a newly developed fluorescent DNA sequencer, the Fluorescent Type DNA Sequencer SQ 3000, that enables DNA base sequences comprising human genes to be decoded in about 3 hours, or 5-10 times faster than by existing systems. Since this system does not use a radioisotope, special precautions are unnecessary, unlike conventional systems.

The new system consists of a base cleaving unit, an electrophoresis unit, and a base sequence analysis unit.

The DNA bases whose sequences are to be determined are marked with a fluorescent substance, then reconstructed and cleaved in such a way that their terminal bases comprise fragmentary groups consisting of A, C, G, or T. DNA fragments cannot be seen with the naked eye, so the electrophoresis method is used for classification. When an electric field is impressed on an electrophoresis gel containing the DNA fragment groups, these groups undergo electrophoresis on a migration plate, with the short fragments moving rapidly and the longer fragments moving more slowly, eventually becoming aligned in length order.

Next, a laser beam is directed onto the migration plate from its side, the light reflected from the fluorescent marks implanted earlier on the DNA fragments is photographed with a camera, then data related to the detected positions and time are processed with a computer to determine the base sequences of the target DNA. (Source: JETRO, February 1989)

New microscopes reveal molecular mysteries

The latest techniques in microscopy are giving scientists a bird's-eye view of individual molecules. Soon, scientists may be able to watch biochemical reactions take place.

Researchers at IBM have announced that they have formed an image of the internal structure of an isolated molecule with a scanning tunnelling microscope (STM). Previously, microscopists could form images only of molecules arranged in tightly packed layers.

Robert Wilson and his colleagues at IBM's Almaden Research Center in San Jose, California, have successfully imaged single molecules of a blue pigment, copper phthalocyanine. The molecules were "mounted" on a layer of copper. The images reveal clearly the internal atomic structure of the distinctively shaped molecule.

The scanning tunnelling microscope works by applying a small voltage between an atomically fine needle and the object to be imaged. The electrical potential encourages electrons to "tunnel" through, either from the surface to the tip or vice versa.

The tiny tunnelling current is about half a nanoamp or so, and depends on the distance between the tip and the surface. The tip scans the surface, moving nearer or further away so as to maintain a constant current.

In crude terms, microscopists are measuring the density of electrical charge over the surface of the molecule. In technical language, they measure the density of states just below the Fermi level.

Until now, researchers have imaged only arrays of atoms or molecules, such as benzene, which have been locked into a crystalline structure. Wilson says that it is difficult to get individual molecules to stay still while being scanned. The only way is to anchor the molecule to a surface, but there are still technical problems to be solved, he said.

Meanwhile, in north California, a joint team from the Lawrence Livermore National Laboratory and the Lawrence Berkeley Laboratory have obtained the first direct image of a double strand of naked DNA. Until now, the best pictures obtained have been using the scanning tunnelling microscope, but this technique requires the DNA to be coated with a metal.

The DNA is mixed with a solution of potassium chloride to prevent the strands from unwinding, and a drop of the solution is deposited onto a graphite surface. The image is not very clear but the researchers say that they can see the helical turns of the double helix - but again microscopists emphasize that they are not quite sure how to interpret the images.

Scanning tunnelling microscopy requires the material being imaged to be electrically

conducting. DNA does not come into this category. According to the researchers, however, there is enough electron mobility to allow tunnelling to take place.

Dixon feels that there is still a lot to learn about improving the image of simpler molecules, rather than advancing to more complicated molecules such as proteins and DNA.

A potentially far more powerful tool for imaging biological molecules is the atomic force microscope (AFM), because it does not require the material to be electrically conducting. Paul Hansma, from the department of physics at the University of California at Santa Barbara, has been using an AFM to image individual molecules of amino acids and proteins.

The AFM was developed in 1986 by researchers at Stanford University. It works like a miniature record player. A shard of diamond scans the surface of the object, and the diamond's movement is relayed to a spring attached to a sensor.

The technique looks set to take microscopy far beyond what the STM can achieve. Hansma has already obtained remarkable real-time images of molecules as they form polymers. He believes that AFMs will eventually allow scientists to see molecules docking onto cells. (Source: New Scientist, 28 January 1989)

New electrophoresis system to observe DNA

Tomy Seiko Co. (Tokyo, Japan) is offering a new electrophoresis system for observing and/or photographing (DNA). The system, which isolates DNA, includes the TI-100 transilluminator and the IC-100 camera unit. Unlike traditional transilluminator systems, the new system does not need a dark room for photography. Also, it needs only a 400 x 200-mm. installation space. The camera, which does not need a stand, features a 1:1 magnification ratio. (Source: JETRO, October 1988)

Cetus unveils DNA sequencing method

Scientists at Cetus (Emeryville, CA) say they have demonstrated a new DNA sequencing method that uses the company's proprietary GeneAmp PCR technology and a thermostable DNA polymerase from a bacteria found in hot springs. Because the DNA polymerase used in the technique is active at high temperatures, rapid sequencing can be done under conditions that eliminate ambiguities encountered with other DNA sequencing methods, according to Cetus. The new method could have applications for large-scale DNA sequencing projects, says the company, including efforts to map and sequence the human genome. (Source: Chemical Week, 4 November 1988)

DNA solvent

J. T. Baker UK has brought out Baker Bio-Analysed, a high purity, low water, acetonitrile solvent, which was developed for biotechnology applications, including DNA synthesis and sequencing.

Specifications include, low residue after evaporation, low levels of trace metal impurities and a small boiling point range. It also has low absorbance at critical wavelengths.

Contact: J. T. Baker UK, P.O. Box 9, Hayes Gate House, 27 Uxbridge Road, Hayes, Middlesex. (Source: Manufacturing Chemist, January 1989)

System for culturing animal cells in high concentration

Hitachi Ltd. has developed a system for culturing anchorage-independent animal cells in high cell concentrations that requires no manual changing of the culture solution and which easily lends itself to scale enlargement.

This new system introduces an innovative technology that eliminates protein foams and therefore enables two technologies to be applied in combination - an oxygen supply technology that permits air to be blown into the culture solution and a cell separation technology utilizing a water repellent film. The company has already succeeded in operating a bench scale system with a culturing capacity of 7 ℓ for the continuous high-concentration culturing of animal cells at a concentration of 3 x 10^7 cells/mℓ/month.

Today, valuable medical drugs such as interleukin and interferon are being synthesized by animal cell culturing, but since only very small quantities of these substances are secreted by the cells, the development of a system for the continuous culturing of these animal cells with a large-capacity tank at a high concentration (1 x 10^7 ~ 1 x 10^8 cells/mℓ) has been in need.

A continuous cell culturing test conducted over a period of a month corroborated that cell viability was as high as about 90 per cent over the entire period, so Hitachi plans to commercialize the system for use on an industrial scale. (Source: JETRO, October 1988)

Horizontal tube reactor

With growing interest in continuous fermentation processes, Maschinenfabrik Andritz AG has developed a horizontal tubular reactor, with a cross-flow gassing tube, in co-operation with the Institute of Biotechnology in Graz, Austria. The reactor has a high level of plug-flow, with Bodenstein numbers between 20 and 80.

The process is currently being tested to produce a biopesticide from Bacillus thuringiensis. Details from: Dr. Klaus Reichert, Maschinenfabrik Andritz AG, Statteggerstrasse, A-8045 Graz, Austria. (Source: Biotechnology Bulletin, Vol. 7, No. 11, December 1988)

Prizewinners develop combined bioreactor-separator

Chemical engineers at Aston University in Britain have developed a cheap and efficient way of making and separating biological macromolecules on a chromatographic column.

The researchers, Philip Barker and George Ganetsos, produced a piece of apparatus that synthesises the polyglucoside dextran from sucrose using the enzyme dextransucrase. The apparatus instantaneously separates the polyglucoside from the other product of the reaction, fructose. This combined "bioreactor-separator" should be cheaper and more efficient than the current methods for making carbohydrates. Biochemists could also use the system to make other large organic molecules.

The reaction takes place on a chromatographic column, packed with a polystyrene resin, that can take chemicals in batches. A solution of sucrose, together with the enzyme, passes continuously down the column, which is 250 centimetres long. As dextran forms, it continues down the column until it

is eluted. The other product, fructose, tends to cling to the resin for a while, so it is eluted more slowly. The whole process takes about four hours.

The neat trick about the process is that it produces good yields of two products that are important for commercial use. Because calcium ions in the resin remove the fructose continuously, more fructose - and dextran - forms to maintain the chemical equilibrium. All the sucrose is, therefore, eventually used up in the reaction.

Ganetsos and Barker are now planning to scale up their process. They believe that it should be possible to design a system to produce 20 kilograms of the products per cubic metre of resin per hour. (Source: New Scientist, 26 November 1988)

Novoclone offers reduced interference

As part of its continuous programme of product development, Novo BioLabs has incorporated the latest in monoclonal antibody technology into its ultrasensitive NovoClone TSH immunoassay. To reduce the possibility of cross-linking and interference in some disease states, a "Fab" fragment antibody has been included. Additionally, the calibration range of assay has been extended to aid the management of hypothyroidism. Details from: Novo BioLabs Ltd., St. John's Innovation Centre, Cowley Road, Cambridge CB4 4WS or on 0223-341060. (Source: Biotechnology Bulletin, Vol. 7, No. 12, January 1989)

Mass production of enzyme for cancer diagnosis

Kyowa Hakko Kogyo Co. Ltd. has succeeded in mass producing N-acetylneuraminate lyase (NAL), an enzyme for diagnosing cancer and inflammatory diseases by genetic engineering. When combined with neuraminidase (NED) for diagnosis, NAL can accurately measure the concentration of sialic acid in the blood and is useful for early diagnosis of inflammatory diseases such as gastric ulcers and hepatocirrhosis. It is particularly useful for identifying the presence of cancer cells after surgery.

NAL is an induced enzyme and cannot be produced unless a costly inducer (N-acetylneuraminic acid, NANA) is added to a medium. This has been a big obstacle to producing it on an industrial scale.

The company has produced hybrid plasmids by cutting chromosome DNA of NAL-producing strain E. Coli K84 and incorporating them into plasmids, and strains which can live on NANA as only one source of carbon by introducing these hybrid plasmids into mutation-treated NAL-defective strains. These recombinants produce NAL with about 3,000 times the efficiency of wild strains even when no inducer is added. The company plans to proceed with the cloning of genes for NED. (Source: JETRO, October 1988)

Perkin Elmer's AmpliTaq recombinant Taq DNA polymerase

Perkin-Elmer Cetus Instruments, pioneers of the GeneAmp PCR process, have introduced AmpliTaq, the first recombinant form of Taq DNA Polymerase. The new genetically engineered enzyme offers a number of key advantages. For example, the possible presence of unwanted thermostable nucleases is eliminated, since the enzyme is not purified from a thermostable bacterium. And equivalent thermostability to native Taq DNA Polymerase permits switching to AmpliTaq without modifying current protocols. Details from: Perkin-Elmer Ltd., Post Office Lane, Beaconsfield, Buckinghamshire HP9 1QA or on 0494 676161. (Source: Biotechnology Bulletin, Vol. 8, No. 2, March 1989)

General

Scientists detect DNA using new fluorescent probe method

A new process for detecting and measuring DNA and RNA could lead to the development of faster, more efficient diagnostic tests for diseases such as cancer and AIDS and for birth defects. Scientists at the Worcester Foundation for Experimental Biology (Shrewsbury, MA) have developed a gene detection method that uses two fluorescent dyes to "tag" gene detectors. The transfer of energy between the two dye markers is then measured, which reflects the presence of the DNA or RNA being sought.

The development is "a wonderful example of how physical techniques can be used to solve important problems in cell biology", according to Dr. David E. Wolf, leader of the Worcester group. The research was a collaborative effort between Drs. Wolf and Richard A. Cardullo, who are biophysicists, and Drs. Sudhir Agraval and Paul C. Zamecnik, who are experts on DNA and RNA chemistry. The Worcester Foundation has filed for a patent application on the new technique.

The fluorescent gene probe technology is based on the synthesis of two oligonucleotide probes that are complementary to adjacent sequences of the nucleotide to be detected. Each complementary sequence is labelled with a different fluorescent molecule, i.e. fluorescein or rhodamine. The emission spectrum of fluorescein overlaps the absorbance spectrum of rhodamine. Fluorescein is excited by blue light; rhodamine is not. When fluorescein absorbs blue light, it emits green light. This wavelength is absorbed by rhodamine which, it turn, emits red light. Such a phenomenon, involving emission by fluorescein and absorbance by rhodamine, however, does not occur in solution.

The scientists' technique relies on non-radiative energy transfer. This electrostatic transfer of energy only occurs if the emission spectra of the fluorophores overlap and if they are close to each other. Thus, when the probes are in solution, there is no energy transfer. If, however, both detector fragments hybridize adjacently to the target nucleotide, they will be close enough for direct non-radiative energy transfer from fluorescein to rhodamine to occur (the optimal distance is 50 to 70 angstroms). Rhodamine emits red light as a result of the transfer; if the detector fragments are not bound adjacently, fluorescein emits green light only, signalling that the target nucleotide is not present.

The novelty of the technique lies in the use of dyes rather than the more cumbersome radioactive isotopes used in most procedures. According to Dr. Wolf, the sensitivity of their system rivals that of isotopic methods, and without the need to perform blotting or auto-radiography.

The probe technology can be used to detect DNA or RNA in intact cells or liquid suspensions of solubilized cells or tissue samples. It is not necessary to isolate or purify the target nucleotide prior to analysis. Time-consuming techniques of immobilizing the target material on a solid substrate are eliminated. In addition, the use of two adjacent detector probes should decrease the incidence of false positives associated with binding to single, larger probes.

The potential applications to diagnostics are obvious. As long as there is enough sequence information to create complementary probes, and the DNA is expressed in a high enough amount to be detected (this can be accomplished via the polymerase chain reaction, if necessary), this procedure can be performed.

Another application of this technology is the measurement of inter- and intra-molecular distances. (Source: Genetic Engineering News, February 1989)

Method brings gene therapy one step closer

When molecular biologists try to substitute a foreign DNA sequence for a specific chromosomal gene in cultured cells, the foreign sequence often becomes integrated into the chromosomes at random sites. Researchers at Howard Hughes Medical Institute in Salt Lake City now have developed a procedure that makes it easier to select out cells that contain a targeted substitution from those containing random insertions. The work thus brings practical gene therapy one step closer to reality. Mario R. Capecchi, Suzanne L. Mansour, and Kirk R. Thomas targeted a mouse oncogene called int-2 for replacement with a cloned version. If the cloned version became randomly integrated into the cell's genome, the cell would become resistant to one drug (G418), but not to another (gancyclovir). If, on the other hand, the cloned version replaced int-2 specifically, the cell would become resistant to both drugs. Capecchi and co-workers found that their method enriches 2,000-fold for those cells that contain the targeted int-2 substitution. They believe the method "should be applicable to any gene". (Reprinted with permission from Chemical and Engineering News, 28 November 1988, p. 21. Copyright 1988 by the American Chemical Society)

MBI develops host vector system for gene cloning in Bacillus

MBI molecular geneticists Dr. Michael Bagdasarian and Dr. Lakshmi Bhatnager and MBI Trainee Chan Lee of Michigan State University have established a host vector system to clone and express genes derived from foreign organisms in Bacillus subtilus, an aerobic, food-safe organism. The Bacillus strain used does not contain proteases (protein-degrading enzymes), so secreted proteins are not degraded. To test the system, a thermostable glucose isomerase from an anaerobic organism was cloned and expressed into Bacillus.

Dr. Bagdasarian, Dr. Bhatnagar and Lee found the cloned enzyme, used in producing high fructose corn syrups, is expressed very well.

Protocols for cloning and expression in Bacillus subtilus were originally developed in Japan by Professor T. Imanaka, Osaka University, Osaka, Japan, under a contract from MBI. Modifications were made at MBI for maximum enzyme expression, in collaboration with researchers from Professor Imanaka's laboratory.

Additional studies continue at MBI to further optimize the gene cloning system. This system will allow production of enzymes for food processing that are not normally found in food-safe organisms. (Source: Bio-Connection, Winter 1988)

Gene targeting

A new technique might allow genetic engineers to precisely control where an implanted gene attaches to a chromosome. Gene targeting might pave the way for effective treatment of genetic diseases. Perhaps a defective gene could be totally replaced, according to B. Hogan of Vanderbilt University School of Medicine. Although gene transplants have now become routine, it is not yet possible to direct a gene to a particular location of a specific chromosome. Pioneering work by O. Smithies of the University of Wisconsin (Madison) showed that a gene might be taken up spontaneously if it was similar to a native gene. To determine if a gene has reached its target, a second gene is attached to it, so that it can drop off when the primary gene is incorporated into its target chromosome. The characteristic of the secondary gene will not be expressed in cells which have incorporated the primary gene at its target location. (Extracted from New York Times News, 29 November 1988)

New enzyme isolated

Mitsubishi-Kasei Institute of Life Sciences' (Tokyo, Japan) Laboratory of Glycoconjugate Research has isolated a new enzyme for dissecting saccharide chains (oligosaccharides) out of cell surfaces without killing cells. The new Endoglycoceramidase (EGC'ase) can separate the saccharide chain and ceramide of different glycosphingolipids on the cell membranes of living animal cells. This will help to clarify the functions of glycosphingolipids, which were implicated as modulators for cell growth, differentiation, and adhesion via cell recognition and interaction; receptors for bacterial toxins and viruses; and cell surface antigens, including those related to tumours. Also, cerebrosides, glycoglycerolipids, and glycoproteins are not hydrolyzed by the new enzyme. (Extracted from New Technology Japan, November 1988)

Clever molecules for "thinking computers"

Biology rather than electronics may hold the key to tomorrow's "thinking computers".

Michael Conrad, of Wayne State University, Detroit, discussed what he called "high-IQ materials" whose molecules could recognize patterns in tomorrow's living computers. At a symposium on bioelectronic and molecular devices Stuart Hameroff, of the University of Arizona, presented work on computers based on structures called microtubules, minute filaments of protein which exist in cellular cytoplasma. He calls these "nature's biological computers". Both scientists said that the process of cognition consists of molecular activities in the brain's neurons.

The symposium heard how early biomolecular devices will consist of an organic substance connected to an electronic circuit. Researchers are already working on a chip for processing visual information which contains bacteriorhodopsin, a light-sensitive substance related to the visual pigment, rhodopsin, in human eyes.

A second, more advanced, class of device will consist entirely of artificially engineered proteins and organic polymers. The device could be used for detecting chemicals. Isao Karube, of the Tokyo Institute of Technology, has developed a "freshness chip" which by 1991 will be built into packets of fish sold in supermarkets. It detects aromatic chemicals produced when fish decays, and will tell customers, perhaps by a patch on the packet which changes colour, if the fish inside is spoilt.

Hameroff's research suggests that the signal which a neuron transmits along its axon, or nerve fibre, may not be the key event in neural activity, but an effect of microtubular activity within the

axon. The signal may simply cause changes in cell membranes which allow ions to flow through the cells.

Hameroff's long-term goal is to create an artificial brain made from genetically engineered cytoplasm. Looking far ahead, he sees the possibility of programming human characteristics into such a structure.

Hameroff added that a more immediate application would be an artificial cytoplasm which would duplicate the matrix of microtubules. Such a structure, he feels, would start to show unexpected properties, which researchers associate with intelligence. In the next century, these matrices might form the "brains" in self-correcting calculators or intelligent word processors.

Another early application of biomolecular devices, proposed by Toyesaka Morizumi of the Tokyo Institute of Technology, is an artificial nose: a logical place to start in trying to create an artificial nervous system; the earliest brain structures were devoted to the sense of smell. Hameroff predicted that an artificial nose might appear within a decade. (Source: New Scientist, 24/31 December 1988)

Unfolding the structure of proteins

The way that proteins fold up into their characteristic shapes is not random. Proteins, biologists now believe, follow definite patterns during folding, and fold into specific intermediate forms before acquiring their final, stable shapes. Studying the intermediate forms, however, is not easy because these are so transient - an intermediate structure may form, for example, within the first second of folding.

To analyse the structure of these intermediates, scientists slow down the refolding, or trap the intermediate forms during folding. Researchers now use a new technique to determine how many protons are chemically "hidden".

As the protein begins to fold, protons become protected within the folds. By immersing the folding protein at a specific time in a solution designed to label unprotected protons, researchers can trap intermediate forms. From the position of the protected protons, the researchers can then analyse how the protein has folded at each intermediate stage.

Two groups of scientists have recently used this technique to study protein folding. Jayant Udgaonkar and Robert Baldwin at Stanford University in California looked at the way the enzyme ribonuclease A, folded, and Heinrich Roder and his colleagues at the University of Pennsylvania in Philadelphia, studied the intermediates formed during folding of the protein cytochrome c.

Both groups found that some components of the final structure are formed quite early. These structures form a framework from which the final shape is assembled. (Source: New Scientist, 3 December 1988)

Powerful immunosuppressant synthesized

Chemists at Merck Sharpe & Dohme Research Laboratories in Rahway, N.J., have achieved the total synthesis of the immunosuppressant agent, FK-506. The compound is about 100 times as potent as cyclosporin A, the leading drug now used to suppress patients' immune systems to prevent rejection of transplanted organs.

In the short term, this accomplishment gives Merck a supply of the compound for further research in the US. Further, it provides Merck chemists with experience in the chemistry needed to make improved analogs that may have advantages over the natural substance and to make subunits that may reveal its mode of action.

In the long term, chemists everywhere will study the synthesis for knowledge of how to effect changes at one functional group without damage to the wide variety of other groups in such a complicated molecule. The Rahway workers' strategy was to make "northern" and "southern" portions of the molecule, which contained most of the dissymmetric carbon atoms, in high optical purity. They then linked these subunits through additional groups to close the 23-membered ring.

Interestingly, the synthesis of FK-506 was carried out not by the company's pioneering medicinal chemists but by the process research department. Led by executive director Ichiro Shinkai, this department specializes in commercial scaleups of reactions.

FK-506 was originally discovered about two years ago by medicinal chemist Toshio Goto and co-workers at Fujisawa Pharmaceutical Co. in Japan. They isolated 13.6 g of the agent from 1500 L of fermentation broth of Streptomyces tsukubaensis No. 9993.

Fujisawa deposited a sample of the organism in a culture bank in Japan. To protect the company's interest, however, the culture was not to be made available to others for two years. So Shinkai mobilized his group to get Merck its own supply of the compound sooner.

Though FK-506 and cyclosporin A seem chemically dissimilar, their modes of action are remarkably alike. FK-506 is a mostly carbocyclic lactone-lactam. Cyclosporin A is a macrocyclic polypeptide. Both compounds inhibit production of interleukin-2 and interleukin-3 as well as } -interferon. These compounds stimulate the overall function of a part of the immune system based on T-lymphocytes.

One goal of all the synthetic effort that has gone into FK-506 worldwide is to learn what part of the structure is responsible for its immunosuppressive action. In particular, chemists have zeroed in on an N-ketomalonylpipecolate segment. The three sequential keto groups of this segment may have unusual reactivity. (Extracted with permission from Chemical and Engineering News, pp. 29-30, 6 February 1989. Copyright 1989 by the American Chemical Society)

Commercializing research

Two Cornell University (Ithaca, NY) professors are attempting to determine the most effective ways to finance and manage the transfer of basic biotechnology research to the marketplace. In a study expected to take three to five years, John Freeman of the Johnson School of Management and Stephen Barley of the School of Industrial and Labor Relations will marry two theoretical bases of organizational research - population ecology and social network analysis.

By first categorizing the patterns of relationships existing biotechnology companies have generated, then examining how each company's products were developed, tested, financed, and marketed, the two hope to devise an organizational

model for "optimal" successful product commercialization. The study - which is being funded in its first year by a $89,000 grant from the National Science Foundation (NSF) - may also be useful to the US Government and industry in their efforts to remain competitive with Japan and Western Europe. Freeman and Barley would be open to allowing private sector organizations to help support their research beyond the first year. (Extracted from Bio/Technology, Vol. 7, March 1989)

New family of adhesion proteins discovered

To fight disease effectively, the white blood cells of the immune system have to circulate around the body in the bloodstream, while remaining ready to move into any site where they might be needed. The cells reach their destinations with the aid of adhesion proteins that allow them to stick to cells only in appropriate target tissues.

Several researchers report that they have cloned and sequenced the genes for two of the proteins that participate in these interactions. They find that the proteins have similar, but unusual structures that mark them as belonging to a novel family of adhesion proteins. They are joined in the new family by a third protein, with an as yet unknown function.

Not only is the research helping to explain how white blood cells find their way around the body, but it is also producing a better understanding of inflammation. It may, for example, provide new therapeutic strategies for preventing the damage that may be done by the white cells that participate in acute inflammatory reactions.

The two proteins described in this issue mediate different kinds of white cell interactions. One protein, the gene for which was cloned by Mark Siegelman, Matthijs van der Rijn, and Irving Weissman of Stanford University School of Medicine, is the "lymph node homing receptor".

The homing receptor directs the cells that carry it, which include blood lymphocytes of both the B and T type, into the peripheral lymph nodes. It does this by binding to sites on the lining of blood vessels called high endothelial venules that serve as the port of entry to lymph nodes.

Lawrence Lasky of Genentech Inc., in South San Francisco, Steven Rosen of the University of California, San Francisco, and their colleagues have also cloned the lymph node homing receptor gene.

Michael Bevilacqua, Siegfried Stengelin, Michael Gimbrone, and Brian Seed of Harvard Medical School cloned the gene for the second adhesion protein, which is known as ELAM-1 for "endothelial leukocyte adhesion molecule 1". This protein is not located on white cells, but appears on the lining of blood vessels that have been stimulated by inflammatory lymphokines, such as interleukin-1 and tumour necrosis factor. ELAM-1 attracts the white cells called neutrophils to inflamed sites where the cells help to clean up the area by ingesting bacteria and other detritus.

The third member of the new family is the protein GMP-140, which is so called because it is a granule membrane protein with a molecular weight of 140,000. Rodger McEver and his colleagues at the University of Oklahoma in Oklahoma City have cloned and sequenced the gene for this protein. The function of GMP-140 is unknown, but it, too, may be an adhesion protein and perhaps also involved in inflammation.

All three proteins have a mosaic structure, made up of a tandem array of sequences apparently adopted from sequences occurring in three other types of proteins with diverse functions.

Each protein is embedded in the membrane of the cells that carry it so that a short segment on the carboxyl end projects to the cell interior while most of the protein sequence is on the outside. The outermost portion of each protein consists of a sequence of about 120 amino acids with a structure typical of those of the animal lectins. "This family is quite different from the other families of cell-cell adhesion molecules", Bevilacqua says, "and the first prominent difference is the lectin domain".

Understanding the function of the adhesion molecules may have clinical implications. The presence of the lymph node homing receptor can influence metastasis sites for mouse lymphoma cells, according to the Stanford workers.

ELAM-1, because it helps draw neutrophils into inflamed sites, is a possible target for drugs to combat potentially harmful inflammatory conditions. Although the white cells are part of the body's defenses against foreign invaders, they can harm normal tissues.

Activated neutrophils may contribute to the lung damage sometimes experienced by people who have been given high oxygen concentrations while on a respirator and to the heart muscle damage that may occur when a blocked coronary artery is suddenly reopened, as may happen in heart attack patients who are given clot-dissolving drugs. GMP-140 is likely to be present on blood vessel walls at clot and injury sites and may also play a role in these conditions.

Further work on the adhesion molecules will include efforts to determine whether blocking ELAM-1 and GMP-140 is helpful in reducing the untoward efforts of neutrophil activation. (Extracted with permission from Science, Vol. 243, 3 March 1989, p. 1144, (J.-L. Marx). Copyright 1989 by AAAS)

Looking for new ways to read the genetic code

Genetic engineering took off with the discovery of restriction enzymes which cleave strands of DNA at specific base-pair sequences. Now, researchers at Trinity College, Dublin, in collaboration with colleagues in Paris and Belfast, are seeking new ways to cleave DNA without having to use these enzymes.

If successful, the research could lead to the development of newer and simpler techniques for reading the base-pair sequence of DNA, the molecule which codes the genetic information in cells. Typically, DNA is sequenced by cleaving it into fragments, lining up the fragments in order and reading off the base pairs at the end of adjacent fragments.

Ultraviolet (UV) light and lasers are used in the latest research to explore the complex biochemistry which arises when UV radiation splits a DNA base pair. New dyes and metal complexes, which will oxydise or reduce specific bases after irradiation with UV light, are also being developed.

TCD photochemist, Professor John Kelly, Professor David McConnell, TCD department of genetics, and researchers at Queen's University, Belfast, and at the National History Museum in Paris are participating in a project which has drawn EC funding worth 230,000 ECU.

It has been known for some time that exposure to UV light can damage DNA, either by altering the base-pair sequence, hence causing mutations, or by inducing adjacent thymidine bases to form dimers, linked by strong co-valent bonds, thus preventing DNA replication essential to cell division. Most organisms have repair mechanisms to overcome this damage but, as is evident from the rising incidence of human skin cancers, these mechanisms, do not always work.

The chemistry of DNA damage and repair is not fully understood. Knowledge of how the damage takes place and how a cell responds has important implications in mutagenesis and in environmental carcenogenesis, a timely consideration given the recent much-publicized concern about the "ozone hole".

The research team wants to look particularly at forms of UV damage which are rare and for which repair mechanisms are unlikely to exist. This could point the way towards treatment of UV induced cancers.

Work has already been done in this area using naturally occurring DNA, but the Trinity team will use synthetic DNA oligonucleotides, small but functionally characteristic strands of between 20 and 40 base pairs each. "We are going to use these small DNA molecules as well as biological DNA", Dr. Kelly said, to look for the effects in DNA of exposure to UV of varying intensity and wavelength and to pulsed UV laser light.

There are three key areas of study: the comparison of the photoreactivity of the synthetic oligonucleotides when subjected to low and high intensity excitation; an examination of any base specificity which may become apparent under these varied exposures; and the design and use of photosensitive reagents which can be introduced to help control DNA cleavage.

A UV-based process either with or without photosensitive reagents would provide a useful alternative to restriction enzymes, Dr. Kelly explained. White light, in the presence of strong oxydizing/reducing agents which can attach to specific bases before irradiation and then cleave the strand at the required sites, is another possibility.

Another major objective will be to study two-photon DNA excitation induced by nanosecond or picosecond UV laser pulses. Single photon excitation can cause cleavage at guanine bases, and guanine and thymine bases in particular will be examined during double photon absorption.

"Standard" oligonucleotides will be used - the base sequence remaining constant while other factors, including presence or absence of air, alteration of light source and introduction of reagents, are varied. Analysis of the results will be done using a range of techniques such as gel electrophoresis and high performance liquid chromatography. (Source: Technology Ireland, April 1989)

D. APPLICATIONS

Pharmaceutical and medical applications

Antidepressant drug fights malarial parasite

Doctors may soon be able to treat patients who have malaria that resists antimalarial treatment - with drugs normally used to combat depression. Since 1961, new strains of the single-celled parasite that causes malaria, Plasmodium falciparum, have emerged. These strains are resistant to chloroquine, the drug that doctors have used successfully to treat malaria for more than 40 years.

It appears that the parasite's cells resist the drug by preventing it from accumulating inside themselves. The cell pumps the drug out across its membrane. Scientists have recently discovered that this process depends upon the level of calcium present around the cells. Some drugs used to treat depression, the tricyclic antidepressants, can block the action of calcium on cell membranes. Doctors have also observed that these drugs have a weak antimalarial effect.

These observations led Alan Bitonti, a researcher at the Merrell Dow Research Institute at Cincinnati in Ohio and colleagues, to investigate how the antidepressant drugs affect the accumulation of chloroquine by the parasite's cells.

Bitonti and his colleagues took three strains of Plasmodium: one was susceptible to chloroquine, the second was a West African strain, resistant to chloroquine, and the third, the Indochina strain, was resistant to a range of antimalarial drugs including chloroquine. The researchers incubated each strain with a mixture of chloroquine and desipramine, one of the tricyclic group of antidepressant drugs.

Desipramine, the researchers found, had no effect on the amount of chloroquine accumulated by cells of the strain susceptible to chloroquine. The amount of chloroquine accumulated by the Indochina strain of the parasite increased tenfold in the presence of desipramine, while the amount accumulated by the West African resistant strain increased threefold. Once accumulated inside cells, the chloroquine could exert its toxic effect upon them.

Bitonti and his colleagues then tested the effect of desipramine on malarial parasites in owl monkeys. They injected the monkeys with a resistant strain of Plasmodium, then assessed the effects of the two drugs, desipramine and chloroquine. Five days after the end of treatment, the parasites in the control monkey had multiplied. The animal had 568×10^{-3} parasites in each microlitre - a thousandth of a millilitre - of blood. The monkeys given chloroquine alone had, on average, about 300×10^{-3} parasites per microlitre. But the number of parasites was close to zero in the blood of monkeys given both chloroquine and desipramine. (Source: New Scientist, 18 February 1989)

Human trials planned for malaria vaccine

Phase I clinical trials soon will get under way on an antimalaria vaccine developed by Biocine Co., Emeryville, Calif. The vaccine consists of a polypeptide fragment of the protein coating of the sporozoite stage of Plasmodium vivax, one of the principal causes of malaria throughout Asia and Central and South America. Vaccinated subjects should generate an immediate immune response when the micro-organism is injected into their bloodstream by the female Anopheles mosquito. Any side effects and immune responses to the vaccine will be monitored during the one-year trials. A commercial product probably is at least five years off, however Biocine uses recombinant-DNA techniques to produce the protein in yeast cultures. The company is a joint venture between Chiron Corp., headquartered in Emeryville, and Ciba-Geigy. (Reprinted with permission from Chemical and Engineering News, 5 December 1988. Copyright 1988 by the American Chemical Society)

Oriental therapy for AIDS

Chinese herbs form the foundation for the most recent anti-AIDS drug to receive a patent in the US. Yeng Hin-wing, a biochemist at the Chinese Medicinal Material Research Centre in Hong Kong, discovered GLQ223, a purified plant protein, in collaboration with colleagues at San Francisco General Hospital and at Genelab, a company in California.

GLQ223 is a component of one of 11 herbs that slowed the growth of the human immunodeficiency virus (HIV) in human cells during laboratory trials. According to the research centre in Hong Kong, the drug inhibits the replication of the virus, which causes AIDS, in T-lymphocytes and macrophages. In laboratory tests, it does this more efficiently than zidovudine, a drug used at present to treat people with AIDS. (Source: New Scientist, 4 February 1989)

Relative of zidovudine up to ten times more active

Scientists in Sweden have announced the discovery of a new drug to fight the human immunodeficiency virus. It is a relative of zidovudine. Both drugs inhibit the viral enzyme, reverse transcriptase, which is vital to the virus's survival.

The new compound is called 3'-fluoro-3'-deoxythymidine, or FLT for short. Where zidovudine has a nitrogen atom, FLT has an atom of fluorine.

Bo Oberg, leader of a group of scientists from the Karolinska Institute and the Swedish Bacteriological Institute who tested FLT, says that because FLT has a stronger effect on the virus than zidovudine, it might be used in smaller doses than zidovudine. Oberg says the drug is five to ten times more active than zidovudine in laboratory tests. Tests on human cells from the bone marrow suggest that, like zidovudine, FLT has an adverse affect on the bone marrow. (Source: New Scientist, 4 February 1989)

Transatlantic approach brings double-acting vaccine closer

Researchers in the US are developing a new strategy for a vaccine against AIDS which relies on priming the cells of the immune system with a highly specific antibody. The technique complements a second approach to a vaccine against the human immunodeficiency virus, in collaboration with British scientists, which involves inducing antibodies against antibodies.

The two techniques could ultimately work together to produce a vaccine which would stimulate both "arms" of the immune system - cells and antibodies. Most researchers now accept that a vaccine to protect against HIV would need to have such a dual effect.

The work on stimulating antibodies against antibodies - the so-called anti-idiotype strategy - is already well under way. The idiotype of an antibody is the region of the molecule that recognizes the shape of a particular antigen. An anti-idiotype antibody is an antibody that binds to the idiotype of another antibody.

If an animal - a mouse, say - receives an injection of purified antibodies which bind to a particular antigen, the immune system of the mouse recognizes those antibodies as foreign antigens. Some of the antibodies produced in response will be anti-idiotype antibodies. These antibodies are shaped like the original antigen.

Tran Chanh, Ron Kennedy and their colleagues at the Southwest Foundation for Biomedical Research in San Antonio, Texas, have been collaborating with Angus Dalgleish at the Clinical Research Centre at Harrow in Middlesex, and his colleagues, in applying these strategies to the problem of AIDS. The technique could lead either to a therapy for infected people or to a vaccine against HIV. For example, it might be possible to induce antibodies which mimic the molecule to which HIV attaches in order to enter its target cells. These antibodies would "mop up" the virus, preventing it from infecting cells.

Alternatively, if such antibodies were present in uninfected people following vaccination, these might be able to prevent the virus from gaining a hold on the body. But a vaccine also needs to stimulate the cells of the immune system, which is where the new line of attack comes into play.

Once the researchers have identified individual cells specific for proteins from HIV, they will grow each cell into a clone. These cells will have receptors on their surfaces which will bind to the viral proteins. The next step is to determine what the functions of the cells are. The researchers will be most interested in identifying cytotoxic cells, which recognize cells that are infected with virus and kill them.

After immunizing mice with the clones, the researchers should be able to identify antibodies in the mice that bind to the cells. It is then a relatively simple step to produce monoclonal antibodies of the appropriate kind, which can be purified.

Chanh and Kennedy are working on the hypothesis that if those antibodies are then injected into a person, they will seek out and bind to cells bearing the particular receptor that the antibodies recognize. By binding, they will stimulate these cells to proliferate and become more active.

No one knows whether such a reaction would be capable of protecting a person against infection with HIV. One reason to think that the strategy may work, however, is that it can protect mice against another viral disease, caused by Sendai virus. Anticlonotypic antibodies against cells which recognize Sendai virus, injected into a mouse that has never been infected with this virus, will protect the mouse against what would normally be a lethal dose of this virus.

One objection to the anti-idiotype approach is that, at present, it would mean injecting people with antibodies made by mice. As well as producing the desired anti-idiotype antibodies, the people would also produce antibodies against the other end of the antibody molecule. Some scientists fear that this "anti-mouse" response could be harmful. A vaccine for use in healthy people would need to be as safe as possible. (Source: New Scientist, 4 February 1989)

AIDS drug patented

Genelabs Inc. and the University of California at San Francisco have received a patent for their new anti-AIDS drug, GLQ223. The drug, composed of purified plant protein, has demonstrated selective inhibition of HIV antigen in both T-lymphocyte and macrophage cells. Genelabs has filed an IND application with FDA and expects phase I clinical

trials to begin in early 1989. (Source: Chemical Marketing Reporter, 16 January 1989)

FDA approves five-minute AIDS test

A simple test that in five minutes can determine whether antibodies to the acquired immune deficiency syndrome (AIDS) virus are present in a drop of blood has been approved for sale by the Food and Drug Administration. It is intended primarily for rapid screening of blood samples in emergencies and in doctors' offices.

The test, called the Recombigen latex agglutination test, is the first AIDS-related diagnostic test that uses a genetically engineered protein instead of pieces of human immunodeficiency virus (HIV) itself. It was developed by Cambridge BioScience, a biotechnology company based in Worcester, Mass.

Because the test does not require sophisticated equipment or highly trained personnel, it would be a boon for blood screening in developing countries. However, the test kit will cost $10 in the US, and this would be too expensive for some of its intended users. (Extracted with permission from Chemical and Engineering News, 19 December 1988, p. 5. Copyright 1988 by the American Chemical Society)

AIDS treatment?

Averol, a substance developed from sea sponges, may be effective against AIDS, a German-Japanese research team at the University of Mainz has discovered. Professor Werner Müller's team showed Averol to be capable of blocking the suppressor transfer RNA found in HIV cells, thus slowing the spread of the virus.

The Frankfurt-based pharmaceutical concern Marz, which holds the patent on Averol, is developing an injectable solution of the drug and hopes to begin clinical trials within a year. (Source: Manufacturing Chemist, December 1988)

US firms push ahead with AIDS drug trials

US firms are pushing forward with the development of the CD4 protein that may be able to prevent the AIDS virus from attacking the key immune system T4 cells. Researchers at Biogen, SmithKline & French, Genentech and their respective collaborators are starting phase one human clinical trials with genetically engineered forms of the protein.

Researchers from the Harvard Medical School and Biogen Research Corp. have reported that the gene-spliced CD4 protein reduces levels of the AIDS-related simian immunodeficiency virus (SIV) in rhesus monkeys. Moreover, levels of red and white blood cells from bone marrow were raised simultaneously.

In the monkey study, conducted at the New England Regional Primate Centre, the researchers were unable to isolate SIV from infected monkeys two weeks after the trial started. But two weeks after treatment stopped the virus reappeared at original levels.

SmithKline & French expects to start phase one human clinical trials early in February 1989 following the decision by the US Food and Drug Administration to give the firm the green light. The first two trials will take place at the Walter Reed Army Institute of Research in Washington and at Duke University.

Genentech started its phase one human clinical trials last August and is scheduled to complete them in February but does not expect to report the findings until later this year. The six month study is being conducted at the US National Cancer Institute, San Francisco General Hospital and the Deaconess Hospital at Harvard University. (Extracted from European Chemical News, 30 January 1989)

AIDS vaccine tested

MicroGeneSys Inc. will begin clinical testing of its "VaxSyn" HIV-1 AIDS vaccine in people who test positive for the AIDS virus but who have not yet developed symptoms of the disease.

The vaccine was the first to receive FDA approval in August 1987 for use in clinical trials and represents a potential therapy that might benefit the 1.5 to 2 million Americans as well as many others worldwide estimated to be infected with the virus but who are as yet disease-free.

"VaxSyn" is currently undergoing preliminary testing at the National Institute of Allergy and Infectious Diseases in Bethesda, Md., and at six other NIAID-supported centres across the US. So far it has been tested only in healthy, non-HIV-infected people, many of whom have developed immune responses to the vaccine.

"VaxSyn" HIV-1 is produced by genetic engineering technology and contains the AIDS virus envelope protein gp160. Antibodies and T-cells directed against envelope proteins often figure critically in the body's defense against viruses.

Researchers know that HIV gp160 elicits a strong antibody response in people infected with the virus, and the latest study seeks to determine whether boosting the immune response can stave off disease.

MicroGeneSys notes that as with the non-HIV-infected volunteers in the ongoing studies, the risk of this vaccine to HIV-infected volunteers is unknown. However, investigators working with the vaccine have stated that immunization with "VaxSyn" appears safe during short-term follow-up with initial doses of up to 640 micrograms. (Source: Chemical Marketing Reporter, 13 March 1989)

Healthy donors with HIV help patients fight AIDS

A team of researchers in the UK is quietly optimistic about a new treatment for AIDS. The researchers have found that a small group of patients with AIDS have made remarkable recoveries following infusions of antibodies taken from healthy people infected with the human immunodeficiency virus (HIV).

The researchers, from three hospitals and the University of Cambridge, found that "passive immunisation", as the therapy is called, is harmless for the patients involved, unlike the most famous AIDS drug, zidovudine, which has some side effects. The researchers found that the therapy removed signs of infection with HIV from the blood of the patients in the study - viral proteins disappeared soon after the first infusion of antibodies. Subsequently, the patients became well enough to leave hospital.

The study, which began in the spring, involved 10 people with AIDS or the early symptoms of AIDS. The chief aim of this first phase of the trial was to see whether the therapy was toxic. One of the researchers, Michael Youle from St. Stephen's Hospital in west London, said that a larger study,

involving between 100 and 150 people, will begin next year to evaluate the therapy more rigorously.

The present study involved healthy, HIV-positive people. They donated quantities of their blood plasma to the subjects of the study, who had early symptoms of AIDS. All of the subjects had suppressed levels of antibodies against HIV and had high levels of viral antigens, notably the p24 protein from HIV, in their blood. High levels of p24 in an individual correlate with a higher risk of AIDS.

The researchers found that, following treatment, the level of p24 antigen in the patients' blood fell dramatically - probably due to the antigen being bound with the antibodies from the healthy donors. The group of donors suffered no apparent ill effects.

The researchers say: "Unexpectedly, most patients increased their level of antiviral titres [antibodies to HIV] to levels beyond those expected from the amounts of antibodies administered". They stress that suggestions that the patients begin to manufacture antibodies to HIV again remain "speculative" at this stage. (Source: New Scientist, 3 December 1988)

Vaccines run up against a long incubation period

Researchers have tested, or are testing, at least three vaccines in over a quarter of a million people for their ability to protect against leprosy. It will be some years before they know whether the vaccines have been successful, because the first signs of leprosy can take from 5 to 15 years to appear after infection. It may be possible to detect protection against mild leprosy within about five years, and severe leprosy within about eight years.

One of the vaccines being tested is a mixture of BCG, the bacterium that provides immunity against tuberculosis, and killed Mycobacterium leprae, which when live causes leprosy. Health workers are testing this vaccine in 30,000 contacts of leprosy patients in Venezuela. The first results of this trial, which has been funded by the WHO's Tropical Disease Research Programme, should be available by 1990. In Malawi, the researchers are testing the same vaccine in a trial jointly supported by the British Leprosy Relief Association and the Tropical Disease Research Programme. Once its initial phase is completed - probably at the end of 1989 - the trial will involve all 120,000 inhabitants of a northern district where leprosy is highly endemic. Results should be available after 1995.

The Indian Cancer Research Centre in Bombay has developed the second vaccine. It comprises a mycobacterium called the ICRC bacillus. Unlike most strains of M. leprae, which are impossible to grow in the laboratory, this one can be cultured. A trial of this vaccine is under way in India's Maharashtra State. It will eventually involve 40,000 household contacts of leprosy patients.

Researchers have also studied the ability of vaccination with BCG alone to protect against leprosy. BCG, one of the most powerful stimulants of the immune system known, belongs to the same family of mycobacteria that includes the bacterium that causes tuberculosis (Mycobacterium tuberculosis) and the one that causes leprosy (M. leprae).

Scientists have tested the ability of BCG to protect against leprosy over the past 30 years in four major trials involving a total of 70,000 people in Burma, India, Papua New Guinea and Uganda. The efficacy of the vaccine in protecting against leprosy ranged from 20 per cent (in Burma) to 80 per cent (in Uganda).

Another approach is to stimulate the deficient immunity of patients who have very severe or "lepromatous" leprosy with vaccines made of BCG and killed M. leprae, or based on other mycobacteria. Trials currently under way in China, France, India, the Philippines and Venezuela suggest that these so-called "immunotherapeutic vaccines" show some promise. Only a few hundred patients have been treated so far, however, so the results are still inconclusive.

Meanwhile, the race is on in several laboratories to produce a synthetic vaccine which includes proteins or sections of proteins from M. leprae. A team from the Albert Einstein College of Medicine in New York is also studying the possibility of using BCG as a vehicle for proteins from several disease-causing organisms, including M.leprae and M. tuberculosis. The aim would be to exploit the low cost of BCG (5.5 US cents), as well as its good safety record, to produce a multipurpose vaccine against these and perhaps several other diseases. (Source: New Scientist, 4 February 1989)

Possible treatment for muscular dystrophy

Immature muscle cells injected into mice with a form of muscular dystrophy were effective in treating the condition, according to G. Karpati of the Montreal Neurological Institute. Similar studies have been done by researchers at Harvard Medical School and Charing Cross and Westminster Medical School (London, UK). Although D.S. Wood of the Muscular Dystrophy Association is excited about the possibilities raised by the research, applying the technology to treatment of human disease is still far in the future. Some preliminary tests could begin in humans in 1989. The injected muscle cells apparently produced dystrophin, the protein that is missing in muscular dystrophy patients. The injections in humans would have to be made about every two inches, so total treatment might not be feasible. Duchenne muscular dystrophy affects about 1 in 3,500 male births in the US. Most patients die by their early 20s. The myoblasts injected into the afflicted mice fused with muscle fibres in 39 of 70 test mice. The fused fibres produced 40 per cent of the normal amount of dystrophin. (Extracted from New York Times News, 7 March 1989)

New production process for endocerine precursor

Takeda Chemical Industries has developed a practical process for endocerine precursor production that employs gene recombination methods rather than biological extraction of the substance, which is only present in trace amounts in natural sources. Endocerine, a 2,500 molecular weight polypeptide, is a powerful vasoconstrictor possibly implicated in abnormal hypertension. Takeda hopes to develop an antihypertensive drug with the endocerine precursor. (Extracted from New Technology Japan, March 1989)

Spider venoms for use in possible neurological drugs

Cambridge NeuroScience is screening spider venoms for possible neurological drugs. The firm has received two $50,000 grants from NIH: one for the research itself and one for developing the techniques needed for the research. The researchers must deal with extremely tiny samples (perhaps 0.1 microlitres). Some spider venoms block glutamate, which is an important neurotransmitter,

but which also can cause nerve death in stroke and perhaps Alzheimer's disease.

Pfizer is also researching spider venoms for any biologically active substances, which is a tedious process. Merck is researching a variety of venoms, more for gaining a better understanding of neurological function than for finding a specific drug.

Cornell University developed a technique in the 1960s to collect bee venom for desensitizing people allergic to bee stings, but arachnids, wasps and other venemous invertebrates must be "milked" individually, which is time-consuming. T. Eisner of Cornell University says the threat of extinction of many plant and animal species makes it imperative that research into biological compounds they produce be stepped up. (Extracted from Chemical Week, 8 March 1989)

Kaketsuken unveils vaccine

Kaketsuken, the Japanese research institute, is planning to launch a recombinant hepatitis B vaccine into the South East Asian and Chinese markets. The institute expects to finalize its export plans within the first six months of this year.

The vaccine was developed by the institute in collaboration with Osaka University's Institute of Molecular and Cellular Biology and Japan's Science and Technology Agency. The agency and the institute have applied for patents in Japan, the US and Europe, for the recombinant plasmid used in vaccine production.

The vaccine is made from viral proteins mass produced by a genetically manipulated yeast. While other Japanese firms are seeking similar deals, Kaketsuken is the only native recombinant hepatitis B vaccine maker. The institute is unlikely to prosper outside Japan until it reduces its manufacturing costs. (Source: European Chemical News, 23 January 1989)

Cel-Sci plans IL-2 trials in UK

Cel-Sci, the US biotechnology concern, will begin UK phase II clinical trials of its mammalian cell-cultured interleukin-2 (IL-2) as an anti-cancer therapy early next year. The trials will be headed by Professor Dudley Dumonde and involve 30 patients suffering from metastatic malignant melanoma at St. Thomas's Hospital in London.

Previously, genetically engineered bacterial IL-2 given in very large doses has caused significant toxic side-effects. Cel-Sci says it gets round this because its therapy involves a mixture of lymphokines rich in the mammalian rather than bacterial IL-2. In addition, the mixture of lymphokines act together to boost potency and lower the necessary dosage. (Source: European Chemical News, 19 December 1988)

IL-2 as treatment for metastatic renal cell carcinoma

Cetus Corporation has submitted a product license application to the Food and Drug Administration for approval of "Proleukin" interleukin-2 (IL-2) as a treatment for metastatic renal cell carcinoma (kidney cancer).

Currently, there is no approved or effective treatment for metastatic renal cell carcinoma. Prognosis is quite poor, with the majority of patients surviving less than one year after diagnosis with metastatic disease.

The total number of renal cell cancer in the US and Europe today is estimated at 80,000, with 35,000 new cases each year. More than 18,000 people die annually from this disease.

The company began clinical investigation of its "Proleukin" IL-2 as an anticancer agent in 1984. Since then IL-2 has been widely tested against numerous cancer types in human clinical trials conducted at the National Cancer Institute and several other cancer centres througnout the US and Europe.

Scientists believe the mechanism of action for IL-2 is to harness the body's immune system to fight off invasive cancer cells. As a member of the family of immune system proteins known as lymphokines, naturally occurring IL-2 acts as a messenger between white blood cells, carrying important information used by the cells to regulate immune response. Interleukin-2 also promotes the growth and development of certain other cells and can stimulate antibody production. Cetus' Proleukin IL-2 is a genetically modified version of naturally occurring interleukin-2. (Source: Chemical Manufacturing Reporter, 12 December 1988)

Anticancer therapeutic trials

Phase I and II clinical trials are under way to test Genetics Institute's (Cambridge, MA) genetically engineered version of macrophage colony stimulating factor (M-CSF), a possible anticancer agent. M-CSF occurs naturally in the body and regulates the growth and activity of monocyte and macrophage blood cells - cells that are involved in protecting the body from foreign matter. The firm says M-CSF "enhances the cancer cell-killing ability" of human white blood cells in laboratory studies. Genetics Institute also will look at the compound's performance in bone marrow transplantation, infectious diseases, and leukemia. (Source: Chemical Week, 8 March 1989)

Brain cancer treatment advances

More than 200 patients will be involved in Phase III clinical trials of Nova Pharmaceutical's (Baltimore) Biodel polymer drug-delivery system. The polymer patch, surgically placed at the site of a brain cancer, gradually biodegrades, releasing the common cancer drug N,N-bis (2-chloroethyl)-N-nitrosourea, known as BCNU. (Source: Chemical Week, 8 March 1989)

Breast cancer drug succeeds

One in every ten women in the US will have breast cancer; 40,000 women died from it last year. Even after successful surgery, the cancer can of course recur. But ICI Pharma, a division of ICI Americas (Wilmington, DE), says a recent study shows that postoperative use of its Nolvadex tamoxifen citrate cuts the number of recurrences "significantly". The anti-estrogen drug was tested against a placebo in 2,644 "node-negative" women - those whose cancer had not spread to the lymph nodes under the armpit. Such cases represent 50 to 60 per cent of newly diagnosed patients, ICI says, but in a third of those cases the cancer spreads to other organs within ten years. In this study, only 118 of the 1,318 women who received tamoxifen had recurrences, versus 193 of the 1,326 women who

received placebos. Results of this part of the National Surgical Adjuvant Breast and Bowel Project appeared in the New England Journal of Medicine. (Source: Chemical Week, 8 March 1989)

Vector system to boost yields

UK biotechnology company, Oxford Virology Limited, and Qlone Limited of Brisbane, Australia have signed an agreement to exploit the baculovirus expression vector system, which they hope will reduce the costs of pharmaceutical and vaccine production.

The objective of the research programme is to obtain higher yields of valuable proteins which would normally be expressed only in mammalian cells. Dr. Finlayson, Qlone's research manager, says that the baculoviruses would overcome many of the limitations associated with the use of bacterial, yeast and animal cell culturing systems and produce large amounts of protein relatively inexpensively.

Products under consideration, already in development by Oxford Virology, include diagnostics and vaccines for Hepatitis B, AIDS and the cattle disease Bluetongue, as well as a bio-compatible polymer with adhesive properties, developed by Qlone. The adhesive will have applications for dental and bone glues, underwater glues and antifouling agents for ships.

Baculoviruses only infect insect cells. The genome contains one of the most active promoters known. Foreign genes from animals or organisms of interest are introduced into the baculoviruses. The baculovirus are then used to infect insect cells which will be grown in large tanks, "tricking" the insect cells to produce the large amounts of the substance for which the foreign gene is coded e.g. Hepatitis B antigens.

The process is environmentally safe as baculoviruses are non-infectious to humans, animals and plants. (Source: Chemical Marketing Reporter, 12 December 1988)

Mononucleosis test

Ortho "Monolert", a rapid test for infectious mononucleosis, is now being offered internationally by Ortho Diagnostic Systems Inc., a subsidiary of Johnson & Johnson.

This product is the nation's first in vitro diagnostic test to employ a synthetic peptide. It is claimed that the new test can precisely pinpoint acute mononucleosis earlier than existing tests, which enables physicians to immediately rule out more serious illnesses that have similar symptoms.

Ortho "Monolert" is able to distinguish between the disease in its acute stage and a patient's previous exposure to the Epstein-Barr virus, the causative agent of infectious mononucleosis. Such a distinction was not possible through a single test until now.

The product combines the accuracy of lengthy, specialized tests detecting antibodies specific for the virus with the speed of current screening assays. With existing screening tests, about 20 per cent of patients with acute mononucleosis do not show a positive result and therefore are difficult to diagnose. Among young children, up to 50 per cent may be difficult to diagnose for this reason. In these cases, further specialized and expensive tests are required to help make a diagnosis. (Source: Chemical Marketing Reporter, 12 December 1988)

MS drug gets orphan status

Triton Biosciences (Alameda, CA) has started Phase III clinical trials of Betaseron, a genetically engineered derivative of human interferon beta. The compound is being tested in patients with relapsing or remitting forms of multiple sclerosis, and the Food and Drug Administration has awarded it an orphan Drug designation. Triton hopes the drug will slow or stop progression of the disease. The trials will involve 300 patients over a two-year period. (Source: Chemical Week, 15 February 1987)

New DNA probe developed

A new probe, developed for testing DNA contamination in drugs made by recombinant DNA or monoclonal antibody techniques, cuts the hands-on time required for that test from about 18 hours down to 0.5 hours, and lowers the cost from $200-1,500 down to about $100. According to Molecular Devices (Menlo Park, CA), who developed the new test, those are the standard times and rates for conventional radioactive DNA hybridization methods. The company also notes that its device is sensitive to DNA levels as low as two picograms, well below the mandated maximum contamination level of ten picograms that is typically the detection limit of the other methods. The device makes use of a biosensor: A biological reaction is initiated on the surface of a silicon chip; the rate of change in potential that occurs during the reaction indicates the reaction rate and gives a measure of the amount of reactants (in this case DNA contaminants) originally present. The entire Threshold System includes a semi-automated workstation, a reader containing the biosensor unit, an instrument control terminal, and software for data collection, analysis, and report generation. It sells for $28,000. (Source: Chemical Week, 1 February 1989)

New TNF releasing system

Suntory (Japan) has developed a releasing system for recombinant-gamma human tumour necrosis factor (TNF) in collaboration with two university research teams. The drug delivery system consists of super-miniature capsules, or nano-capsules. Gamma human TNF and other cytokinens are drawing interest to their anti-tumour properties, but their survival time in the human body is very short, and large doses would bring serious side reactions. The nano-capsules suggest a method of spreading out a small dose over several days.

The capsules are polyalkyl cyanoacrylate, and are formed into 200-nm-dia. shapes in an emulsion with an aqueous solution of gamma human TNF. Test tube release continued to 3 to 4 days, and rat experiments showed 30 hours continuous release. (Extracted from New Technology Japan, December 1988)

GM-CSF cuts cholesterol

In a discovery which they described as "a shocker" and "totally unexpected", medical researchers at the University of California, Los Angeles (UCLA), found that granulocyte-macrophage colony stimulating factor (GM-CSF) cut blood cholesterol levels in seven out of eight patients by between 27 per cent and 53 per cent.

GM-CSF is a genetically engineered version of a chemical naturally found in the human body, where it stimulates the multiplication of certain white blood cells which fight infections. The unexpected results showed up during research on the impact of GM-CSF on eight patients suffering from severe anaemia.

The GM-CSF used in the experiments, carried out by UCLA's haematology-oncology division, was produced by Genetics Institute, the US biotechnology company. Other US companies producing GM-CSF include Biogen and Immunex. But it may not be a commercial success, given that it must be injected at least once daily - in contrast to Mevacor, an anticholesterol drug manufactured by Merck & Co. (Source: Biotechnology Bulletin, Vol. 7, No. 11, December 1988)

New anti-inflammatory compound

Synergen's efforts to develop proprietary products continued to make progress, including the development of a promising new protein for the treatment of arthritis and other inflammatory diseases. Their scientists achieved an important scientific milestone when they determined the structure of a newly identified human protein that appears to play an important part in regulating the body's response to inflammation. This protein acts as an antagonist of interleukin-1 (IL-1), which is one of the primary inducers of inflammation. The development of this protein may open the way to new anti-inflammatory treatments for such conditions as rheumatoid arthritis. With the completion of the initial phases of research, attention is being turned to the preclinical testing and production process development that are crucial to this compound's commercial application. (Source: Company News Release, November 1988)

Scripps work on vaccine

Scripps Clinic and Research Foundation (La Jolla, CA) will carry out preclinical and clinical studies of a vaccine for B-cell lymphocytic leukaemia. Scripps has developed synthetic protein fragments that mimic antigens on the surface of malignant B cells. The antigens drive an immune response against the malignant cells. Scripps will make vaccines containing adjuvants such as Detox to hike the response. Each year, about 13,000 new cases of lymphocytic leukaemia are diagnosed, and more than 5,000 deaths occur. (Source: Chemical Week, 22 February 1989)

Leukaemia test products win approval from FDA

Food and Drug Administration has approved three tests for the detection of antibodies in blood to a retrovirus called Human T-Lymphotropic Virus Type I or HTLV-I, which has been linked to a rare form of leukaemia.

The companies licensed for the new test are E.I. du Pont de Nemours & Co. together with Biotech Research Laboratories, Abbott Laboratories, and Cellular Products Inc.

HTLV-I is a distinct retrovirus associated with a leukaemia called Adult T-cell lymphoma which may appear in a small number of virus-infected individuals 20 to 40 years after they are infected. HTLV-I has been separately associated with a degenerative neurologic disease called tropical spastic paraparesis.

Because there is evidence this virus is transmitted through blood products, FDA recommended that blood banks screen donated blood and cellular blood components. FDA advised that blood banks should quarantine and destroy units of blood that are determined to be reactive to the tests.

The agency also advised that donors should be deferred when follow-up tests confirm antibodies to HTLV-I or when the donor has a repeatedly reactive screening test on more than one donation.

Although studies show only about 1 per cent of HTLV-I infected people develop leukaemia and even fewer suffer from the blood disorder, Dr. S. Gerald Sandler, American Red Cross associate vice-president for blood services, says his organization plans to use the screening test at all of its blood banks

The Red Cross is in contract negotiations with Abbott Labs for its test kits and wholesale screening of blood donations should begin by early next year, he says.

In its recommendations, FDA asked that blood banks consider notifying and counselling donors whose blood has tested positive by both the HTLV-I screening test and follow-up tests. FDA further said that the new tests cannot reliably distinguish between antibodies to HTLV-I and HTLV-II, another retrovirus whose ability to cause disease is unknown. Deferred donors should be told not to share needles for injections, should be discouraged from breast feeding infants and should be counselled about sexual activities.

HTLV-I is spread by the same means as the more virulent retrovirus HIV that causes AIDS. Both are transmitted by sexual contact, exposure to contaminated blood, contaminated needles and from infected mothers to nursing babies.

HTLV-I is a major problem in Japan, where an estimated half million people are infected. To a lesser extent, it also is prevalent among Japanese-Americans in Hawaii. Infection also exists in the Caribbean, Central Africa and some metropolitan areas of the US. (Source: Chemical Marketing Reporter, 5 December 1988)

Poison-less gas

Until now, civilians have had little defense against chemical warfare weapons. Soldiers have used gasmasks and clean suits to ward off the "winds of death", but civilian populations have suffered slow, painful death or crippling injury from the poisonous clouds. Now, researchers at the Southwest Foundation for Biomedical Research and the University of Texas at San Antonio have found a vaccine which may make a particular chemical weapon called mycotoxin T-2 as harmless as an aerosol room freshener. Mycotoxin T-2 penetrates the cells of the skin and lung, causing them to peel away. The vaccine, developed through a three-year $1.3 million grant from the US Army, counters the gas by keeping the toxic substance from attaching to the cells. Foundation researchers are now working on a vaccine against the nerve gas Soman. (Source: BioBytes San Antonio Biotechnology News and Information, Dublin - McCarter & Associates, March 1989)

New process for producing anti-inflammatory agent from blue-green algae

A research team of the Department of Applied Chemistry for Resources, Faculty of Engineering, Tokyo University of Agriculture and Technology, has developed a new process for producing an anti-inflammatory agent, or superoxide dismutase (SOD), from marine algae. The gene recombination process is known as a method for

producing SOD, but the new method cultures blue-green algae and produces SOD efficiently by supplying the algae with light and oxygen.

Micro-algae represented by Chlorella, are used in various foods as a source of protein and fat, but research is in progress to use various algae for producing a number of biologically active substances of high added values in addition to nutrients. For example, attempts are being made to produce anticarcinogens from algae. The new process is a result of research in pursuit of high added values.

SOD decomposes superoxide radicals which are toxic substances in the body, inhibits skin tissue aging and prevents freckles.

In the experiments, blue-green algae were added to 80 ml. of potassium phosphate buffer to make a cell concentration of 3 mg./ml., then cultured for two days at 30° C under a light condition and a dark condition. To ascertain the influences of the gas phase during culture with respect to SOD generation, culture was performed in a gas phase consisting of air and in a gas phase in which the air was replaced with oxygen.

As a result, it was found that culture under a light condition provides twice as much productivity as under a dark condition, and that culturing in a gas phase by replacing air with 100 per cent oxygen provides a productivity twice that of in air. It was also found that when light is irradiated and culture is performed in a gas phase by replacing air with 100 per cent oxygen, productivity is improved by 3.5 times that of culture in a dark, air environment.

Research will be continued with the objective of commercializing the new process. (Source: JETRO, January 1989)

Implantable glucose sensor expected soon

For patients afflicted with insulin-dependent diabetes mellitus (IDDM), controlling blood glucose at near-normal levels can best reduce the disease's long-term, life-threatening cardiovascular side effects. An implantable glucose sensor would greatly aid in controlling insulin delivery to IDDM patients.

Over the past ten years, experimenters have been attempting to devise a sensor of suitable selectivity and stability that can be implanted in an appropriate site in the body. Now, it appears that the first such sensor, using subcutaneous needle placement, should be available soon for 24- to 48-hour test monitoring of glucose levels in hospitalized patients.

Both enzymatic and nonenzymatic approaches for constructing an in vivo sensor have been under study. Within the next 6 to 12 months, needle-type prototypes based on the enzymatic approach should be available for initial clinical studies in Europe. These first sensors will be from groups headed by E. Pfeiffer (University of Ulm Medical Clinic, Ulm, FRG) and Uwe Fisher (Central Institute of Diabetes, Karlsburg, GDR).

In the US, Food and Drug Administration investigational device exemption approval will be needed before commencing initial clinical studies. Extensive animal testing most likely will continue throughout the clinicals to work out any material or design problems - especially difficulties in the stability of the tissue-prosthesis interface, particularly for longer-term implants.

Lemuel Wingard (University of Pittsburgh) and Manuel Alvarez-Igaza at Cranfield Institute of Technology (Cranfield, UK) are experimenting with alternative stabilized-enzyme-based approaches to solve problems of selectivity and long-term stability, using immobilized mediators or structures to give direct electron transfer without the use of oxygen or the formation of hydrogen peroxide.

Further research breakthroughs are needed, however, to reduce these alternatives to practice. These include devising methods to obtain direct electron transfer from the glucose-oxidase enzyme-cofactor complex to an electrode surface without the need for mediators, and the synthesis of less labile oxidation-reduction catalysts that retain a high selectivity for glucose. Crystallization and X-ray diffraction studies of deglycosylated oxidase to obtain evidence for the active site three-dimensional structure of the enzyme-cofactor complex should aid progress on newer glucose catalysts.

Also, to devise a longer-term implant, the problem of tissue encapsulation - which can alter response time - must be addressed. Edmund Spaeth (Baxter Technology and Ventures Division of Baxter Healthcare, Irvine, CA) presented promising animal data on minimizing and stabilizing tissue capsule formation by means of sensor membrane surface texturing. (Extracted from Bio/Technology, Vol. 7, February 1989)

Livestock applications

Wellcome advances on virus

Researchers at Wellcome Biotech and Oxford University have unveiled a potential route for the design of foot and mouth and other vaccines. The scientists have determined the structure of the foot and mouth virus. According to Dr. Fred Brown, head of virology at Wellcome Biotech, this should assist in the development of improved and novel vaccines and may lead to the design of antiviral drugs.

Brown and his colleagues have discovered that the virus has a protruding peptide on the surface which acts as a potent peptide vaccine. As this protrusion is believed to be involved in viral attachment to cell surfaces, this may also be a target for synthetic anti-viral drugs.

Foot and mouth disease is a commercially devastating condition of farm animals. Brown believes developing countries would benefit from synthetic vaccines because they would not have to spend resources keeping virus-based vaccines cool. (Source: European Chemical News, 27 February 1989)

Ozone reaction control system for fish cultures

Tohoku Air Conditioning Engineering Co. Ltd. has developed an ozone reaction control technique and, by applying it, has developed a culture system, called Bio-Mate (BM) System, that is remarkably effective in growth promotion and disease prevention.

Ozone, known for its disinfection properties and for promoting biotic activity, is sometimes referred to as the vitamin in air. When it exceeds a fixed concentration, however, it generates toxity at a rapid reaction speed, so its range and method of use is limited.

To cope with this disadvantage, the company developed an ozone reaction control technique jointly with academic circles, such as Tohoku University, and announced the technique as an Ozone

Reaction Variabilization Technology. Specifically, it developed a technique to give ozone a secondary plasma treatment that suppresses the ozone effect and, at the same time, expands the range of the effect. In the BM System that applies this technique, high-tension electricity is discharged in air compressed by a compressor to obtain air in which ozone atomic nuclei and electrons are well-balanced in plasma form. By bubbling the plasma ozone air in water, the water is disinfected and the volume of dissolved oxygen is notably increased.

The technique's outstanding characteristic is that plasma ozone control enables selective disinfection, so in the BM System the ozone's disinfection effect is so controlled as to kill off only bacteria of less than 10 μm and to prevent the ozone's effect on algae (50-100 μm) which are necessary for fish subsistance.

The BM System kills various bacteria in water to prevent infectious diseases and, at the same time, has the effect of helping diseased fishes recover. Using this system increases oxygen dissolved in the water from 100 ppm to 500 ppm, or to 5 to 10 times that of the ordinary method of blowing oxygen into the water (20-50 ppm), which has the effect of activating fish metabolism and promoting growth. Operating the system with 15 goldfishes about 2 cm. long in a water tank showed that five of them grew to 25 cm. in one year and the others to over 15 cm. At the present stage, eels and other fishes are being cultured at public experiment stations, and reports are that their growths are 3 to 5 times faster than other methods.

The system prevents oxygen deficiency, enables mass fish culturing in limited spaces, eliminates the need for drugs, enables reduction of running costs, and the water in the culturing tank is not contaminated so much due to the ozone's cleansing effect. (Source: JETRO, February 1989)

Vaccine against theileriosis parasite

A vaccine for the theileriosis parasite might be developed to prevent East Coast fever or muguga in cattle. The parasite, which is transmitted by ticks, has a life cycle similar to that of the malaria parasite. The tick injects sporozoites into the bloodstream of cattle. Monoclonal antibodies to the coat proteins might be effective in keeping the sporozoites from entering lymphocytes. The parasites then develop a pyroplasm stage that infects red blood cells. At this stage it is possible to analyze viral DNA without contamination with bovine DNA. A problem in ridding a cow of the infection is that the virus can replicate as the cell is dividing, so each daughter cell has the virus within it. Viral antigens can appear on the surface of infected cells, and this can allow cytotoxic T cells to attack the infected cells. Scientists would like to find out what the antigen is that prompts such an attack. The antigen is probably very small, which makes it hard for the immune system to detect. The disease threatens 25 million cattle in 12 countries in East and central Africa. (Extracted from New Scientist, 11 February 1989)

New rinderpest vaccine available

A new recombinant vaccine against rinderpest has been developed by researchers at the University of California (Davis), under an $870,000, three-year co-operative agreement with the US Agency for International Development. Rinderpest has wiped out herds of cattle in Asia and Africa for hundreds of years. After USDA approves the vaccine for export, further small-scale testing will be performed in Africa on cattle held in containment, pending the approval of the host governments. Ranchers will be able to vaccinate their cattle against the rinderpest virus at a low cost, after the testing is completed, according to the Agency for International Development. Rinderpest is a viral disease that kills two million cattle and buffalo per year. It causes pneumonia and bloody diarrhoea in livestock. Although the disease is under control in the Western World, it is still prevalent in Africa and Asia. Previous attempts at eradication have met with mixed success.

Virologists at the University of California at Davis predict that their vaccine will wipe out rinderpest, because it is as easy to administer in developing countries as the smallpox vaccine. Farmers can grow their own supply of the vaccine in the form of scabs on a single vaccinated calf. This is similar to the scab made by a smallpox vaccination, and contains enough material to produce between 200,000 and 300,000 doses of the vaccine.

If successful it will be made available free of charge to any country that wants it. Scientists have already tested the vaccine in the US at the Plum Island Animal Disease Center in New York. The tests were successful: 15 vaccinated animals survived doses of rinderpest 1,000 times as strong as levels which are normally fatal. Four unvaccinated animals died within seven days of being exposed.

All that farmers have to do is to shave hair from the abdomen of a vaccinated animal, scratch the area, and wait for a scab to form. They then scrape off the scab and make a suspension of it in salt solution. To vaccinate another animal, a farmer need only break the skin, and apply the virus suspension to the cut.

Rinderpest - which means "cattle plague" in German - attacks the gut, and causes bloody diarrhoea and pneumonia. Infected animals rarely recover.

The virus in the new vaccine is not affected by heat so farmers do not have to store it in the cold.

The new vaccine may have other uses. It will be tested on a disease related to rinderpest called peste des petits ruminants that kills goats and sheep, especially in West Africa. The vaccine may also offer protection against human measles and canine distemper.

The vaccine was developed by placing two genes from the rinderpest virus into the vaccinia virus. The haemagglutinin and fusion genes code for rinderpest virus proteins that set off an immune response in animals inoculated with the vaccine. (Extracted from Chemical Marketing Reporter, 28 November 1988 and New Scientist, 3 December 1988)

Brucellosis vaccine test

Recently several research groups, including one led by Texas A & M University veterinarian Garry Adams, have developed experimental vaccines to prevent brucellosis, a devastating disease that causes abortions in animals and can cause undulant fever in man, using alternative technologies. The Texas research group used transposon-based mutagenesis to inactivate normal outer-membrane lipopolysaccharide synthesis in B. abortus. The

resulting mutant bacterium no longer causes disease in mice or goats. And so far it does not revert to its original pathogenic state, Adams says.

To begin testing the product, Adams and his colleagues inoculated cattle with a killed version of the bacterial vaccine early in 1988. Because the B. abortus pathogen and other experimental vaccines behave very differently in mice and goats than in cattle, the latter must be used to evaluate vaccines. To get statistically valid results, at least 25 animals are needed in each of the four test groups in the current study. (Extracted from Bio/Technology, Vol. 7, February 1989)

Algae and bacteria bring a breath of fresh air to pigs

The combined efforts of algae and bacteria could provide a solution to the Dutch manure mountain. Howard Fallowfield and Ivo Svoboda, of the West of Scotland College near Ayr, have developed a process that acts like an ecosystem in miniature, doing exactly what nature would do with the waste - but in a limited space and without harming the environment.

The traditional way of disposing of pig slurry (faeces) is to spread or spray the muck on the land. But most pig farmers, in Britain as well as the Netherlands, have too little land on which to spread their slurry. If they put on too much, or spread during the winter when the soil is waterlogged, the slurry simply runs off into the river system. Pig farmers also face frequent complaints from the public about the smell of their farms.

Pig slurry is not only very smelly, but it is also a formidable pollutant. The slurry is rich in organic matter, which uses large amounts of the dissolved oxygen in freshwater as it decays, and in nutrients such as nitrogen and phosphorus. These nutrients encourage algae to grow, which also use up valuable oxygen, both at night when photosynthesis stops and when they decay. Nitrogen, in the form of nitrates, is also troublesome in freshwater supplies. In many parts of Britain, the nitrate levels in drinking water exceeds European Commission guidelines.

What Fallowfield and Svoboda have done is to develop a process in which bacteria and algae use the nutrients in pig slurry in a useful way. Bacteria break down the organic content of the waste to produce heat and the raw materials to feed the algae. The algae then take over and use the nitrogen and phosphorus left behind.

The two scientists have built a pilot plant that deals with the excrement of 300 pigs and 100 weaners. The slurry from the pigs collects in a large underground tank. Every hour, some of the slurry is pumped into another tank, the aerobic reactor, which holds about 24 cubic metres of liquid. A motor-driven aerator keeps the oxygen at the right level for the various bacteria to get to work on the organic matter.

In the reactor, the bacteria produce heat, carbon dioxide, ammonia and other nutrients. The heat is siphoned off and transferred to warm the pig house, while the carbon dioxide is released into the air. By the time the temperature inside the reactor reaches about 35° C, the nitrifying bacteria have converted all the ammonia into nitrate. This is the best form of nitrogen for the algae to use.

After about two-and-a-half days in the reactor, the slurry is pumped out and allowed to settle. The result is a liquid that looks rather like cold tea and is virtually odourless. It is now ready for the second stage, the algal pond.

The treated slurry trickles into the pond or raceway, a shallow system of channels where the algae are installed. The pond, about 13 square metres in area and 34 centimetres deep, is open to the air so that sunlight can supply the energy needs of the algae, while the slurry provides the nutrients. An electrically driven paddle keeps the algae-laden solution circulating in the raceway until, after about four-and-a-half days, the effluent overflows into a collection tank.

The slurry is now safe to disguard - after treatment, the amount of oxygen it needs for the final stages of decomposition is reduced by 95 per cent, and the algae have removed between 40 and 60 per cent of the phosphorus and nitrogen. The solution left is almost pure water and algae.

The algae remaining at the end of the treatment could be a useful by-product. While Fallowfield and Svoboda have not yet identified the best use for the algae, animal feeds and petroleum spirit are two possibilities. These, however, involve extracting the algae from the solution, which is a costly exercise. Fallowfield prefers the idea of selling the algae-laden solution to fish farms for feeding rotifers, a type of zooplankton. Many farms use rotifers for rearing fish, particularly marine species, and are already large consumers of algae.

The Department of Agriculture and Fisheries for Scotland funded the pilot plant. Now Fallowfield and Svoboda are seeking other sponsors so that they can build a full-size plant. They say that the treatment system is not expensive to run - the motors to drive the aerator and the paddle in the algal pond are the only continuous drain on power. And the heat-recovery system could produce about four times as much energy as is needed to power the plant. (Extracted from New Scientist, 26 November 1988)

Agricultural applications

Technology for mass cultivation of rice seedlings

The National Agriculture Research Center of the Japanese Ministry of Agriculture, Forestry and Fisheries has developed a technology for mass cultivation of rice seedlings in a short period of time. The new technique theoretically enables roughly three billion rice seedlings to be grown from a single rice seed in about six months.

Usually only one seedling sprouts from a rice seed, but in past examples of cultivating rice seedlings using an agar culture bed, a few thousand to several tens of thousands of seedlings were obtained in about six months. With the new technique, a liquid culture bed is used instead of the usual agar culture bed and a gyrated drum placed obliquely is used to culture the seedlings while revolving the seeds in a test tube. By this new method, up to 44 seedlings are obtained in about five days, and these seedlings multiply at a rate of four times every ten days. At this rate, the number of seedlings will amount to roughly three billion in six months.

This new technique can be used for mass cultivation of first filial hybrid (F1) seedlings by using the heterosis phenomenon of the first filial hybrid of a crossbred seed featuring a better growth potential and resistance to diseases than its parents. For this, the research centre says it will

be necessary to develop a robot for root separation of seedlings grown by the new technique. (Source: JETRO, February 1989)

Genetically improved cotton

Monsanto claims it has genetically improved the ability of cotton to resist insects by stimulating plants to produce high levels of a protein that is toxic to such pests as cotton bollworms, tobacco budworms and beet armyworms. A naturally occurring bacterium, bacillus thuringiensis, is inserted into the plant to bolster its defenses. The firm first introduced genetically insect-resistant plants in 1986 that killed such pests as cabbage loopers and tobacco hornworms, but not enough protein was produced to control heartier insects. By modifying the structure of the bacterium's gene, protein production has been increased. Separately, researchers at Cornell University applied for regulatory approval for what they claim is the first US field test of an altered virus to fight off a number of agricultural pests without harm to the environment. If approved by the FDA, an altered baculovirus will be sprayed on a cabbage patch in Geneva, NY, in summer-1989 to test its effect against the cabbage looper, which kills nearly a dozen different varieties of vegetables. (Extracted from Wall Street Journal, 29 March 1989)

New pesticide to prevent crown gall disease introduced

Bio-Care has introduced NoGall engineered pesticide to prevent crown gall disease. The Government of New South Wales, Australia, has approved the compound "with no questions asked", according to Bio-Care. NoGall can be retailed in two states in Australia and can be sold directly to farmers anywhere in Australia. The firm hopes to win approval to retail the compound anywhere in Australia, and will submit the compound to US EPA. Worldwide, crown gall disease causes $150 million in damage per year. The K84 strain of Agrobacterium tumefaciens produces an antibiotic that kills pathogenic strains of the same species. The altered cells, which are packaged 10 billion/L., do not affect mammals, and the antibiotic kills no organism except A. tumefaciens. (Extracted from New Scientist, 4 March 1989)

Plant gene markers to speed breeding

Agricultural Genetics Co. (AGC), the UK-based biotechnology concern, has reached licensing agreements with a number of seed companies covering research into genetic markers used in wheat and barley breeding. According to AGC, the markers, which are called restriction fragment length polymorphisms, will have a significant impact on plant breeding programmes.

Companies involved in the agreements include Cambridge Plant Breeders, Ciba-Geigy, ICI, Nickerson International Seed Co. and Plant Breeding International.

The markers can locate genes in much the same way as genetic fingerprinting does in diagnostic and forensic work. Plant breeders can use the markers to select genes of significant agronomic importance. The method could replace the difficult and time-consuming plant screening methods used currently. (Source: European Chemical News, 23 January 1989)

New test developed to detect pesticide resistance in insects

A simple enzyme test can determine if an insect is resistant to certain pesticides, according to W. Brogdon of CDC (Atlanta, GA). The method now used exposes insects to samples of pesticides, waiting 24 hours and seeing how many survive. But that technique has serious flaws. For one thing, it may be that the pesticide sample (generally a piece of paper soaked in a pesticide) may be ineffective by the time it is used in the field. It may also be difficult to collect enough of a particular insect to conduct the test. And the test does not indicate the mode of action of the pesticide.

The new test, however, requires only one insect to be captured, exposed to a pesticide, crushed and diluted to perform up to 30 tests. The insect solution is placed in wells of a microtitreplate with reagents. If the solution changes colour, the insect is resistant to that insecticide. One test, for example, detects the presence of acetylcholinesterase, which is generally destroyed by organophosphate pesticides. The new kit will cost $38, although the WHO bioassay tests now in use cost $232. (Extracted from New Scientist, 4 March 1989)

Transgenic plants offer molecular farming

Plants can be engineered to become molecular factories for pharmaceutical proteins, says Walter De Logi, managing director of Plant Genetic Systems, an agricultural biotechnology company in Ghent, Belgium. With the firm's new system, genetic engineering is used to introduce genes for economically important peptides into plants. The peptides are produced and stored in a stable form in specific plant organs, from which they can be extracted. In experiments on oil-seed rape in the greenhouse, high amounts of valuable peptides were produced in the plants' seeds. The products were efficiently extracted and purified, De Logi says. He predicts molecular farming techniques will have many advantages over production of such compounds in transgenic animals, a strategy that many biotechnology firms are pursuing. (Reprinted with permission from Chemical and Engineering News, 23 January 1989, p. 18. Copyright 1989 by the American Chemical Society)

Possibilities of fast growing kenaf

The fast-growing kenaf plant could produce high-quality newsprint and other fibrous products now made from trees, according to USDA after 30 years of trials It could help save forests, reduce dependence on imported newsprint, become an important source of income for US farmers and reduce environmental contamination from paper mills. Kenaf newspaper is brighter, and has high contrast and good colour, reducing the amount of ink needed to print, and ink does not rub off on hands and clothing. Even after one year in storage, kenaf newspaper did not turn yellow. In addition, mills would use less energy and chemicals to produce pulp and whiten the fibres. Kenaf could be used to make poultry litter, carpet backing and padding, cattle feed, moulded fibre automotive parts, fire logs, cardboard and roofing felt. In Africa and Asia, it is used to make nautical rope, twine and cigarette paper.

Kenaf can produce three to five times more paper pulp per acre than trees do at roughly 50 per cent the cost, according to field trials. While a tree takes seven to 40 or more years to mature to harvestable size, kenaf, an annual crop, reaches 18 ft. in 120 to 150 days after seeds are planted. It can be grown without pesticides throughout the Cotton Belt, and with irrigation in the drier areas. It can even tolerate some salinity without affecting yield much. Kenaf International (Bakersfield, CA) and Canadian International Paper (Montreal, PQ) may jointly build a $400 million,

215,000 tons per year kenaf newsprint plant near McAllen, TX, to be operational by the end of 1991. (Extracted from New York Times News, 13 December 1988)

Pathogen against crop pests to be tested

Permission to field-test genetically altered Autographa californica nuclear polyhedrosis virus, fatal to cabbage looper caterpillars, is being sought from EPA by the Boyce Thompson Institute for Plant Research at Cornell University. The Ithaca, NY, researchers deleted the gene that codes for the protective coat, rendering the virus incapable of long-term survival. If tests this summer show lack of persistence in the environment, scientists would later add genes for increased virulence against insects, possibly arresting their development, feeding, or reproduction. Cabbage loopers attack more than a dozen vegetables, including cabbage, beets, broccoli, brussels sprouts, cauliflower, collards, and kale. EPA is supporting development of these altered viral strains. (Reprinted with permission from Chemical and Engineering News, 6 March 1989, p. 27. Copyright 1989 by the American Chemical Society)

Corn with a bigger protein punch

Corn kernels, says the University of Minnesota (St. Paul), are less than 10 per cent protein. That does not match up too well against soya beans, which contain 38 per cent. In addition, the protein corn it does possess is low in two nutritionally vital amino acids - lysine and tryptophan. Work begun in the 1970s to increase corn's lysine content has now come to fruition, and the scientists involved are seeking a patent on the technology. Cytogeneticist Ron Phillips and his research group have found a gene that affects lysine production, sometimes increasing it as much as 20 per cent. The university notes that an improved corn twice as nutritious as the ordinary variety was recently introduced in Mexico, but that variety gives "floury, soft kernels that do not store well", and the improvements depend on "a complex genetic system, rather than one gene that gives high lysine", Phillips says. The Minnesota research group claims their material brings no undesirable effects, and the fertility and quality of the corn is completely normal. (Source: Chemical Week, 8 February 1989)

Grace picks up centuries-old pesticide

The Neem tree, a tropical evergreen, has been used for centuries as a source of pesticides to which insects have not developed resistance, according to W. R. Grace (New York City). Now the firm has acquired Vikwood Botanicals' (Sheboygan, WI) rights to the patents, Environmental Protection Agency registration, and technology for producing the pesticide Margosan-O from the tree's seeds. The main ingredient in the extract is Azadirachtin. The product has "low- to no-" mammalian toxicity and is thought to be effective against a broad range of insects resistant to many chemical pesticides, including the sweet potato white fly, green peach aphid and Western floral thrips. Grace plans to test-market the pesticide with greenhouse growers later this year, and to seek an expanded registration allowing it to be used by food growers and on pests in and around the house. (Source: Chemical Week, 8 February 1989)

Firmer tomatoes get protection

Calgene (Davis, CA), which developed technology to produce longer-lasting tomatoes, has now won US patent No. 5,801,540 for the process. Calgene uses recombinant DNA technology to introduce an "antisense" polygalacturonase (PG) gene. PG is an enzyme involved in tomato softening. The antisense gene produces messenger RNA that binds to the naturally occurring mRNA, blocking it from expressing PG. Calgene says the patent is the first to be issued covering the use of antisense technology in genetically engineered plants. The firm is now conducting field trials in Mexico. (Source: Chemical Week, 22 February 1989)

Flower pests are target of biocontrol

W. R. Grace & Co. will seek to commercialize a first-of-its-kind biological control for floral plant diseases under a co-operative research agreement with the US Department of Agriculture.

The biocontrol is based on a naturally occurring fungus that attacks other fungi in the soil causing diseases in floral crops, said R. Dean Plowman, administrator of USDA's agricultural research service.

In tests at the research agency's florist and nursery crops laboratory, the biocontrol fungus, or agent, suppressed disease on major floral crops including zinnias, snapdragons, chrysanthemums and poinsettias. The agent was first isolated by a scientist of the agency's Biocontrol of Plant Diseases Laboratory. Both laboratories are located at the Beltsville, Md., agricultural research centre, close to Grace's research centre in Columbia, Md.

Grace intends to evaluate the agent and then market the first commercial product for use against a fungal pathogen of greenhouse crops, such as flowers.

USDA and Grace signed the research agreement under the Technology Transfer Act of 1986. The act made possible increased co-operation between private companies and individual federal research laboratories, encouraging the movement of federally developed technology into the marketplace. (Source: Chemical Marketing Reporter, 16 January 1989)

Wider tests of engineered biopesticide sought

Crop Genetics International is seeking permission from the Environmental Protection Agency and Department of Agriculture to test the use of its InCide biopesticide to protect corn plants against European corn borers at five sites in three Midwestern states - Illinois, Nebraska and Minnesota - and at three sites in Maryland. The Midwest tests would be carried out in co-operation with four seed companies with which Crop Genetics signed joint development and marketing agreements.

Crop Genetics is also seeking approval from EPA and USDA for the first time to conduct field trials on rice, at its Ingleside, Md., research farm. It will use the same genetically engineered micro-organism as was used on corn to protect against rice stem borers. The trials will focus on the bacterium's colonization ability in rice and its environmental safety.

The InCide technology, on which patent protection is being sought, is based on enabling a plant to produce its own pesticide. As a carrier, it uses an endophytic (plant-dwelling) single-cell bacterium, Clavibacter xyli cynodontis (Cxc), which is viable only inside the vascular system of a plant. Cxc is native to Bermuda grass, but it also colonizes corn and a number of other plants. Cxc is genetically altered to carry the delta-endotoxin

gene from the widely used biopesticide, Bacillus thuringiensis kurstaki (Bt).

When inoculated into corn, Cxc multiplies inside. The endotoxin it produces is an insecticidal protein toxic only to caterpillars with alkaline stomachs, and is inactivated and rapidly digested in the acidic stomachs of mammals, fish, reptiles and birds.

Last year's small-scale field tests, at two sites in Maryland "proved the safety of the technology", Crop Genetics says. The recombinant micro-organism did not spread from test sites by any natural phenomena or normal agricultural practice, and did not survive outside its host plant, it adds.

The 1988 trials were done by injecting Cxc/Bt directly into corn stalks. This year's trials will test the projected commercial treatment method - inoculating corn seeds with Cxc/Bt before planting. The trials also will test corn yields and whether improved plant nutrition with micronutrients can offset small yield losses caused by Cxc/Bt. (Extracted with permission from Chemical and Engineering News, 6 March 1989, p. 28. Copyright 1989 by the American Chemical Society)

Towards more fertile soil

(by Dr. Janet Sprent, Department of Biological Sciences, Dundee University, United Kingdom. This article first appeared in Spectrum/5, No. 216/1988)

There is now intense interest in the use of multipurpose trees and shrubs of the legume family to improve soil fertility and to provide basic resources such as food, fuel and shelter in under-developed countries. But before this can be achieved we need to know which legumes can fix nitrogen in a given environment and how we can use them to the best advantage. In seeking the answers to some of these essentially practical questions, we have obtained new insights into the structure and function of the nodules of legumes, which are the sites of nitrogen fixation, and we have learned more about legume taxonomy and evolution.

Felling trees often has disastrous effects on soils in tropical areas. These range from accelerated mineral cycling with concomitant leaching in humid rain forests, such as in Amazonia, to making desertification worse when the cooling by shading and the soil binding benefits of trees are removed. Intense international effort is now concentrated on the use of shrubby and woody species, both to slow and reverse these trends and to provide resources for native peoples.

Among the most promising species are members of the legume family, because many of them can harbour nitrogen-fixing bacteria, rhizobia, in nodules on their roots (rarely on the stems) and so have the ability to take nitrogen gas from the air and incorporate it into protein. Although legumes have been in integral part of crop rotations since before Roman times, most research into nitrogen fixation has been on crops vital to the developed world, such as soya bean in the USA and subterranean clover in Australia. Many of the thousands of legume species abounding in Africa, Asia and South America have never been examined for nodules, let alone studied to see how much nitrogen they can fix.

Although it may seem simple to dig around legume plants and look for nodules, this is not so. Tropical legume nodules may be hard to find (Dr. Peter Högberg, an experienced nodule hunter from Sweden, took five days to find one on a Tanzanian species he felt certain should have some) and they are hard to recognize. Many of them are quite unlike those on soya beans, peas and clover which provide the illustrations for most elementary and advanced textbooks. Additionally, some legume roots produce small swellings which can be mistaken for nodules.

Which legumes nodulate?

The legume family is generally divided into three subfamilies, namely the Caesalpiniodeae, the Mimosoideae and the Papilionoideae. The last of these has members in all regions of the world from equatorial to polar. Nearly all of those examined can nodulate. The Mimosoideae are found only in the warmer parts of the world; very few tolerate frost. However, many are drought-tolerant, occurring particularly in South Africa and Australia, and can be used for many purposes. Most, but by no means all those examined, can nodulate. The Caesalpiniodeae are mainly trees of tropical regions, often producing valuable timber: few are known to nodulate.

Many of the scattered reports of nodulation in the literature are of doubtful veracity. This statement should not be taken as a slight on the scientists concerned: proper identification of both plants and nodules is very difficult. Paradoxically, certain structures which are nodules may have been rejected because it was not possible to isolate from them rhizobia which could induce nodulation on other plants. The rather heretical statement stems from the work of Sergio Faria, a Dundee Ph.D. student from Brazil.

With a large team of taxonomists, foresters and others, Faria recorded a number of new nodulated genera and species from the Caesalpinioideae. When we started to examine the structure of these nodules, during a visit to Brazil as part of an exchange programme with Dr. Johanna Dobereiner's group in Rio de Janeiro, we found they were literally "tough nuts to crack". Several of them, when we tried to slice them, shattered and the pieces shot off in all directions: to our surprise they had many layers of woody cells, rather like the shell of a nut. This opens up the interesting possibility that they might fossilize easily; fossil legume nodules have never yet been found.

When we brought some back to Dundee, detailed microscopic examination revealed an internal structure which was unique in that the nitrogen-fixing bacteria remained tightly wrapped in plant cell wall material throughout, unlike the generally accepted nodule structure in which they are enclosed merely by rather delicate membrane vesicles. We believe that this plant cell wall material may have contributed to the problem of isolating bacteria from such nodules. Similar unusual structure has been found in all Caesalpinioid nodules examined, in five Papilionoid genera and in the one non-legume genus, Parasponia, which forms nodules with rhizobia.

Requirements for nodulation

The general term rhizobia covers at least three genera, Rhizobium, Bradyrhizobium and Azorhizobium. They can live in the soil, but in nature do not fix nitrogen outside their legume hosts. They vary in specificity for different hosts and in the effectiveness with which they fix nitrogen in their particular hosts. Obvious requirements for

nodulation are compatible and effective rhizobia. In countries such as Australia and the USA, there has been a legume inoculant industry for many years. This is big business. What is needed in many countries is small-scale production of inoculants for local use and techniques for it are being developed in various countries. However, apart from certain species, mainly pulse crops such as cowpea and various lentils, good rhizobia have not been isolated or tested.

The UK Overseas Development Administration has been supporting work on legume trees in Africa and Central America, mainly through the Oxford Forestry Institute (OFI) for many years. A recent contract with our legume tree group is enabling Dr. Joan Sutherland and technician Shona McInroy to build up a collection of rhizobia from Africa and elsewhere and to test them for efficiency and tolerance to drought. In this work there is active collaboration with OFI staff: recently, for example, Dr. Richard Barnes from OFI collected nodules in Zimbabwe.

Reciprocal collection has its limitations, however, because the OFI Group are selecting tree provenances and therefore need seed. Seeds tend to mature in the dry season when nodules are at their most difficult to find. Moreover, nodule hunters are at the mercy of unpredictable rains, which makes the advance planning of trips very difficult.

We are developing local contacts, such as Dr. Odera and colleagues at the Kenya Forestry Institute, to help with this. Because of problems of correct identification of unfamiliar host plants we also rely heavily on local taxonomists and on legume experts at the Royal Botanic Gardens, Kew. We also exchange strains of rhizobia with the NifTAL (Nitrogen Fixation in Tropical Agriculture) group in Hawaii.

Not only must the correct rhizobia and host plants be brought together; conditions must be right for the rhizobia to enter into symbiosis with the host. This led us to examine legume root systems in detail under the microscope. Most of us are conditioned by elementary textbook pictures of young roots with abundant production of root hairs in a highly organized pattern, but we rapidly realized that many tropical legumes do not produce root hairs and, in those that do, production may be very erratic and subject to environmental constraints. This was confirmed in discussions with Dr. Tom Corby, who worked for many years in Zimbabwe collecting nodules (on his retirement he gave us over 1,500 preserved nodule specimens, a great reference source). The generally accepted "normal" pathway for infection of legume roots by rhizobia is *via* root hairs! So we began to reassess the pathways by which rhizobia gain entry into plant roots and found that entry through breaks where lateral roots emerge, previously known for peanut (*Arachis*) and a few others but thought to be rather exceptional, and directly between epidermal cells may be very common. Because the only detailed studies on how environment affects infections have been carried out on root hairs, we have opened up yet another area of research which needs to be carried out before we can understand and hence fully exploit many shrub and tree legumes.

Legumes and fertility

Obviously, if legumes are to enrich soil with nitrogen they must nodulate. In dry environments even legumes with a potential for nodulating usually fail to do so. Exceptions to this are deep rooted trees such as some species of *Acacia* and *Prosopis*. Pioneer work on the latter has been carried out in Texas and Arizona, where it was found that nodules are probably restricted to roots near the deep water table. Deep rooted legumes can grow on such palaeowater when surface soils are very dry. Some have special attributes, for example *Acacia albida*, which grows in dry areas of North Africa, and uses this ground water to make leaves in the dry season.

Such useful attributes have no direct relationship to the ability to nodulate. Indeed, a number of legumes which grow well in dry areas apparently *cannot* nodulate; one example is the carob *Ceratonia siliqua*. Non-nodulated legumes clearly cannot produce a net gain in soil nitrogen. What they and other deep-rooted species may do is to bring soil nutrients up from lower layers, and from ground water, to upper layers where annual crop plants may use them.

To obtain a net gain in soil nitrogen, not only must legumes fix nitrogen, but they must fix more than is removed in any crop. In the case of a pulse legume such as cowpea, where the seed is harvested and is rich in nitrogen, more nitrogen may be removed than is fixed. The result is a depletion in soil nitrogen. This is probably more common in soils of developed countries, which may contain significant quantities of combined nitrogen (which all legumes prefer to use instead of fixing their own). To return most nitrogen to the soil means keeping the amount taken off the field to a minimum. All debris should be returned and used as mulch or ploughed in. This is where the developed world has a great deal to learn from less developed areas, where nothing is wasted.

Development of multipurpose trees is likely to ensure the optimum use of fixed nitrogen. Systems such as so-called alley-cropping are proving very effective in countries as far apart as Nigeria, Brazil, India and Sri Lanka. Long-term studies of nitrogen cycling in these and other systems are needed if we are to understand them properly and sustain improvement of the soil. Short-term benefits of irrigation followed by longer-term problems of salinity (see *Spectrum* 203) should be a lesson to all who think that a three-year research project can provide quick answers.

Frustrations and benefits

Many of the species of tropical legume trees with which we work are difficult to germinate. Some will germinate only if sown within a few days of the seed maturing; others need a good soak in concentrated sulphuric acid. Growth may be slow and erratic. Woody nodules are difficult to prepare for microscopy; absence of root hairs makes the study of infection very difficult because you do not know where to start looking. Nevertheless, these difficulties are outweighed by the interesting discoveries we have made. What started as an apparently straightforward extension of studies on temperate species has enabled us to put forward ideas as to how legume nodules may have evolved, and to point out that some of the stages hitherto considered to be essential in the setting up of a functional legume nodule in fact are not.

Natural infections between epidermal cells have a great deal in common with those found with genetically engineered rhizobia. Retention of nitrogen-fixing rhizobia by host cell wall material, thought to be a consequence of an abnormal symbiosis between a non-legume (*Parasponia*) and rhizobia now appears to be a primitive state. By studying these plants we can help to define those properties which are truly essential for functional symbioses. This

will aid attempts to extend the ability to nodulate to a new genera, complementing the highly focused studies of our genetic engineering colleagues. We need now to select species for intensive study, while maintaining the broad framework of surveying nodulation in legumes and setting up field trials to assess their local significance. This calls for major resources, but on the other hand promises major benefits to the environment and to our better understanding of one of the largest and most important families of flowering plants.

Food production and processing

Light-emitting bacteria for food probes harnessed

Genetically engineered bacteria that emit light are being used to find out how sub-lethally injured food poisoning and spoilage bacteria survive in foods after processing. Luminescence genes can be introduced into different types of bacteria, including salmonellas. The amount of light emitted depends on how well the bacteria are metabolizing and growing.

Dead cells emit no light, and those damaged but not killed by processes such as freeze-drying, heating or freezing emit much less light than normal "healthy" bacteria. Unlike conventional procedures which are slow and detect only those bacteria capable of reviving to full capacity at the time of testing, this technique provides a rapid measure of the total number of injured bacteria, including those alive but not yet capable of growth, that could revive and pose a spoilage or safety hazard in foods.

Based on this research, Amersham International is developing a prototype food bacteria test, using a method developed by the company for detecting mastitis in cows. A disposable dipstick is coated with bacteriophages, virus-like agents that destroy bacteria, impregnated with a luminescent substance. When the dipstick is applied, the phage makes contact with the bacteria and passes on its luminescence. Amersham says it will be at least a year before the test gets into production, however. Details from: Dr. Gordon Stewart, University of Nottingham, on 0602 484848, ext. 8370. (Source: Biotechnology Bulletin, Vol. 8, No. 2, March 1989)

Dipstick test pinpoints fishy suspects

A smear of typists' correction fluid on a stick of bamboo may soon become an essential utensil for lovers of fishy delicacies from tropical areas. The instrument could help them to avoid nausea, vomiting, diarrhoea, itching and an upset in the sense of what is hot and cold. All are symptoms of a type of food poisoning caused by eating fish contaminated with ciguatoxin.

The toxin tends to accumulate in certain species of tropical or subtropical fish, but it does not affect all members of a species. Scientists believe that a common microscopic alga, called Gambierd'iscus toxicus, produces the toxin which then builds up in the tissues of herbivorous fish that eat the alga. The toxin can also accumulate in the tissue of carnivorous fish that prey on the herbivores.

Ciguatoxin can kill a mouse but does not appear to affect fish. The toxin can be found in eels, snappers, surgeon-fish and Spanish mackerel, which are all common to areas such as Florida, Hawaii, Japan and Australia. The western and south Pacific islands have the highest incidence of ciguatoxin poisoning, with up to one per cent of residents in the Tokelau Islands, northwest of Samoa, developing symptoms every year.

The problem for fishermen is that a tropical red snapper that contains high concentrations of ciguatoxin looks and smells no different from one that contains little or none of the poison. Fishermen in the Pacific often throw the catch back, fearing that the fish might be contaminated.

Yoshitsugi Hokama, professor of pathology at the John A. Burns Medical School, at the University of Hawaii, has developed a simple dipstick that he believes will solve the problem of separating the safe from the unsafe fish. The stick is made of bamboo and coated with typists' correction fluid, which, when dried, absorbs ciguatoxin very quickly when the stick is pressed into the meat of the fish, Hokama says.

Hokama then places the dipstick in a solution of monoclonal antibodies that have been developed to attach themselves exclusively to molecules of ciguatoxin, like tiny magnets. The antibodies are also bound to a chemical that will change colour in the presence of other chemicals.

The next step is to place the dipstick into a solution of methanol to wash off any antibodies not sticking to the toxin on the bamboo stick. The final step is to dip the stick into a solution of chemicals that will turn purple in the presence of the antibody-toxin complex. The dipstick will only turn purple if the toxin is present in the meat of the fish.

Hokama hopes to develop a dipstick that requires just a single step. He is working with a company in Honolulu called Moana Bio-products, and a Japanese company, Ube Kosan, may help to develop the product for marketing. (Source: New Scientist, 18 February 1989)

Amino acid from sugar fermentation

A University of Melbourne research team, has developed a process for low-cost production of the amino acid, tryptophan, from bacteria. Tryptophan is one of the "essential" amino acids, used in pharmaceuticals and health foods, and as an animal food additive. Unlike other amino acids such as lysine and methionine, which are used in large amounts to enrich fodder, tryptophan has proved difficult to produce cheaply, so its use is more restricted than that of the other amino acid food additives.

Although animals are generally not able to manufacture this amino acid, bacteria can synthesize it via fermentation from sugar. But bacteria produce only enough tryptophan for their own needs - they have developed a number of control mechanisms that regulate production of the substance.

What the team did was to identify these control mechanisms and "switch" them off. To further increase the production of tryptophan, the researchers added copies of certain genes to the bacteria's DNA to enable the organisms to make 100 times more tryptophan than usual.

Although the current world market is only about $US16 million annually for tryptophan, a dramatic reduction in price brought about by the new, cheaper process will encourage more animal feed producers to incorporate the substance in their products. This

could boost the total market to $US150 million a year. For details contact: Quest Investments Limited, 270 Queen Street, Melbourne, Vic 3000, Australia. (Source: Asia-Pacific Tech-Monitor, November-December 1988)

Bacteria as food preservative

Bacteria that produce bactericide could be added to food instead of chemical preservatives, according to S. Harlander of the University of Minnesota. Bacteria could also be engineered to reduce cholesterol in foods. The bacterium Lactococcus lactis is already used to ferment dairy, meat and vegetable products. Genes that govern fermentation are on plasmid DNA in L. lactis, making the bacterium susceptible to alteration. DNA added to the bacterium is first incorporated in the plasmid, and then transferred to chromosomal DNA, where it is stable. Added genes are generally linked to a marker gene so that scientists can determine when the new gene has been incorporated. Most marker genes make the host bacterium resistant to an antibiotic, but the US FDA would not allow such a marker in bacteria in food, so Harlander has developed a marker gene that makes an enzyme to counteract the bactericide nisin, which the bacterium produces itself. The anti-nisin antibiotic is commonly found in fermented foods, so FDA would have no objections to its use. (Extracted from New Scientist, 4 March 1989)

Chemical applications

New biodegradable plastic

Japan's Government Industrial Research Institute, Shikoku has developed an opaque plastic sheet compounded with the natural high polymers in plants and microbes. It is decomposed in soil into a substance that does not disrupt human ecology. It is stronger than polyethylene and vinyl chloride, and since its raw materials are amply available, it can be mass produced at low cost.

Petroleum-based plastics are widely used, including their use for wrapping and packaging various foods and for use as an agricultural sheet. Since they generate a tremendous amount of heat and damage incinerators when burned and generate toxic gas, and as they do not decompose in soil, they exert adverse influences on the surrounding environment. Their disposal method has long posed a serious social problem.

The new plastic is produced by extracting the same kinds of macromolecular saccharides as the starches in several kinds of plants and microbes, producing their respective components, then chemically bonding two or three of these components. When buried in the ground, soil microbes (rod-shaped bacilli) decompose it without leaving any contaminant, and it becomes fertilizer for natural plants without disrupting the ecology. It is opaque; its strength is one-to-two times that of polyethylene; and, depending on the treatment, its decomposition time in soil can be controlled. (Source: JETRO, February 1989)

Bacterium which converts sugars to ethanol

University of Florida researchers claim to have created a bacterium that converts vegetable and wood sugars into ethanol. About 800 million gallons per year of ethanol are added to gasoline in the US to make it burn more efficiently. The researchers say their new process will halve the costs of the current yeast-fermentation process, in which ethanol is derived from corn. Microbiologist L. O. Ingram reports that genes of the bacterium Zymomonas mobilis, which is found in cactus plants, were inserted into Escherichia coli, a common intestinal organism. Ingram claims the bacterium converts 90 to 95 per cent of the main forms of sugar in biomass into ethanol, which is more efficient than the rate at which yeast converts corn. However, concentrations of ethanol have been only 4 to 6 per cent against a 10 to 12 per cent rate for corn-based ethanol. Ingram says his goal is to reach 7 to 8 per cent concentration. (Extracted from Wall Street Journal, 1 February 1989)

Industrial microbiology

New enzyme discovered

Some 60 per cent of the enzymes used in industry belong to a group known as proteases, which attack proteins. They are used to make cheese, to make meat more tender and to improve dough, among other things. A few proteases are added to detergents, but many enzymes cannot stand temperatures much above 40° C. Washing machines can. An enzyme's activities may also be impaired or destroyed when it finds itself mixed with other chemicals. So there are limits to their usefulness.

Dr. Todd Gusek, a food scientist at Cornell University in Ithaca, New York, has discovered a protease without the usual shortcomings. He isolated it from a rare strain of a heat-loving soil bacterium, Thermomonospora fusca. So far his particular strain - dubbed YX - has been found only in a mangrove swamp on the Yucatan Peninsula in Mexico.

The enzyme is rather good at breaking down all sorts of plant and animal proteins at temperatures of up to 85° C. The hotter it is, the better it works. At 80° C it works 13 times faster than subtilisin, the most popular protease in current detergents. And it is unworried by high concentrations of detergents or by chemicals such as salts that are sometimes added to them.

YX protease could help with any number of processes for which other proteases are already used. Its efficiency means that relatively small amounts of enzyme are needed; the high temperatures it works at mean that the risk of contamination of a product by microbes is vastly reduced. It has already been employed to clean filtration membranes that are used to concentrate milk. In one test, it cleaned the membranes in an hour, instead of the day that existing cleaners take.

Another application for the enzyme might be to help make protein hydrolysates. These are protein-rich liquid foods administered through tubes to patients recovering from operations. They consist of the soluble components of proteins - peptides and amino acids. Another idea is to use it as the base for a contact-lens cleaner, to get rid of proteins from the eye's surface.

The enzyme is still being tested, but already companies in America, Western Europe and Japan are showing interest in it. The next step is to find a way to mass-produce it. Thermomonospora secretes its protease in minute quantities. The plan is to tinker with the genes of another species of soil bacterium which is used to make antibiotics. Dr. Gusek and his colleagues aim to take the gene that codes for YX protease in Thermomonospora and put it into ring-shaped DNA molecules, called plasmids, from the other microbe. The hope is that

once these altered plasmids are returned to their original owners, large quantities of the enzyme should be forthcoming. (Source: The Economist, 4 March 1989)

Energy and environmental applications

Sediment bacteria degrades most toxic PCB's

Prior to the 1970's, polychlorinated biphenyls (PCB) were widely used for a variety of industrial purposes, including fluid-filled capacitors and transformers, hydraulic fluids, plasticizers and carbonless copy paper. Commercial mixtures - called Aroclors - were later found to be highly persistent in natural environments, such as soils and sediments.

A Michigan State University research team, headed by Dr. James Tiedje, Dr. John F. Quensen II and Dr. Stephen Boyd, collected Hudson River sediments contaminated with PCBs. Anaerobic bacteria in the sediments were exposed to varying concentrations of PCBs. After 16 weeks, many of the most toxic PCBs were dechlorinated to less toxic products that could be more readily degraded by aerobic bacteria.

Further experiments added PCBs to cultures of anaerobic bacteria from non-PCB-contaminated Hudson River sediments. No evidence of PCB degradation was found, suggesting that the PCB-contaminated sites favour PCB degraders over other anaerobic species.

The next step is to see if systems can be devised that capitalize on this natural selection process. The driving force to make a biological system practical is cost. There are probably thousands of anaerobe species in sediment. The challenge ahead is to isolate only those capable of dechlorination. (Source: Bio-Connection, Winter 1988)

Long live the enzymes

All life is terminal, and biomolecules are no exception. Extracted at high cost from living cells, they soon lose the specific activity which makes them so valuable as diagnostic tools or therapeutic agents. Conventional stabilization methods include freezing in liquid nitrogen, freeze-drying or chemical additives. Such methods are either expensive, of limited effectiveness or they produce undesirable side effects.

Previous research by Professor F. Franks and his colleagues, previously in the Cambridge University Botany Department, and since 1985 in the Pafra Laboratory on Cambridge Science Park, led to a process by which the stabilities of biomolecules can be extended to several years. The principle is simple: low temperature is beneficial, but freezing kills. By studying natural cold resistance in overwintering plants and animals, Franks discovered the tricks used by such organisms to "undercool" their body water to subzero temperatures without allowing it to freeze. The undercooling principle has been applied to enzymes at the Pafra Biopreservation Division: a deep freeze contains hundreds of samples at -20° C, but unfrozen. Enzymes taken from the freezer and warmed to room temperature are shown to have retained their full activity. The process is also useful for the preservation of living cells, for instance the cultures used by many branches of medicine and industry.

The dream of every technologist and clinician is for stable products, not at -20° C, but at room temperature. The businessman has the additional wish that such products can be produced at low cost. For further information:
Professor Felix Franks, Biopreservation Division, Pafra Limited, 150 Cambridge Science Park, Cambridge CB4 4CG, UK. Tel: (0223) 420921
(Source: ABA Bulletin, Vol. 4, No. 1, February 196

Biodegradable packaging material

Environmental pressures are forcing industry to look for more environment-friendly methods of packaging products. Battelle in Frankfurt has developed a packaging material which is totally biodegradable. The starch-based material is specially designed for products such as one-way boxes or blister packs.

The material is transparent and flexible. Under normal conditions, it is resistant to biodegradation, but in water or wet soil conditions micro-organisms degrade it completely to carbon dioxide and water in just a few days. Additives make the material easy to process and the first production experiments suggest that it could be used with the usual methods: injection moulding, extrusion, blow moulding and various foil-making methods.

Battelle is now looking for industrial partners to take the development process further. It expects that it will be one or two years before the production technology is ready for industrial application. The total costs of further development are estimated at DM 1 to 2 million. Details from: Renate Siebrasse, operations manager, Battelle Institute Limited, 15 Hanover Square, London W1R 9AJ or on 01-493 0184. (Source: Biotechnology Bulletin, Vol. 8, No. 2, March 1989)

New bioreactor developed

Researchers at Kyoto Institute of Technology have discovered bacterial capture properties in a cross-linked insoluble pyridinium-type resin. The poly (n-benzyl-4-vinyl-pyridinium halide) material can capture 10 billion live bacterial cells per gram of resin and has been used to develop a bioreactor that immobilizes whole microbial cells on the resin surface; a biochemical oxygen demand (BOD) electrochemical sensor that produces results in minutes; and may be applicable to water purification. The corresponding linear pyridinium-type polymer, which is soluble, has antibacterial activity equal to conventional disinfectants and acts by promoting coagulation and subsequent settling of microbial cells. (Extracted from New Technology Japan, March 1989)

Immunoassay used to diagnose environmental hazards

Consumer concern about pesticide residues in foods is helping to create a market for rapid, easy to perform diagnostic tests. One of the companies moving into this fast-paced market is EnSys Inc. EnSys is a privately-held US company engaged in the development of rapid, on-site test kits to detect environmental contaminants.

As restrictions on insecticide and herbicide usage tighten, manufacturers and governmental agencies will need the sort of tests EnSys is developing to monitor levels of agricultural chemicals in the soil, on produce before it is harvested and in drinking water. A recent US Office of Technology Assessment report, Pesticide Residues in Food, called for new testing technology for pesticides and pesticide metabolites.

Badges that change colour when exposed to toxic chemicals are another EnSys target. The badges are designed to be worn by workers in industries where certain toxic chemicals are used. EnSys has a co-operative development and marketing agreement with Assay Technology Inc., a privately held company based in Palo Alto, California. Assay Technology has shipped over one million personal monitoring badges to customers in nearly 2,000 hospitals, industrial facilities and offices worldwide. The main target are chlorinated hydrocarbons, used in manufacturing plastic, foam, rubber, paint and other coatings; in cleaning and degreasing metals; and in printing. Details from: EnSys Inc., 300 Park Offices Drive, Suite 115, P.O. Box 14063, Research Triangle Park, NC27709, USA or on +1 (919) 549 8572. (Source: Biotechnology Bulletin, Vol. 7, No. 11, December 1988)

Biopesticides for lawns

Ecogen Inc., Langhorne, Pa., and ChemLawn Services Corporation have signed a co-development and license agreement, the companies announced today. The companies will collaborate on the development of biological insecticides to control lawn and ornamental plant insect pests.

Under the agreement, Ecogen will identify and produce strains of Bacillus thuringiensis (Bt) - a bacterium with insecticidal activity - which are active against common lawn and ornamental plant insect pests. ChemLawn will carry out field tests with the Bt strains supplied by Ecogen.

The products resulting from the collaboration will be formulated and marketed by ChemLawn. According to the agreement, the Bt used in the products will be manufactured by Ecogen. (Extracted from Chemical Marketing Reporter, 27 March 1989)

Knot plant "devours" heavy metals

A major research is in progress in the grounds of Bremen port using selected knot plants to check their suitability for removing heavy metals by "devouring" them. A university working group has discovered that a specially cultivated knot plant can take up large quantities of cadmium and lead by means of its roots. It may therefore clean up soils that have been treated with sediment from clarifiers as fertilizer so that these soils can be used again for producing foodstuffs. The plants needed for this purpose were hitherto cloned. But they are now being produced by a process of meristem culture developed by Elke Haase. This involves growing complete plants with identical genetic material and therefore identical properties, from small parts of plant tissue.

The researchers are also investigating if the plants, thus enriched with heavy metals after cleaning up the ground, must be deposited as special waste, or whether the metals eventually can be won back from the plant ash. Further details may be obtained from: Professor Roland Megnet, Universität Oldenburg, Ammerländer Heerstrasse 114-118, D-2900 Oldenburg, Federal Republic of Germany. (Source: New Materials World, March 1989)

Gene technology could spot pollution damage at an early stage

Modern gene technology could help ecologists to diagnose a "sick" environment before the situation is almost irreversible, according to Dr. Göran Bengtsson in the Department of Ecology at the Lund Institute of Science and Technology, Sweden. He has, together with Dr. Lennart Torstensson at the University of Agricultural Sciences, Uppsala, determined the type of research required to improve early detection of environmental problems like acidification, heavy metals, dioxins and organic solvents.

The current theory is that organisms in the soil adapt to environmental changes and studies of their germ plasm with DNA technology could therefore indicate a process of change in the environment. As project one under the National Environment Protection Board scheme, a research group has now been set up at the Lund Institute of Science and Technology to look into this hypothesis.

The overall aim is to develop new sensitive methods to spot early stages of change in the environment that at present go undetected. The problem with soil testing is that changes take place very slowly over decades and centuries. But once the tolerance level is reached, the deterioration rate escalates rapidly to reach a "beyond repair" stage within a short period. (Source: SIP, March 1989)

Extraction industry applications

Oklahoma to test bugs for oil recovery

A petroleum research team from the University of Oklahoma has received funds from the US Department of Energy to field test techniques for using microbes to coax trapped oil from existing reservoirs. The goal of the experiment is to tap oil that is too thick or otherwise unsuitable to pump out by conventional techniques. The microbes to be tested by the Oklahoma researchers produce gas that builds up pressure and forces oil out of the reservoir; produce surfactants to help dislodge oil droplets; and block areas of the reservoir where the oil already has been removed. The researchers chose these strains of microbes after a yearlong series of experiments to find organisms that could withstand the harsh underground conditions. (Reprinted with permission from Chemical and Engineering News, 9 January 1989, p. 27. Copyright 1989 by the American Chemical Society)

Research into de-sulphurization of coal

Idaho National Engineering Laboratory is studying micro-organisms capable of chelating metal ions to enable coal liquefaction and to reduce the sulphur and ash content of coal. By chelating metal-ions, which are integral to coal's solid structure, the microbes allow coal to become soluble in alkaline solutions up to 1,000 per cent, which enhances de-sulphuring steps. The microbes used are bacillus, trametes and candida. Researchers would like to extend the work to encompass microbes capable of de-polymerizing coal. (Extracted from Research and Development, March 1989)

E. PATENTS

Court rejects genetic engineering "invention"

On 10 August 1988 the US Court of Appeals for the Federal Circuit in Washington DC (CAFC) issued its first decision on the patentability of a recombinant DNA invention. In re O'Farrell the CAFC rejected the patent because the key element of non-obviousness in US patent law was not satisfied. O'Farrell's invention related to the use of bacteria to express a foreign protein of interest as a fusion protein, in particular, a fusion with beta-galactosidase. The CAFC argued that employing the prior art available in 1976 there was a

reasonable chance of success in producing a heterologous protein of choice in bacteria by passthrough expression. Therefore O'Farrell's invention was obvious.

Fewer than one in 20 appeals from the CAFC are taken up by the US Supreme Court. Thus this case may have an immense impact on US patent law and, in particular, biotechnology patents. (Source: Australian Journal of Biotechnology, Vol 2, No. 2, September 1988)

Europe tries to untangle patenting laws

Variety may be the spice of life. But in Europe, the biological definition of variety is standing firmly in the way of those seeking to patent new types of living plants and animals.

The current situation on biotechnology patents is, as one industry scientist describes it, "highly confused". There is uncertainty over precisely what can be patented under European law, and this is causing problems both for researchers and the industry - especially in sorting out intellectual property rights in collaborative or sponsored research.

In an attempt to reduce the confusion, the European Commission - the executive body responsible for carrying out the activities agreed to jointly by the 12 member States of the European Economic Community (EEC) - has recently published proposals for "harmonizing" national patent laws by establishing a legal framework under which genetically manipulated plants and animals could be patented.

The Commission argues that all European national patent laws should be based on the premise that "a subject matter of an invention shall not be considered unpatentable for the reason only that it is composed of living matter". In other words, biotechnology inventions should receive the same treatment as any other invention.

The European Patent Convention (EPC) of 1973 in fact specifically adopts this approach for micro-organisms, since it states that "microbiological processes or the products thereof" are not excluded from patent protection. Higher life forms are another matter, however, for the convention also contains a clause stating that patents cannot be granted on plant and animal varieties.

The main thrust of the Commission's proposal is that all EEC member States should interpret the clause in a way that would to a large extent define away the problem. The goal of this strategy, which was initially suggested in a report by the Organization for Economic Co-operation and Development (OECD) is to avoid the daunting prospect of renegotiating the convention.

In particular, the Commission is proposing that all EEC countries adopt in their national legislation a narrow definition of the concept of "variety". The OECD had suggested that, rather than starting from a biological definition based on stable genetic differences (however small), the concept be confined to those plants or animals a country wants to protect through a system of breeders' rights. In essence, a new plant or animal would be considered a new variety only if it is explicitly described as such.

The Commission's proposals have not yet been approved by the Council of Ministers representing member States, or debated by the European Parliament. But they have been attacked by environmentalists and animal rights groups.

Europe's biotechnology industry is cautious about the new proposals. While welcoming their general aims, some industry spokesmen have expressed concern that the proposals do not go far enough in allowing patents on new plants and animals. They also argue that too many concessions have been made to traditional plant breeders.

Industry is also concerned about the lack of precision in the Commission's proposals as they currently stand. Some of industry's concerns are specific. They include a clause, added at a late stage in the drafting process, which specifies that plants and plant material cannot be patented if they have been produced by the non-patentable use of a previously known biotechnological process.

The biotechnology industry's criticisms have, at least in public, been relatively muted, reflecting a feeling that the directive points in the general direction that industry favours. Gaining public acceptance will be more of a problem. Already Denmark, for example, which is a member of the EEC but has not signed the Patent Convention, has a law on its books prohibiting the patenting of plants and animals. This law would probably have to be changed if the directive is approved by the EEC's Council of Ministers; but already this possibility has sparked a sharp public debate in Denmark.

There is a growing feeling that a clear decision on the patenting of novel life forms will not be obtained either through a process of political consensus-building, or by seeking a ruling on the scope of existing legislation. What will be required is a clear signal from Europe's political leaders about the importance they attach to patent rights on living organisms for the future health of their biotechnology industries. (Extracted with permission from Science, Vol. 243, 24 February 1989, p. 1003, D. Dickson. Copyright 1989 by the AAAS)

EPO rejects patent application for transgenic mouse

The European Patent Office (EPO) in Munich has provisionally rejected an application from Harvard University for a European patent on a mouse that has been genetically altered through the insertion of an artificial cancer gene.

The decision is likely to lead to a major legal controversy, since it is the first to have been made in Europe on an application for patent protection for a transgenic animal. As a result, the eventual outcome of what is being seen as a key test case will be closely watched by molecular biologists and biotechnology companies on both sides of the Atlantic.

The Harvard mouse was developed by Philip Leder of Harvard Medical School and his co-worker Timothy Stewart, now with Genentech in San Francisco. By introducing an activated myc oncogene into an early mouse embryo, they created an animal that is highly susceptible to cancer, and is able to play an important role in research into, for example, the detection of carcinogens or the evaluation of potential anti-cancer drugs.

Harvard was awarded a US patent on the same mouse last April, and the rights to the patent are now owned by Dupont, which paid for the research. The university has already responded to the arguments put forward by the EPO for rejecting the European patent application. If the rejection stands, Harvard would essentially be prevented from obtaining patent protection in any country in Europe.

The EPO's detailed response to Harvard's arguments - which will have to be considered by a panel of three EPO lawyers - and the eventual outcome of any appeals process, will carry the same significance in Europe as the 1980 Chakrabarty decision, which allowed the patenting of micro-organisms, did in the United States. As in the US case, the appeals process is being seen by both sides as a way of clarifying current uncertainties in European law over the extent to which plants and animals can be patented.

But in contrast to the US patent decision on the myc-mouse, which was made with relatively little public debate - although it subsequently led to several congressional calls for a moratorium on the further patenting of animals - the EPO has apparently decided that it is unwilling to take this step without substantial further discussion of the issue.

The letter of rejection to Harvard from the EPO examiner states that the decision was based on the fact that the European Patent Convention of 1973, under which a European patent is automatically valid in each of the 11 states that have signed the convention, prohibits the patenting of "transgenic animals per se". The EPO has referred Harvard in particular to a clause in the convention that forbids the patenting of plant and animal varieties (see accompanying story). It has also suggested that the myc-mouse does not meet the patentability criterion of non-obviousness.

European groups that are opposed in principle to the extensive patenting of living organisms have reacted cautiously to the EPO's decision, pointing out that it is merely the first step in what promises to be an extensive legal tussle.
(Extracted with permission from Science, Vol. 243, 24 February 1989, p. 1003, D. Dickson. Copyright 1989 by the AAAS)

IBA files "Friend of the Court" brief in US tissue ownership case

The US Industrial Biotechnology Association (IBA) has filed an Amicus Curiae ("Friend of the Court") brief with the California Supreme Court in the case of Moore v. Regents of University of California. The IBA supports a reversal of an appellate court decision that granted plaintiff John Moore the right to sue for profits resulting from commercial use of cells derived from his spleen. The appellate court had favoured Moore by a vote of two to one, reversing an earlier trial court decision that denied Moore the right to sue.

The IBA believes that bodily tissue should not be considered "property" and that the appellate court's decision has no legal basis. It asserts that it would be detrimental to medical research and to the biotechnology industry. The decision, it argues, would result in an enormous financial and time cost to the research community.

"If this ruling is permitted to stand", said IBA President Richard D. Godown, "it will have a wide-ranging, chilling effect on biotechnology research and development. The most likely result would be a considerable slow-down in actual research performed". He added that even routine laboratory procedures would be plagued by delays and legal negotiations.

Patient Moore brought a complaint against his doctor (David W. Golde), the research hospital where he was being treated (UCLA Medical Center), and other parties, alleging he had a right of ownership to tissues that were removed as part of his medical treatment - including a royalty on the patented Mo cell line and any products developed from it. After plaintiffs were given leave to amend the complaint three times, defendants demurred, and the trial court dismissed Moore's claim. The reversal by the California Court of Appeals is itself now being appealed - to the California Supreme Court and possibly the US Supreme Court after that. It may be years before the courts actually find facts. The economic value, if any, of the Mo cell line has not been established and may never be with any certainty. No commercial product may result from the research.

This case has heightened public perception of the tissue ownership rights question to the point where doctors must now face the prospect of negotiating with patients on the scope of rights and uses for tissue - even though no one knows if the cells are even interesting at the time consent is given. The publicity from this case has effectively thrust upon the doctor the burden of obtaining consent and ensuring that it is an informed consent, well before a court has even established whether a patient has a property right to removed tissues.

Companies wanting to use such cell lines developed by third parties to manufacture new products are now similarly worried about obtaining warranties of good title. They will be bogged down in determining whose tissues were used - and in what way, - to assess who and what has contributed to the value of an ultimate product. Again, this is well before any ruling has been made that tissue taken from a patient has an economic value.

Further clouding the question is the fact that, even if this case does one day go to trial, it is unlikely that it will set sweeping precedent because of the particular circumstances.
(Extracted from Bio/Technology, Vol. 6, October 1988 and Biotechnology Bulletin, Vol. 8, No. 1, February 1989)

Biogen interferon patent reinstated by the EPO

The European Patent Office has decided to reinstate Biogen Inc.'s patent for genetically engineered alpha interferons. The decision was handed down by the technical board of appeals, the highest legal authority of the European Patent Office.

This decision reverses the previous revocation of the Biogen patent by the European Patent Office opposition division. The Board held that Biogen's alpha-2 interferon claims were patentable in all respects.

It remanded Biogen's broad, generic claims for processes and intermediates for producing recombinant alpha interferons to the opposition division, solely for decision on one issue, "inventive step" - an issue not addressed in the June 1987 decision of the opposition division. In all other respects, the board found these claims to be patentable.

The Biogen patent, filed in 1980, is based on the pioneering work of Professor Charles Weissmann of the University of Zurich. Schering-Plough Corporation markets recombinant alpha-2 interferon under the brandname "Intron A" through an exclusive world-wide licensing agreement with Biogen. (Source: Chemical Marketing Reporter, 27 February 1989)

Biotechnology firms agree patent suit ceasefire

US biotechnology majors, Genetics Institute and Genentech, have agreed not to dispute patent positions on genetically engineered Factor VIII, a blood clotting agent for treating haemophilia. A cross licensing deal struck up between the two companies could set a trend in the biotechnology industry which is plagued by costly and time consuming patent disputes.

As well as agreeing not to sue each other over potential patent breaches, the firms believe it will be more difficult for other Factor VIII producers to launch suits against them.

The agreement covers Genetics Institute and its Factor VIII licensee, Baxter Healthcare, and Genentech and its licensee Cutter Biological, a unit of Bayer USA's subsidiary Miles. The accord also covers gene cloning techniques, but other patentable technologies arising during development are excluded, as are know-how exchangos and marketing deals. (Extracted from European Chemical News, 3 April 1989)

Vaccine battle waged by Upjohn

Upjohn Corporation has obtained a patent on a virus used as a vaccine for pseudorabies - a serious disease in swine - and has filed an infringement lawsuit against Syntro Corporation, a San Diego, California, manufacturer of similar product.

The virus, while similar to natural pseudorabies, uses a genetic coding material that does not produce gX glycoprotein found in natural antibodies. It is used to create Upjohn's "Tolvid" vaccine.

Elimination of the glycoprotein gX, allows the status of a vaccinated hog to be determined by means of a blood test. It was previously impossible to separate vaccinated swine from naturally infected ones. (Source: Chemical Marketing Reporter, 13 March 1989)

F. BIO-INFORMATICS

The emerging market DNA

According to a just-released Business Communications Co. study, Expanding Horizons for Gene Probes, the market has great potential - although it is still in its infancy. Gene probe sales at the manufacturer's level are estimated to have reached over $13.3 million in 1988, with BCC forecasting a 67 per cent average annual growth rate in constant dollars through 1993. This rate of growth would yield sales of $172 million in 1993.

Gene probes offer the ability to identify specific genes through hybridization technology. "Among its major applications", says BCC, "are infectious disease diagnosis, forensic testing/paternity testing and identification of genetically transmitted diseases. Future applications include tests to determine the risk of developing diseases such as cardiovascular disease or manic depression and tests to diagnose cancer".

Among the conclusions of the study are the following:

- Microbiology testing is currently the major application for probe testing, generating an estimated $7.5 million in sales in 1988, a 56.4 per cent share of the gene probe testing market. This segment is expected to grow to $130 million in 1993, a 76 per cent share of the total market;

- Limitations attributed to current probe methods include the fact that many methods require radio-isotopic tags and that the tests are often costly and require specially handled specimens;

- Recent developments in the ability to amplify testing samples will facilitate the development of more probe tests;

- Patent protection is an important factor in this market, with many companies filing for extensive patent protection worldwide;

- Since many of the start-up companies within this industry are small and the development of probe technology is capital intensive, many companies have entered into joint ventures to aid in marketing and distribution as well as to receive fresh capital. Details of the report, priced at $1,950.00, from: Business Communications Co., 25 Van Zant Street, Norwalk, CT 06855, USA or on +1 (203) 853-4266.

(Source: Biotechnology Bulletin, Vol. 8, No. 2, March 1989)

Biopesticides: markets, technology, registration and companies

A new report on biopesticides from CPL Scientific Information Services says that protecting crops by non-chemical means is likely to become far more widely practiced in the near future. Although alternative means of pest control, including biopesticides, have thus far failed to achieve earlier predictions that they would take a significant share of the world agrochemicals market, they are now poised to pose a real challenge to agricultural chemicals.

In the current climate of anxiety about contaminated food and water pollution, consumers are suspicious of chemicals and would like to see their use reduced. In the past biopesticides did not represent a feasible alternative to "conventional" chemicals as they were frequently unreliable and expensive. Farmers attempting to grow "organic", non-chemical food found it difficult to obtain the same quantity and apparent quality of produce grown with chemicals.

Now, new technology is being used to improve biopesticides so they represent a real alternative to chemical crop protection. The past two years has seen vigorous research activity using a number of new methods. These include genetic engineering to make plants resistant to insects and to make micro-organisms like bacteria, fungi and viruses take on different properties to enhance their potency as biopesticides.

Around 50 companies are taking an active interest in Biopesticides including established producers such as Abbott Laboratories and Sandoz, major oil and chemical companies as Shell, Monsanto and ICI as well as new, dedicated biotechnology venture companies as Ecogen and Mycogen. New products coming to the market include biopesticides for control of potato beetle, specialty products for

insect control in vegetables and many others. Although the total market is no more than $20-$30 million at present and R&D expenditures exceed product sales, new technology and the new products will make it grow.

A newly published report from CPL Scientific Information Services reviews the current status and future prospects of biopesticides in considerable detail. BIOPESTICIDES: Markets, Technology, Registration & Companies, 100,000 words in two volumes is available for 1,500 pounds or $2,500 from: CPL Scientific Limited, Science House, Winchcombe Road, Newbury RG14 5QX, UK. (Source: Company News Release)

East European biotechnology

A report from the Financial Times Business Information, Biotechnology in Eastern Europe, provides information on the development of biotechnology in the Soviet Union and other Eastern bloc countries. Among the subjects covered are opportunities for western suppliers, traders and investors. Details of the report, priced at 185 pounds, from: Marketing Department, Financial Times Business Information, 7th Floor, 50-64 Broadway, London SW1H 0DB. (Source: Biotechnology Bulletin, Vol. 7, No. 11, December 1988)

AAAS Committee on Scientific Freedom and Responsibility report

Based on papers presented at two symposia during the 1987 American Association for the Advancement of Science (AAAS) annual meeting, plus material added subsequently, a new 112-page AAAS report focuses on Biotechnology: Professional Issues and Social Concerns.

"Given the virtual explosion of interest in biotechnology", says Committee chairman Sheldon Krimsky, "the Committee believes that this volume, with its focus on the consequences of increased industry-university collaboration and on the safety of biotechnology research, advances the public and professional dialogue - and offers new insights into how biotechnology research is proceeding and with what impact."

The experience reflected is almost entirely American, but anyone interested in the ethics of commercial biotechnology should track down a copy. Details of the publication, which is available free, from: American Association for the Advancement of Science, 1333 H Street, NW, Washington, DC 20005, USA or on +1 (202) 326-6792. (Source: Biotechnology Bulletin, Vol. 7, No. 11, December 1988)

Drug delivery is key to success for genetically engineered protein products

Over 100 companies and 70 other organizations are involved with the development of protein delivery technologies - including the use of liposomes, monoclonal antibodies, nasal delivery, encapsulation, polymers, transdermal systems and collagen.

According to Drug Delivery of Proteins: A Worldwide Market Study on Liposomes, Monoclonal Antibodies, Nasal and Other Methods for Biotechnology Products, the market for such delivery systems will be worth over $1.7 billion worldwide by 1998. Indeed, the market for the delivery of proteins will account for a quarter to a third of the market for the delivery of all drugs.

In some cases, successful delivery techniques will directly expand the market for the proteins. For example, easier use will increase the number of people who use insulin. Furthermore, less insulin is absorbed nasally, increasing the amount that is needed per dose.

Where companies are competing with similar products, such as interferons and interleukins, delivery methods will differentiate the companies and could provide the key to gaining a competitive advantage. Details of the report, priced at $1,495.00, from: Technology Management Group, 25 Science Park, New Haven, CT 06511, USA or on +1 (203) 786-5445. (Source: Biotechnology Bulletin, Vol. 7, No. 11, December 1988)

Layman's guide to deliberate release

A "lay summary" of the first International Conference on the Release of Genetically Engineered Micro-organisms (REGEM I), has been produced by Dr. Bernard Dixon. REGEM I took place in Cardiff in April 1988. It covered the enormous promise of recombinant DNA-based organisms for medicine, agriculture and pollution control, as well as the attendant environmental risks.

The 50-page booklet, Engineered Organisms in the Environment, will provide a useful overview of the technology and issues even for readers who feel they know a fair amount about biotechnology. Copies of the booklet, priced at 5.00 pounds including postage, are available from: Professor Alan M. Paton, School of Agriculture, University of Aberdeen, 581 King Street, Aberdeen AB9 1UD. (Source: Biotechnology Bulletin, Vol. 7, No. 12, January 1989)

New journal on methods in cell and molecular biology

Increasingly, advances in cell and molecular biology are driven by developments in technology. New methods are constantly developed, and existing procedures refined in the search for the ultimate in sensitivity and resolution. In such a rapidly moving field, it is vital that scientists are aware of the latest developments in methodology.

TECHNIQUE will publish papers that are concerned with the methods and technical aspects of experiments within the broad field of cell and molecular biology. The major aim of the journal is to provide a vehicle for the rapid dissemination of methods in greater detail than normally accepted in non-specialist publications.

Papers will be accepted based on the relevance of the method to the development of the scientific area that it refers to. The journal will be intended for laboratory bench use, therefore detailed step-by-step protocols will be considered desirable for acceptance for publication.

TECHNIQUE will feature three categories of papers:

1. Reviews of particular technical areas, which will mainly be commissioned and contain sets of related protocols.

2. Full papers that will document new individual methods or major modifications to existing procedures.

3. Short communications that will deal with more minor, but nevertheless significant, modifications of existing protocols.

The whole range of techniques applicable to cell and molecular biology will be covered including molecular cloning, expression of cloned sequences, characterization of nucleic acids and proteins, mutagenesis and protein engineering, and protein-nucleic acid interactions. Any other method representing an advance on current technology for cell and molecular biology will be welcome. Papers highlighting new theoretical insights and those describing new computer programs for the handling of data will also be acceptable.

A Letters-to-the-Editor section will serve as a forum for the discussion of the merits of published protocols. Another section will deal with product reviews which will be genuine tests of new commercial kits and reagents.

TECHNIQUE will be published on a bi-monthly basis, with the first issue in February 1989.

To submit manuscripts or for more information and authors' instructions on TECHNIQUE please write to one of the following addresses:

Peter Little, Editor, TECHNIQUE, Department of Biochemistry, Imperial College of Science and Technology, Prince Consort Road, London SW7 2AZ, England, Telephone: (01) 823-7518, Fax: (01) 823-7525

Editorial Office, TECHNIQUE, W.B. Saunders Company, The Curtis Center, Independence Square West, Philadelphia, PA 19106, USA

British Library's Biotechnology Information Seminars

The pace and breadth of bio-innovation generates a wealth of information in science, industry and business. A series of one-day seminars organized by the British Library's Biotechnology Information Service (BIS) will provide an all-round introduction to the subject, focusing on books, journals, online services and information centres used by BIS. The seminars, entitled "Biotechnology Information", will be held on 21 March, 20 July and 14 November at the Science Reference and Information Service, 25 Southampton Buildings, London WC2A 1AW. Details from: Sean Heatley at this address. (Source: Biotechnology Bulletin, Vol. 8, No. 1, February 1989)

New AIDS resource

WorldAIDS is a news magazine focusing on the global issues surrounding the spread of AIDS. In a field where there is a flood of literature giving detailed accounts of the latest developments in vaccines, drugs and epidemiological data, WorldAIDS stands back and provides a global perspective on the spread of the human immunodeficiency virus (HIV).

In the first issue, WorldAIDS provides a statistical portrait of a region, giving a country-by-country breakdown of the latest seropositivity figures, number of cases reported, travel restrictions and national action.

WorldAIDS is published every two months by the Panos Institute in association with the Bureau of Hygiene and Tropical Diseases (London). It is available from Panos, 8 Alfred Place, London WC1E 7EB, UK, at 12.00 pounds or from Panos, 1409 King Street, Alexandria, VA 22314, USA, at $25.00 per annum; it is free to organizations and individual in the third world. (Source: Development Forum No. 9, March-April 1989)

Journal from Scottish Development Agency

The Scottish Development Agency (SDA) publishes a free newsletter on the Scottish healthcare and biotechnology industry. The latest issue of Nostrum profiles several companies and focuses on how the National Collections of Industrial and Marine Bacteria Limited in Aberdeen have now become the first seed depository in Europe to function as an International Depository Authority (IDA). The NCIMB already serves as one of the 19 IDAs worldwide receiving microbiological material for patent deposit. Details from: Dr. Carol Bainbridge, Scottish Development Agency, 120 Bothwell Street, Glasgow G2 7JP or on 041 221 3217. (Source: Biotechnology Bulletin, Vol. 8, No. 2, March 1989)

New information centre

The National Center for Biotechnology Information has been established at the US National Library of Medicine.

According to director, Donald A. B. Lindberg, "It not only acknowledges the importance of computer and information science as applied to molecular biology but it reaffirms the Library as the focus for developing cutting-edge information systems in the health sciences".

The Centre has been given responsibility for carrying out four basic functions: to create automated systems for knowledge about molecular biology, biochemistry, and genetics; to perform research into advanced methods on how to handle information about the vast number of biologically important molecules and compounds; to enable those engaged in biotechnology research and medical care to use the systems and methods developed; and to co-ordinate efforts to gather biotechnology information worldwide.

Among current biotechnology information work going on at the NLM are projects connected with GenInfo, a prototype multitype database access system which allows researchers to express a question in their own words and have it answered by information retrieved from a dozen different databases; a project to develop a computer program to support analysis by investigators who use the techniques of "shotgun sequencing" of DNA; the developments of linkages among disparate biotechnology information sources; the development of a unique directory of biotechnology information resources, and the installation of high-speed computer communications lines to facilitate research connections between NLM and other advanced computing centres. Contact: NLM, 8600 Rockville Pike, Bethesda, MD 20894 (Source: Information Hotline, February 1989)

New US computer database describes Japanese companies working in biotechnology

Detailed information on about 250 Japanese companies working in biotechnology is available through a new computer database created by the US North Carolina Biotechnology Center. The Japan Database focuses on Japanese companies that use the new technologies of genetic engineering, monoclonal antibody production, new fermentation processes or large-scale cell culture. It includes information on the companies' research and product areas, locations, financial structures, employees, top management, major investors and US addresses.

"We now have the ability to provide detailed reports to answer specific questions about Japanese

biotechnology", says Dr. Mark D. Dibner, director of the Center's Biotechnology Information Division. "For example, if someone were interested in Japanese firms working on diagnostics, waste treatment, energy or any one of 31 topics, we would be able to provide specific reports on these potential collaborators, customers or competitors." Details from: North Carolina Biotechnology Center, Box 13547, Research Triangle Park, NC 27709, USA or on +1 (919) 541-9366) (Source: Biotechnology Bulletin, Vol. 8, No. 1, February 1989)

Genetic software available

New software for computer-aided genetic engineering is available for licensing. The software, named "Computer-Aided Genetic Engineering/Genetic Engineering Machine" (CAGE-GEM™), was developed by Battelle.

CAGE/GEM has applications in food and agriculture, petroleum, pharmaceuticals, chemical engineering, and nearly any genetic engineering product or process.

CAGE/GEM gives genetic engineers a level of expertise that previously was unavailable. No other computer software system offers this combination.

The system uses and integrates genetics, and provides information with DNA protein sequences to generate colour graphic displays of complex structures. Sometimes these structures can involve thousands of bases or amino acids.

With expanded capabilities, CAGE/GEM now provides comprehensive systems analysis, complete genetic cloning simulation, data base searching and information management, and accessibility from other computer terminals.

It also offers compatibility with advanced analytical packages and routines such as sequence analysis software packages of the National Biomedical Research Foundation and University of Wisconsin Genetics Computer Group. (Source: Battelle Today/3)

Online Biotechnology Directory introduced

From February 1989, BioCommerce Data's online services were substantially expanded and improved. Abstracts in BioCommerce (ABC), a twice monthly current awareness bulletin on business aspects of biotechnology, has been available since December 1984 on Data-Star (file CELL) and since November 1986 through Dialog (file 286 - BioCommerce Abstracts). The Dialog file has now been expanded to include directory style entries on nearly 1,000 organizations worldwide, and renamed BioCommerce Abstracts and Directory.

Detailed profiles are now available on many of the organizations mentioned in the abstracts. These directory records include the full name including acronyms, alternate name (foreign language version), a unique number also used in abstract indexing, a four line address, a description of the history and activities of the organization, controlled terms describing its areas of business and the names and job titles of senior executives.

Initially much of the data will cover British organizations, including all those listed in the UK Biotechnology Handbook '88, BioCommerce Data's new printed directory produced in collaboration with the Association for the Advancement of British Biotechnology. About 1,000 entries on European, Canadian and US organizations will be online initially with many more being added over the next year. Information included is checked to ensure its accuracy and updates every two weeks will ensure that it remains current.

This is the first time a biotechnology company directory has been available online, and its use has many advantages over printed books. Searching the data is far easier and can be done by country (or even city!) as well as area of business or type of organization. This enables you to retrieve precisely what is needed, at a lower cost than buying a complete directory, while the frequent updating ensures that the information received is really current.

At the time of writing, only the Dialog version of ABC (file 286) includes directory entries but the Data-Star version should be similarly expanded in the near future. To become a Dialog user, contact either BioCommerce Data Limited, Old Crown Building, Windsor Road, Slough SL1 2DY, UK, Tel: (0753) 74201, Telex: 849793, Fax: (0753) 31145 or Dialog Information Services, 3460 Hillview Avenue, Palo Alto, CA 94304, USA, Tel: (415) 858-3810)

Computer models to monitor food spoilage

Computer models to predict food spoilage have been developed by R. Buchanan of USDA's Microbial Food Safety Research Unit (Philadelphia). The model predicts the growth of bacteria in foods. Varying input to the model can show what changes in food composition will do to shelf life. Actual tests of bacterial growth are not standardized, and food companies do not get reproducible results. Buchanan's model is for cured meats. Users provide inputs to the Lotus-developed program, including pathogen and food composition. If the model shows no growth, it indicates that the pathogen will not reproduce under the conditions specified. Data for the model came from Buchanan's own experiments and from other food researchers. The model can be run on any IBM-compatible PC. (Extracted from New Scientist, 28 January 1989)

Wound healing subscription service from TMG

Technology Management Group is now offering a subscription information service on growth factors for wound healing. The service is being issued four times a year. Each issue will feature an in-depth analysis of a timely topic, presented in the form of a mini-report. Topics planned for coverage include: developments in drug delivery, immunomodulators for wound healing and hard tissue growth factors. The first four issues are being offered for $2,500.00. Details from: Technology Management Group, 25 Science Park, New Haven, CT 06511, USA on +1 (203) 786-5445. (Source: Biology Bulletin, Vol. 8, No. 2, March 1989

Univer s SETCON to monitor fermentation

The SE Centre for Biochemical Engineering at Birmingham University is to use the SETCON process management system from Scicon Industry as a biotechnology research tool. The system, running on a DEC Micro VAX, will control and monitor fermentation vessels.

The data recorded will be used to develop techniques for identifying mathematical models for a range of fermentations. The models will be used in real-time computer simulations, linked to SETCON, to allow verification against an actual fermentation. (Source: Biotechnology Bulletin, No. 8, Vol 2, March 1989)

Microbial Strain Data Network (MSDN)

MSDN is building an integrated information service for biotechnologists and microbiologists, operating online worldwide. It provides a full electronic communications system (electronic mail, conferencing, bulletin board), a directory to locate microbial features recorded in centres throughout the world, access to other relevant databases, computer support and training.

Internationally sponsored and funded, the system now has about 300 users. Participation from scientists in Australasia is currently low. The system has much to offer the scientific community, and the MSDN hopes to encourage participation in the network, both for communication purposes and for collaborating in developing the Directory. (Source: Australian Journal of Biotechnology, Vol. 2, No. 2, September 1988)

G. MEETINGS

September 1989

3-30 September Edinburgh, UK	Protein Structural Aspects of Bio-technology. Further information from Edith Field, Training Manager, UnivEd Technologies Ltd., 15 Buccleuch Place, Edinburgh, EH8 9LN, Scotland, UK.
5-7 September Churchill College, Cambridge, UK	Prospects for amino acid biosynthesis inhibitors in crop protection and pharmaceutical chemistry. Further information from the Conference Secretariat, Society of Chemical Industry, 14/15 Belgrave Square, London SW1X 8PS, UK.
6-10 September Cold Spring Harbor, New York, USA	Regulation of Eukaryotic mRNA Transcription. Further information from Meetings Co-ordinator, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, USA.
11-13 September Reading, UK	Separations for Biotechnology. Further information from the Conference Secretariat, Society of Chemical Industry, 14/15 Belgrave Square, London SW1X 8PS, UK.
11-15 September Jesus College, Cambridge, UK	International Conference on Drug-DNA Interactions. Further information from Dr. S. Neidle, CRC Biomolecular Structure Unit, Institute of Cancer Research, Sutton, Surrey SM2 5NG, UK.
11-15 September Uppsala, Sweden	Experimental Models for Auto-immune Diseases. Further information from Rikard Holmdahl, Department of Medical Chemistry, Uppsala Biomedical Centre, Uppsala, Sweden.
14-15 September London, UK	International Meeting on Nitric Oxide from L-Arginine: A Bioregulatory System. Further information from Dr. S. Moncada, Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS, UK.
14-16 September Queen's College, Cambridge, UK	The Cell Membrane and Cell Signals as Targets for Cancer Chemotherapy. Further information from The American Association for Cancer Research, 530 Walnut Street, 10th Floor, Philadelphia, PA 19106, USA.
14-17 September The Jackson Laboratory, Bar Harbor, USA	First Biennial Mammalian Developmental Genetics Workshop. Further information from Linda Fournier, The Jackson Laboratory, Bar Harbor, ME 04609, USA.
18-21 September Heidelberg, FRG	Molecular Communication in Higher Plants. Further information from Dr. J. Tooze, EMBO, P.O. Box 1022.40, D-6900 Heidelberg, FRG.
19-20 September Ottawa, Canada	CANBIOCON '89. Further information from Biotech Canada Inc., 100 Alexis Nihon Boulevard, Suite 875, Montreal H4M 2P4, Canada.
24-29 September King's College, Cambridge, UK	EMBO Workshop on Cellular and Molecular Biology of Muscle Development. Further information from Dr. Frank S. Walsh, Department of Neurochemistry, Institute of Neurology, Queen Square, London WC1N 3BG, UK.
25-28 September Cold Spring Harbor Laboratory, USA	Conference on Hepatitis-B Viruses. Further information from Meetings Co-ordinator, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, USA.
25-26 September Royal College of Physicians, London, UK	Adenosine and ATP - Progress in Research and Therapeutic Potential. Further information from Renata Duke, IBC Technical Services Ltd., Bath House, 56 Holborn Viaduct, London EC1A 2EX, UK.
26 September London, UK	Modelling of Drug and Pesticide Processes: I. Kinetics of transport in mammals, insects and plants. Further information from the Conference Secretariat, Society of Chemical Industry, 14/15 Belgrave Square, London SW1X 8PS, UK.
26-29 September Lunteren, The Netherlands	Plant Genetic Engineering, Applications for Agriculture, Horticulture and Industry. Further information from Dr. G. A. van de Schootbrugge, TNO Corporate Communication Dept., P.O. Box 297, 2501 BD The Hague, The Netherlands.
28 September Ghent, Belgium	Forum for Applied Biotechnology. Further information from the Scientific Centre FAB, p/a L. Demey, Coupure 653, B-9000 Ghent, Belgium.
28-29 September St. John's College, Cambridge, UK	Biosensors '89. Further information from Renata Duke, IBC Technical Services Ltd., Bath House, 56 Holborn Viaduct, London EC1A 2EX, UK.

October 1989

2-4 October Capri, Italy	Workshop on Molecular Biology of Development. Further information from Dr. Edoardo Boncinelli, IIGB, Via Marconi 10, 80125, Naples, Italy.
2-4 October Heidelberg, FRG	EMBO Workshop on Patterns in Protein Sequence and Structure. Further information from P. Argos, EMBL, Meyerhofstrasse 1, 6900 Heidelberg, FRG.
4-6 October Annecy, France	Progress in Animal Retroviruses. Further information from Dr. Daniel Gaudry, Secretary of the 21st Congress of the IABS, 254 rue M. Merieux, 69007 Lyon, France.
5-6 October London Press Centre, UK	Sixth European Seminar and Exhibition on Computer-Aided Molecular Design. Further information from Renata Duke, IBC Technical Services Ltd., Bath House, 56 Holborn Viaduct, London EC1A 2EX, UK.
11-12 October Johns Hopkins Medical Institutions, Baltimore, USA	Neuroscience: Integrative Functions. Further information from the Programme Co-ordinator, Office of Continuing Education, The Johns Hopkins Medical Institutions, Turner Building, 720 Rutland Avenue, Baltimore, Maryland 21205-2195, USA.
11-14 October Tarpon Springs, Florida, USA	Third Annual North American Cystic Fibrosis Conference. Further information from Cystic Fibrosis Foundation, 6931 Arlington Road, Bethesda, MD 20814, USA.
23-24 October Houston, Texas USA	XXXI. Membrane Proteins: Targeting and Transduction. Further information from Kimberly Nelson, The Robert A. Welch Foundation, 4605 Post Oak Place, Suite 200, Houston, TX 77027, USA.
24-25 October Royal College of Physicians, London, UK	The Platelet in Health and Disease. Further information from Renata Duke, IBC Technical Services Ltd., Bath House, 56 Holborn Viaduct, London EC1A 2EX, UK.
24-26 October Moscone Center, San Francisco, USA	BIOTECH USA. Further information from the Conference Management Corporation, 200 Connecticut Avenue, Norwalk, CT 06856-4990, USA.

November 1989

9-10 November Boston, USA	Gene Manipulation in Biology and Human Disease. Further information from Diana Berger, Nature Publishing Company, 65 Bleecker Street, New York, NY 10012-2467, USA.
24-26 November Eynsham Hall, Oxford, UK	4th Harden Discussion Meeting on Molecular Genetics of Neuromuscular Disorders: Progress in Research Strategies. Further information from Dr. J. de Belleroche, Department of Biochemistry, Charing Cross and Westminster Medical School, Fulham Palace Road, London W6 8RF, UK.
30 November - 1 December London, UK	International Conference on Drug Delivery and Targeting Systems. Further information from Renata Duke, IBC Technical Services Ltd., Bath House, 56 Holborn Viaduct, London EC1A 2EX, UK.

December 1989

10-14 December Hilton Head, South Carolina, USA	Second International Workshop on Cytokines. Further information from Sherwood M. Reichard, Cytokines, c/o RES Society, Box 3044 MCG, Augusta, GA 30912, USA.

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26-29 March Girton College, Cambridge, UK	Stability of Proteins: Theory and Practice. Further information from Prof. F. Franks, Biopreservation Division, Pafra Ltd., 150 Cambridge Science Park, Cambridge CB4 4GG, UK.
3-5 April Churchill College, Cambridge, UK	Opportunities in Biotransformation. Further information from the Conference Secretariat, Society of Chemical Industry, 14/15 Belgrave Square, London SW1X 8PS, UK.
11-16 April Braunschweig, FRG	Post-Transcriptional Control of Gene Expression. Further information from Dr. J. E. G. McCarthy, Gesellschaft für Biotechnologische Forschung mbH, Mascheroder Weg 1, D-3300 Braunschweig, FRG.
25-29 June Amsterdam, The Netherlands	Amsterdam Biotechnology 90. Further information from RAI International Exhibition and Congress Centre, Europaplein, 1078 GZ Amsterdam, The Netherlands.
11-13 September Reading, UK	Second International Conference on Separations for Biotechnology. Further information from the Conference Secretariat, Society of Chemical Industry, 14/15 Belgrave Square, London SW1 8PS, UK.
28-31 October San Francisco, USA	Anabiotec '90. Further information from Shirley Schlessinger, Anabiotec '90, 400 E. Randolph Drive, Chicago, IL 60601, USA.

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7-11 April Southampton, UK	Neurotox '91. Further information from the Conference Secretariat, Society of Chemical Industry, 14/15 Belgrave Square, London SW1 8PS, UK.

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