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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 1300 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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A. POLICY, NEWS AND OTHER EVENTS

UNIDO News

New vistas for genetic technology in Latin America and the Caribbean

UNIDO to organize workshop in Cuba

A boost for biotechnology in Latin America and the Caribbean will come when UNIDO holds a workshop in Havana to promote genetic engineering in the region (8-12 February). Convened in co-operation with the International Centre for Genetic Engineering and Biotechnology, it is being organized with substantive and financial support from the Cuban Government as well as the Havana-based Cuban Centres for Genetic Engineering and for Biological Research.

The workshop will focus on transfer of know-how in plant biotechnology, human applications of genetic engineering and industrial microbiology, the aim being to further industrial and socio-enconomic development in the region.

Discussion of current and future national programmes in biotechnology is on the agenda as well as how to enhance information systems and technology development through co-operation among policy makers, scientists and industrialists of the region.

In the context of the industrial needs of Latin American and Caribbean countries, the workshop is expected to point the way for biotechnological research while helping establish links between research and industry. It will assess the state-of-the-art and exchange knowledge through presentations of recent scientific advances. The workshop will also focus on production and supply aspects of biologicals in the region as well as on co-operative research.

Upgrading capabilities of researchers in the region constitutes another objective of the workshop.

Some 40 international experts will be participating, including representatives from countries in the region.

Why Chile leads the world in researching bacterial leaching of copper ores

With an output of over a million tons annually, Chile is the world's largest copper producer. As elsewhere, however, production relies largely on large-scale smelting of high-grade oxide sulphide ores which, in the long run, will run out. Copper ores are nearly always a mixture of oxide and sulphide materials, but gradually only the more complex, difficult-to-process sulphide ores will remain. The quality of available ores is already perceptably lower than a few years ago, and as the mines go deeper and cover wider areas, it will continue to fall. What is needed, therefore, is a process that not only works economically on these lower grade materials but whose lower investment and operating costs allow small and medium-scale operations to stay in business. The solution, Chilean scientists and technologists believe, is an extraction process that specifically works on the insoluble sulphide ore - a process in which the star role is played by bacteria.

Insoluble sulphide ores are found in many countries. Experts believe that eventually, because of the inherently favourable economics - potentially around one third the net cost of large-scale and energy-intensive pyrometallurgical smelting of oxide ores - leaching them with the aid of bacteria will be of potential interest for large and small-scale copper producers alike. As a smaller-scale, low-energy process for the more abundant sulphide materials, it will particularly benefit small and medium-scale miners. But mastery of bacterial leaching would not only allow Chile to stay ahead as the leading copper supplier; it would also give its mining industry a head start in applying the technique to the recovery of other metals - among them gold (via bacterial oxidation of refractory gold ores) and uranium.

The appetite of certain bacteria for copper sulphide ores is, of course, not new. It has also been exploited in a modest way by copper producers for at least two centuries. Nevertheless the process is only now being investigated at a scientific level. Empirical improvements over the years have raised efficiency, but today are near the limit of what such an approach can achieve, say leaching experts.

Reaching a fundamental scientific understanding of the process, on the other hand, is complex, time-consuming, and involves integrating the work of specialists of several different disciplines - genetic engineers, microbiologists, chemists, physicists, metallurgists, and process and control engineers. Thanks to a modest investment under the United Nations Development Programme (UNDP) and active support by the United Nations Industrial Development Organization (UNIDO), Chile not only leads, but has much more comprehensive R&D and testing programmes than any other country in the world. It has achieved this position, moreover, using local expertise - some 150 national experts, more than half working full time on the project in the country's leading universities, scientific and technological institutions.

Three-pronged R&D programme

Empirically the main reactions are well known. In the presence of air and circulating iron (ferric) sulphate leaching solution, micro-organisms such as Thiobacillus ferro-oxidans (Th. ferroxidans) oxidize normally insoluble copper sulphide ore (or ore tailings) to forms such as copper sulphate which are soluble in aqueous solution, thus liberating metal ions for later recovery. Under certain conditions, the bacteria can increase reaction speed by more than a million times. The copper in the sulphate solution can be precipitated as metal on ferrous scrap in a cementation plant, effluent from which is oxidized - again with the aid of Th. ferroxidans - to ferric sulphate for recycling to the leaching operation.

Unfortunately, the process cannot be optimized or even put on a reliable commercial basis until more is known, particularly about the genetic engineering aspects and the metallurgical characteristics of the leaching system - the mineralogy, granulometry, porosity of the ore heaps in which leaching takes place, aeration, temperature profiles, etc. Other unknowns range from which micro-organism strains work best under which conditions, to the chemical, physical and kinetic data needed for mathematical modelling and plant design.

The aim of the UNIDO-supported programme is to throw light on all these areas by combining research, development and commercial-scale testing to develop a new bacterial leaching methodology that can be applied to treating Chilean and other copper ores. In a three-pronged multidisciplinary approach, one group concentrates on basic research, another on applied research, and a third on pilot plant and industrial-scale testing.

The programme is built around existing Chilean R&D programmes on basic research and large-scale testing. With inputs from the UN, largely for specialized equipment and personnel training, facilities at Chile's universities, technical institutes and at the copper producers, are combined

in a multidisciplinary R&D effort that will be a pace-setter for not only the developing world but also industrialized countries.

Phase I - getting started

Phase I of the project, completed last September, aimed at setting up the programme, its organization and equipment, and initiating the research in each area. Phase II will continue the work on a broader basis, taking in other ores and concentrates, and developing the process to recover other metals.

In the basic research area, teams at the Departments of Biochemistry and cell Biology at the University of Chile, Santiago, are investigating the genetics, physiology and biochemistry of leaching bacteria. To enable genetic manipulation of Th. ferroxidans, the group has developed a method of identifying different strains, producing a kit that will let field personnel with little training characterize different strains. The group also isolated and purified proteins from the outer membrane of bacteria and conducted fundamental research on rusticyanain, carbon dioxide fixation, cell mobility, adherence of bacteria on mineral surfaces, action of attractants and repellants, toxic shock effects and the stress response of bacteria to acidity and heat.

Applied research, at the University of Chile's Departments of Chemical Engineering and Mining Engineering, and at the Catholic University of Valparaiso's School of Biochemical Engineering, focuses on the fundamentals of chemical and biochemical engineering of bacterial leaching. Although this group started from scratch, it soon discovered that the leaching process actually proceeds by way of simultaneous direct and indirect oxidation processes. It set up a central bank of identified and characterized natural flora and strains of Th. ferroxidans from Chilean sources such as ores, pilot plants and effluents. It assembled specific kinetic data on the effect of solvent extraction reagents and flotation frothers on bacterial activity; it determined the relative advantages of stirred-reactor versus air-agitated leaching; and it developed a very sensitive analytical method for detecting traces of ferrous iron in the presence of ferric iron. It conducted a fundamental study of flow dynamics in colums and on an inclined plate, compared ferric iron leaching under sterile conditions to bacterial leaching, used an autoclave technique for bacterial leaching and phase transformation and modelled bacterial growth, mineral transformation and copper extraction mathematically. This group also developed a bioelectrochemical reactor for preparing very dense cultures of bacterial species at rates 50 to 100 times normal.

Testing bacterial leaching processes in the laboratory, pilot plants and eventually on an industrial scale is the responsibility of the Institute of Technological Research (INTEC-CHILE, and the national research agency) and the Mineral and Metallurgical Research Centre (CIMM). These teams designed, built, operated and monitored a 2,000-ton heap leach test using ores from six sources; the heap was also used to prepare a video and manual for distribution to small and medium-sized copper producers. Measurements from a 20-ton heap under locked-cycle conditions were used to generate data for mathematicl modelling and scale-up. The group standardized methodologies for investigating a variety of copper mineral substrates, compared the bacterial activity of natural flora versus isolated and mixed isolated strains, and collected and characterized native micro-organisms from different mine locations. It determined which natural strains had the highest tolerance towards mercury, molybdenum, arsenic, chlorides and temperature changes. It developed a standard solid medium procedure for isolating and purifying strains, and identified the role of bacteria in solvent extraction and crud formation. The group also made pre-oxidation studies on tailing with gold encapusulated in the pyrite, and undertook bioreactor leaching tests using a wide range of copper flotation concentrates and various flora.

Positive evaluation

In line with standard UN practice, phase I was recently evaluated by a team of independent experts comprising Dr. C. Beinhoff, metallurgy expert with Klöckner-Humboldt-Deutz AG, Federal Republic of Germany, K.R. Coyne, senior executive with Bechtel Corporation, and Dr. P. Valenzuela, Vice-President of Chirom Corp. in the US and one of the world's leading genetic specialists. The mission acquitted the project with high praise.

The major achievement, the mission found, was the development of an interdisciplinary national expertise in the bacteriological aspects of copper leaching "equal to or better than that existing in the international scientific and technical community". The assembly of human and physical resources from the fields of genetic, microbiology, physiology, mathematics, chemical and biochemical engineering, metallurgical and associated research and development technologies, all focused on a common objective, in the short space of 30 months was "a remarkable accomplishment". In addition, by international standards, developing this world-class expertise "was done in a most cost-effective manner", the team added.

The evaluators found that although there had been no breakthrough on the scale of, for example, a genetically altered Th. ferroxidans - admittedly an optimistic expectation inside 30 months - achievements in other areas had been impressive and in some cases patentable. New insights had been gained into the bacteriological leaching mechanisms; laboratory, pilot-scale and full-scale testing had yielded data on the dynamics and kinetics of the process as a basis for further modelling of the system; the manual and video explaining bacterial leaching to small-scale miners was an immediate practical benefit.

Benefits to Chile

Alongside the immediate achievements, the project brought a number of long-term benefits to Chile. It considerably strengthened national scientific and technical capacity in the field of biotechnology, and in related areas such as process engineering and metallurgy. Specifically, it increased the number of Chilean scientists with an ability to solve problems of basic microbiology, applied and extractive metallurgy.

In addition, the whole economy stands to benefit from a process to produce additional quantities of copper from sulphurated ores - especially by a method that eliminates the smelting, i.e. avoids discharge of sulphur dioxide into the atmosphere.

Another long-run benefit is that of maintaining Chile as a world copper supplier. The present production of over a million tons annually provides around half the country's foreign exchange income. As elsewhere, the pyrometallurgy routes will continue to dominate the market for the foreseeable future; but unless a new process is developed to handle lower quality ores, the foreign exchange income is threatened. The problem could become even graver if copper prices, already low, drop even lower, and production costs via smelting continue to increase. With low capital investment and low operating costs, bacterial leaching could provide the lifeline.

Future work

Planning for a second phase lasting 2 1/2 to 3 years assumes a broader scope: development of biological processes and their industrial application in the bacterial oxidation of ores and their concentrates. The main aim would still be to control and optimize the bacterial leaching process in order to improve output. This time Chile's copper-producing organizations have already indicated their willingness to participate with funds and project activities - a contribution the UNDP/UNIDO evaluation team saw as imperative. However, in order to obtain their maximum participation, the leaders of each part of the project would have to sell their ideas, and their programmes would have to include some short-term benefits to industry, the team noted.

One primary objective would be setting up a separate business entity - separate from all the organizatons participating in the work - which would provide contract R&D services on a national and international basis. It would implement contracts by subcontracting the human skills and physical resources in Chile's laboratories and universities, its own contribution being confined to marketing of Chilean expertise and funding.

The detailed programme of activities for phase II is still being worked out, but most of the studies in phase I will continue. In addition, the review team recommended studies of:

- Silver-catalysed bacterial leaching
- Stress response of bacteria to hydrostatic pressure
- Effect of increasing iron content on the bacterial leaching of process stream produced in cementation
- Effect of particles that have been fractured by pressure
- Factors limiting the slurry density at which bacteria function in a reaction vessel.

In addition, work would continue on a number of new and interesting possibilities that came to light in phase I, for which either time or funding was lacking. Two institutes are looking into using solar panels as a power source for pumping and electrolytic refining of the leach solution. Apart from their use at sites totally without power, this raises the possibility of a mobile copper refinery that could be driven to different mines for testing and demonstration purposes.

Another institute is working with programmers and hardware suppliers to develop an "expert system" that would train and assist miners to design their own heaps for the bacterial leaching process.

These and other developments will be incorporated in a detailed plan for phase II currently being prepared by the Chilean teams. A key feature will be co-financing by the local copper-producing industry, probably through its three producers' associations. Given the achievements of the multidisciplinary approach to date, and its extreme cost effectiveness, UN officials are confident that phase II will be supported by all parties.

UN organizations play catalyst

Seen by some as a forerunner of the way many UN-assisted development projects could proceed in the future, the project is unusual in two respects. First the scope of the work and the number of people involved is very large in relation to the UN's own inputs - roughly $400,000 from UNDP in 1986. UNDP/UNIDO assists mainly by providing fellowships and study tours for the national experts, and by funding some of the specialized equipment required.

Secondly, because the international inputs are minimal, UNIDO (the executing agency) has no resident project manager. Instead of a permanently present Chief Technical Adviser, the project is being monitored by regular intensive technical review meetings - after 9, 18 and 27 months of the project duration. Designed specifically to facilitate technical evaluation and administration of this project, such technical reviews offer a novel and cost-effective alternative to the traditional project manager, especially for sophisticated, highly technical multi-scientific discipline projects.

The first technical review meetings were conducted by Professor Dr. Joseph Martial, Belgium, one of the world's leading experts on the genetic-microbiological aspects, and Professor Dr. H. Tributsch, Federal Republic of Germany, who reviewed applied research and testing. Mr. B. Crowston, the UNIDO industrial development officer in charge of the project, concentrated on metallurgical and management aspects. All parties agreed that this was the most useful and successful way of monitoring the project. Realignment and rationalization of activities were mutually agreed in the course of the considerable technical interchange between the evaluation experts and the scientists, and realistic goals set for future months. Mechanisms and approaches for improved linkages between each of the subprojects and with local industry were also agreed.

UN and other organizations' news

Help for African States

The World Health Organization is making US$13 million available to four African countries for programmes to control AIDS. Ethiopia, Kenya, Rwanda and Tanzania all now have five-year plans endorsed by WHO - and the money to carry them out. The decision follows a series of meetings, one in each country, organized by WHO and the Ministry of Health concerned. These meetings were necessary, says WHO, because of the magnitude of resource required and because countries need to avoid diverting scarce resources from other important health programmes. WHO, with the Ministry of Health concerned, has set up a national management committee in each country, to co-ordinate the programme. (Source: New Scientist, 20 August 1987)

Goodbye tsetse

A joint project in biological insect control of the International Atomic Energy Agency and the Food and Agriculture Organization has successfully eradicated a species of tsetse fly from a 1,500 sq. km agricultural zone in central Nigeria. It is expected the field project will now be expanded and extended. (Source: Development Forum, September 1987)

Food for rumination

To study the microbial population of the rumen under controlled laboratory conditions, Dr. J. W. Czerkawski of the Hannah Research Institute, Scotland, UK, developed an "artificial cow". The "cow", named RUSITEC (from the acronym of "Rumen Simulation Technique") is today being used as part of a project to analyse different feedstuffs being carried out by the Food and Agriculture Organization of the United Nations (FAO) and the International Atomic Energy Agency (IAEA) at their joint Agricultural Biotechnology Unit at Seibersdorff near Vienna, Austria.

In the artificial rumen micro-organisms can be indefinitely maintained by feeding a normal ruminant diet each day and providing the correct physiological conditions in terms of temperature, pH and flow of saliva. As RUSITEC chews its way through different feeds, scientists use radioactive tracing techniques to compare their digestibility. (The higher the digestibility of a foodstuff, the higher the nutritive value that can be derived from it.) By analysing the quality of different feeding materials in this way, scientists are seeking to propose improved diets for domestic animals in the developing world. (Source: The Courier, March 1987)

Social issues

Formation of the Gen-Ethisches Network (GeNe)

This network has been formed to facilitate an international critical public discussion of research, development, and applications of biotechnology and the new reproductive techniques.

The goals of GeNe are to contribute to the broadest possible democratic dialogue about the societal and ecological objectives and consequences of these new technologies, their dangers, and alternatives, as well as the basic ethical and social questions which they raise.

GeNe will also publish the Gen-ethic information Service (g.id.) from Hamburg, FRG. GeNe is looking for participation by active individuals interested in assuring the development of gene technology in an ethically, socially, and ecologically responsible manner. For further information contact: Linda Bullard, Gen-Ethic Network, Potsdamer Str. 96, D-1000 Berlin 30, Federal Republic of Germany. (Source: GeneWATCH, March/April 1987)

Regulatory issues

Researcher flouts gene-splicing rules

An outdoor experiment initiated in June by a Montana State University (MSU) professor is being condemned by industry and government officials as well as environmentalists. The Environmental Protection Agency (EPA) is expected to levy penalties against Gary Strobel, a plant pathologist, who was seeking to test a method for improving the ability of elm trees to resist Dutch elm disease. Strobel developed a strain of the bacterium Pseudomonas syringae using recombinant DNA techniques and injected it into trees on the university's campus without obtaining a federal permit to release the organism into the environment.

Strobel began his experiment on 13 June by injecting the modified bacteria into a number of elm trees located behind the university's stadium. The bacteria are not perceived as a threat to the environment, but their use in an outdoor experiment was subject to federal review because the organisms had been genetically altered. The strain of P. syringae was modified through the insertion of an Escherichia coli plasmid containing genes that code for an antifungal protein.

On 3 July Strobel infected American elm trees (Ulmus americana) that are 10 to 18 years old with the Dutch elm fungus, Ceratocystis ulmi. The university biosafety committee did not become aware of the experiment until 27 July, when it received a letter from Strobel, dated 13 July, describing the experiment. EPA began investigating the matter shortly thereafter.

Strobel first contacted EPA in May or early June about obtaining a permit and then on 15 June actually applied for one - two days after he had injected the elm trees with the modified organism. EPA officials advised Strobel that it would take about three months to obtain a permit.

Strobel's primary motivation for proceeding with the experiment without a permit was the need to begin in June or July when the Dutch elm fungus is most active. Obtaining a permit would have meant waiting until next summer. It appears, however, that this delay could have been avoided had Strobel submitted his field trial proposal to federal authorities earlier. Strobel had been aware of the potential antibiotic effects of the modified organism for years and even wrote a paper on the subject, which appeared in Plasmid in 1985. (Extracted from Science, Vol. 237, 21 August 1987)

Biotechnology guidelines for animals and plants

Proposed guidelines for research with genetically engineered whole plants and animals - setting four biosafety containment levels consistent with those for micro-organisms - were adopted by the Recombinant DNA Advisory Committee (RAC) to the US National Institutes of Health (NIH). If accepted by NIH Director James B. Wyngaarden, the guidelines will be enforced for all plant and animal experiments funded by the Agriculture Department. Since containment of large animals is not a great problem, concern was really for the containment of micro-organisms used as vectors to incorporate genetic changes in the animals. Level-1, the least restrictive, allows open greenhouses for plants and fenced enclosures for animals. The Environmental Defense Fund had sought stricter containment. RAC referred to another ad hoc group a change proposed by Jeremy Rifkin, president of the Foundation on Economic Trends, to apply the U.S. guidelines more tightly to research abroad. (Source: Chemical Week, 30 September 1987)

General

Flexibility for 'qualified persons' course

Pharmaceutical companies in the south east region of England and the Department of Pharmacy, Brighton Polytechnic, have launched a distance learning course for the training of Qualified Persons as set out in the permanent provisions of EEC Directives 75/319 and 81/851.

The course is based on the syllabus jointly developed by the Pharmaceutical Society of Great Britain, the Royal Society of Chemistry and the Institute of Biology. Potential Qualified Persons must hold a relevant science-based qualification.

The course steering committee says market research and discussions with the Association of British Pharmaceutical Industry showed that the flexibility of a modular distance-learning format would best meet the needs of students with a wide range of educational backgrounds and experience. Thus, the course consists of eighteen modules taken over two years.

Each module requires about 60 hours of study including practical work, some of which will be carried out in-house under the guidance of a personal industrial tutor. Residential courses lasting one week will complement module studies, particularly for those aspects of the syllabus which cannot be conveniently covered in an industrial environment.

Discussions with pharmaceutical companies and informal enquiries are said to have shown an enthusiastic response to the course, Eli Lilly being particularly supportive with the donation of £1 000 towards development costs. After an initial period of operation it is intended the course will provide a foundation on which to build updating courses, and subsequently a part time M.Sc. programme.

Details: Dr. Roy W. Daisley, postgraduate education co-ordinator, Department of Pharmacy,

Brighton Polytechnic, Moulsecoomb, Brighton, East Sussex, BN2 4GJ; Tel. (0273) 693655. (Source: Manufacturing Chemist, March 1987)

Participants needed for task group on preservation and maintenance

The ASTM Subcommittee E48.02 on Characterization and Identification of Biological Systems is seeking participants for its task group on Preservation and Maintenance.

The task group is currently developing a standard practice for low temperature preservation and maintenance of micro-organisms, cell lines, and genetic elements by freezing and freeze-drying. These low temperature methods provide the only real assurance of genetic stability.

For more information about this E48.02 activity, contact Frank P. Simione, American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD 20852, Tel. 301/231-5530; or Teri McMasters, ASTM, 1916 Race Street, Philadelphia, PA 19103, Tel. 215/299-5496. (Source: News Release, 23 July 1987)

Seeds firms

Chemicals companies have spent $10 billion or so in as many years buying up seeds companies worldwide, or on research and joint ventures with them. Among those doing the buying are BP, Sandoz, Sanofi, and Orsan, the chemicals subsidiary of Lafarge-Coppée. Of the big chemicals companies, ICI has probably spent the most. In 1985, it bought Garst, an American maize breeder, and more recently Belgium's Societé Européenne de Semences. ICI has devoted £17 million to new research facilities in Britain and the United States and plans to spend about £10 million a year on plant breeding, particularly genetic engineering. The company is already close to reaching its goal of annual turnover from seeds by 1988 of £200 million. By the end of the century, it plans to more than double that again.

Plant biotechnologists are looking at ways of producing protein-rich crops, of improving the baking qualities of wheat, and of making plants that can grow in all sorts of soils. A new plant can be developed in two to three years using genetic engineering, less than half the time it now takes using conventional plant breeding techniques to produce a hybrid variety that works. Robert Fleming, a securities firm, estimates that genetic engineering should help push seed prices up by 30 per cent over the next few years.

Monsanto, an American chemicals firm which is spending 20 per cent of its $500 million plus annual research budget on plant and human biotechnology, is trying to develop soyabeans that are resistant to Round-up, a herbicide it makes. The idea is that weeds in fields sprayed with the chemical will die but valuable crops will not. The company's efforts could, however, be overtaken if biotechnologists succeed in producing new breeds of disease-resistant plants, which would dispense with the need for chemicals altogether. Monsanto has already managed to engineer the gene of a natural poison belonging to a bacterium into the tomato. The tomato thus produces insecticides of its own accord. In June, Monsanto planted its first genetically-engineered tomatoes in Illinois.

According to Agricultural Genetics, a British biotechnology firm, seeds now account for some 20 per cent of the cost in Europe of producing wheat. That compares with over 45 per cent spent on fertilizers and 35 per cent on sprays. By 2006, says Agricultural Genetics, seeds could account for some 40 per cent of the total, rising in time to more than 50 per cent.

Not everybody in the chemicals business is convinced of the need to buy seed companies. Monsanto plans to licence the marketing of most of its new genetically-engineered crops. ICI and Lubrizol, an American chemicals company, have both been hit by the drop in demand for conventional seeds as American farmers have reduced grain and maize production to obtain subsidies under the American government's set-aside programme. Lubrizol is growing impatient with the losses while it waits for the gains to come from genetically-engineered plants. It is said to be putting up for sale bits of Agrigenetics, a seeds firm it bought in 1985. (Extracted from The Economist, 15 August 1987)

Biotechnology business

Corporate giants are entering the biotechnology industry due to its promising long-term future. As it enters its second decade of existence, the biotech industry is producing a range of medications, medical tests and agricultural and chemical products that amassed $600 million in revenue in 1986. With the industry scaling up from R&D to actual production, the question is no longer whether it can survive but rather who the main players will be - entrepreneurial start-ups or giant chemical firms.

Because development of new biotechnology products demands years of trial and $25-50 million in expenses, the only practical approach for many start-ups is to collaborate with large corporations. Usually, the big company provides needed funds for a specific project. The start-up agrees to licence any new products to its partner in return for a fixed royalty. But many biotechnology executives view licensing deals as a short-term strategy at best, and see actual manufacturing as the way to best maximize shareholder returns. The need to convince investors of the promise of biotechnology is the biggest challenge facing the industry now. Despite the potential commercial value of many biotechnology products, serious obstacles could stand in the way of making them pay off. The biggest problem is patent protection, but failure to win US Food and Drug Administration approval and possible environmental hazards are other concerns. Nevertheless, firms like Kodak, Schering-Plough and Johnson & Johnson are backing start-ups' R&D programmes.

Numerous products produced via biotechnology are being developed for commercialization. Progress has not been as rapid as in pharmaceuticals, where biotechnology has also received more publicity, but it could have a tremendous impact on the practice of agriculture. It will produce vaccines and treatments for animal diseases and will produce plants with greater yields and improved characteristics (resistance to pesticides, drought and salt; nitrogen-fixation; pesticide production; improved nutritional or processing value). Veterinary biotechnology products have benefited greatly from research on human pharmaceuticals. Development of biotechnology for crop plants has been slower because less is known about plant biochemistry. Field tests of engineered microbes to protect crop plants have also been delayed by lawsuits. The need to gather negative data to reassure critics of the non-existence of risks will continue to hamper progress. (Source: Fortune, 6 July 1987) and Chemical and Engineering News, 10 August 1987, pp. 9-14)

Biotechnology impacts to widen

A new study of the economic impacts of biotechnology reveals many potential effects beyond those previously recognized.

Overshadowed by the well-publicized benefits in human health care and agriculture are a number of developments which will heighten public awareness of

potentially harmful contaminants in US food, air and water supplies.

According to Consulting Resources Corporation of Lexington, Mass. which carried out the study, this heightened public awareness is likely to lead to new restrictions affecting food companies, food importers, pesticide and other chemical producers, refineries, solvent users and office workers, among others.

Two critical developments will fuel the enhanced level of awareness and regulation. One will be the continued amassing of data from clinical studies of human exposure to chemicals in the environment.

The other, biotechnology-related development will be the increasing availability of new, sensitive, relatively low cost methods of monitoring environmental contaminants using immunoassay technology.

Several immunoassay-based tests are already available for the detection of pesticide residues and certain industrial chemicals. (Extracted from Chemical Marketing Reporter, 14 September 1987)

Some biotechnology acronyms

ANF - atrial natriuretic factor. A peptide hormone naturally secreted by the heart, ANF is a natural diuretic and acts to lower blood pressure; California Biotechnology leads in ANF development.

EGF - epidermal growth factor. An enzyme that fosters epidermal cell proliferation, EGF likely will find uses in burn and wound healing, cataract surgery and other ophthalmic applications; Chiron leads in EGF development.

EPO - erythropoietin. A peptide hormone produced naturally by the kidney that stimulates production of red blood cells, it will be used to treat anaemia associated with dialysis and possibly other forms of anaemia; Amgen leads in its development.

Factor VIII. One of the many proteins involved in the cascade of reactions responsible for blood clot formation, Factor VIII is the protein deficient in classic haemophilia. Although available to haemophiliacs from pooled plasma, fears of infection with human immunodeficiency virus make development of recombinant Factor VIII a priority; leading companies are Genentech and Genetics Institute.

FGF - fibroblast growth factor. A protein that stimulates angiogenesis, or growth of blood vessels, FGF may find use in treating burns and wounds and in assisting vascularization of skin grafts; California Biotechnology leads in FGF development.

G-CSF - granulocyte colony stimulating factor. A CSF that stimulates white cells called granulocytes, G-CSF could be useful in treating leukaemia and as an adjunct to cancer chemotherapy; Amgen leads in G-CSF development.

GM-CSF - granulocyte-monocyte colony stimulating factor. First of the CSFs to be cloned and expressed, this protein stimulates two important white blood cells and may be useful in treating immune deficiency caused by cancer radiation therapy, cancer chemotherapy, and AIDS; Genetics Institute leads in GM-CSF development.

hGH - human growth hormone. Commercialized by Genentech, a recombinant version of hGH is now on the market to treat pituitary dwarfism; Eli Lilly likely will bring another version of hGH to market soon.

IL-2 - interleukin-2. A lymphokine that effects a number of immune system responses, it will likely most be used to treat cancers both alone and in conjunction with other lymphokines and chemotherapies; Cetus leads in IL-2 development.

IL-3 - interleukin-3. Discovered, cloned, and expressed by Genetics Institute researchers, this blood cell growth factor stimulates blood cells at the earliest stages of development and affects a broader range of cells than any of the CSFs; IL-3 may find use in bone marrow transplants.

M-CSF - macrophage colony stimulating factor. The CSF with the narrowest response, it stimulates only the monocyte/macrophage type of white blood cell and may find use in treating certain infectious diseases; Cetus (which calls the protein CSF-1) and Genetics Institute are developing M-CSF.

SOD - superoxide dismutase. The enzyme that scavenges superoxide radicals in the body, SOD may be used in conjunction with tissue-type plasminogen activator in treating heart attack patients; other possible uses include treating transplant patients; Chiron and Bio-Technology General lead in SOD development.

TNF - tumor necrosis factor. A lymphokine with a large number of physiological effects that, taken as a whole, are not well understood. TNF has been shown to kill cancer cells under certain conditions; several leading biotechnology companies are exploring the use of TNF as a cancer therapeutic alone and in conjunction with other lymphokines such as IL-2 and interferons.

t-PA - tissue-type plasminogen activator. An enzyme that causes blood clots to dissolve, t-PA will be used first to treat heart attack patients; it is being developed by Genentech, Genetics Institute, and numerous other biotechnology companies. (Source: Chemical and Engineering News, 20 July 1987).

The following article has been reprinted from UNESCO Courriers, March 1987, which was written by Dr. Albert Sasson of the University of Paris, and adapted from his recent book "Quelle biotechnologies pour les pays en développement?", published by UNESCO and Biofutur.

A challenge for the developing world

Biotechnologies have much to offer developing countries. Their application to agriculture, horticulture and forestry can contribute largely both to the improvement of cultivated plants and to the protection of species threatened with disappearance. But careful consideration must be given to the choice of the most appropriate techniques and their transfer and adaptation to specific conditions.

Such processes as plant cell and tissue cultures and genetic engineering are tools, not solutions to social problems. For example, the replacement of traditional crop varieties by new ones may cause unemployment if such new varieties require less work. There is also a tendency for research in biotechnology to respond primarily to the needs of international markets rather than the domestic needs of developing countries. Furthermore, since it is the big landowners who possess the financial and management resources enabling them to profit from technological innovations, it is likely that they rather than the small farmers will gain from the application of biotechnology to agriculture.

There is a strong possibility that the poor countries in general will not only reap few direct benefits from the biotechnological revolution, but that their economies will be indirectly hit by the development of new products (such as artificial sweeteners) which will compete with their traditional

export commodities. There is a danger that the technology gap between the rich and poor countries will grow even wider. Searching questions must therefore be asked about the nature of the "Biotechnological Revolution" and its long-term economic, social and geopolitical effects; strategies must be devised to ensure that its benefits are equitably shared both between countries and between different social groups within a given country.

The "Biotechnological Revolution" is irreversible, if only because of the commercial successes that have already been achieved and the size of the investments which have been made in the different fields of biotechnology. It has been estimated that the sales of products derived from the application of biotechnologies to food and agriculture alone may reach between $50,000 million and $100,000 million by the year 2000.

Whereas the "Green Revolution" was largely carried out by the public sector, which made possible the free exchange of new plant strains developed notably in international agronomic research centres sponsored by the FAO, the impetus behind the "Biotechnological Revolution" in agriculture is coming largely from the private sector, although much basic research is being carried out in universities and in State-supported agricultural and forestry facilities.

The privatization of the results of research in biotechnology means that these results do not form part of the universally available body of scientific and technical knowledge that belongs to the common heritage of mankind. In addition, the public sector research institutions and the organisms which subsidize them are tending to take out patents and thus contribute to the privatization of the results of research.

The growing tendency to grant patents to plant breeders as a means of protecting the creation of new strains is causing widespread concern in developing countries where these measures are seen as obstacles to their efforts to increase their agricultural output.

The adoption of legislation to protect the rights of plant breeders by patent (that is, granting to plant geneticists and the bodies which subsidize their research exclusive production and marketing rights over these varieties) has encouraged multinational corporations and several major national chemical and pharmaceutical groups to buy seed marketing companies and to take majority participations in firms engaged in varietal selection and plant genetics research. In Europe and North America, the leading multinational petrochemical and pharmaceutical firms have acquired a dominant position in this field.

One reason for this trend is to be found in the complementary roles played by seeds, fertilizer, pesticides and animal medicines in boosting agricultural output. It is thus possible for one firm to influence the entire production chain.

The market for selected seeds is worth $12,000 million a year, including $2,000 million for hybrid maize and sorghum seeds, and $1,000 million for hybrid oats, soya and cotton seeds. The grip of the multinational corporations and of other major industrial groups on the seed companies is likely to encourage monopolies and sharply reduce the public sector role in plant selection.

The Green Revolution and the "Biorevolution"

Characteristics	Green revolution	Biorevolution
Crops affected	Wheat, rice, maize	Potentially all crops, including vegetables, fruits, agro-export crops (e.g. oil palms, cacao), and speciality crops (e.g., spices, scents)
Other products affected	None	Animal products, pharmaceuticals, processed foods, energy
Areas affected	Some locations in some less developed countries (i.e., if accompanied by irrigation, high-quality land, transport availability, etc.)	All areas, including marginal lands characterized by drought, salinity, aluminium toxicity, etc.
Technology development and dissemination	Largely public or quasi-public sector	Largely private sector (multinational corporations and start-up firms)
Proprietary consideration	Patents and plant variety protection generally not relevant	Processes and products patentable and protectable
Capital costs of research	Low	High
Research skills required	Conventional plant breeding and parallel agricultural sciences	Molecular and cell biology expertise plus conventional plant-breeding skills
Crops displaced	None (except the germplasm resources represented in traditional varieties)	Potentially any

Measures taken by the technologically advanced countries to protect the results of increasingly expensive research into plant genetics and to ensure that such research is profitable include the payment of royalties, notably by the developing countries, for seed varieties selected in the industrialized countries. The latter countries are also tending to use their collections of seeds and plants (germplasm) for commercial purposes; the private sector is playing an increasing role in the collection, preservation and use of germplasm.

Many developing countries do not possess the financial and technical resources to establish seed collections or to preserve such collections in satisfactory conditions. They have no alternative but to buy new strains selected from varieties which have been cultivated or which grow wild in their own regions. Such varieties may have been domesticated, cultivated and improved by many generations of farmers in the developing countries before being crossed with other varieties, protected by patent, and then sold in their countries of origin as "new and different". This paradoxical situation calls in question the validity of the patent system, for to grant ownership rights and royalties to those who have recently improved the genetic heritage of a plant variety is to disregard the efforts of all those who have previously transformed the variety and derived no profit from it.

"The North may be 'grain-rich' but the South is 'gene-rich'." The genetic resources of most cultivated plants are found in the developing countries, notably in the tropics, but the selection and improvement operations relating to these plants mainly take place in the industrialized countries. In 1982, according to the Organization for Economic Co-operation and Development (OECD), the developing countries were contributing an estimated $500 million a year to the United States wheat harvest. This contribution resulted from the use of plant genetic resources which originate in the developing countries and are indispensable to the improvement of cultivated plants and variety selection in the United States and in the other industrialized countries.

In view of the economic importance of their plant genetic resources, the developing countries intend to protect these resources - for example by preventing the export of plant reproducing material. They also feel that the purchase price of varieties of seeds selected and improved from their own phytogenetic stock is excessive and that it is unjust to be thus obliged to buy back indirectly a part of their phytogenetic heritage.

The risk of a diminution of genetic diversity, combined with the question of restrictive practices in the distribution of material needed for the improvement of cultivated plants, has led to a search for an international agreement on the conservation of plant genetic resources, considered as part of the heritage of humanity, and on their equitable use, instead of allowing such use to be regulated solely by national jurisdictions. If the industrialized countries wish to have access to the plant genetic resources of the developing countries and wish to use the hardy local strains which are found there, the developing countries wish to benefit from services provided by gene banks in the industrialized countries and to claim their national sovereignty over plants grown in their countries.

The problems of the conservation of and free access to plant genetic resources have thus assumed a geopolitical dimension in the context of the debate on the exploitation of the Earth's resources for the benefit of all humanity. In November 1981 a resolution presented by Mexico to the 21st Conference of FAO invited the Director-General to prepare a draft international Convention on the conservation of plant genetic resources necessary to increase agricultural production, on the removal of obstacles to the free distribution of plant material and on the improvement of international co-operation in this field.

In November 1983, a draft international Convention was accordingly submitted for examination to the FAO Conference at its twenty-second session. Among its provisions was one which prohibited the imposition of any restriction on the availability or exchange of plant genetic resources for agriculture and food production.

The 156 countries represented at the twenty-second session recognized that "plant resources were part of the common heritage of mankind and should thus be accessible without restriction". Such resources include wild species or those close to cultivated varieties, which should be catalogued and protected, for they are threatened with disappearance, as well as the most recent cultivated varieties and strains which make it possible to produce seeds of more productive hybrid varieties.

In November 1985, at the twenty-third session of the FAO Conference, the industrialized countries opposed the creation of an international mechanism to ensure the free exchange of plant genetic resources and to abolish payment for varieties selected in the industrialized countries and royalties to acquire them. It is thus to be expected that genetic information needed for the improvement of cultivated plants may become a commercial commodity subject to competition between seed companies, between countries, and between seed companies and countries.

However, it is to be hoped that a compromise will be found between the legitimate desire to reward human ingenuity by granting patents to selectors in the industrialized countries and the need for developing countries to obtain selected varieties at a price compatible with their limited means and the imperatives of their agricultural development. It would also be ethically justifiable to take into account, in the sale to developing countries of seed varieties selected from their own cultivated plants, the work of the generations of farmers who have contributed to the improvement of these plants.

In the meantime, much can be done to harness biotechnologies to agriculture, horticulture and forestry in the developing world.

First of all, in each developing country steps should be taken to establish priorities and economic objectives which derive maximum benefit from the available resources. Those biotechnological processes which are most relevant to the country's social and economic needs should be identified and inventories of local resources should be drawn up.

Secondly, developing countries should avoid entering into competition, at least initially, with the industrialized countries in such advanced fields as gene transfer and genetic engineering. They should profit from simpler techniques of plant tissue culture, meristem culture and plant organ culture for the rapid vegetative propagation of the most useful strains and for the isolation of virus-free strains. They should adopt and practise at the appropriate scale low-cost, proven biotechnologies which are easy to transfer and to adapt to local conditions.

Thirdly, biotechnologies should not be considered as the only means of improving species of cultivated plants. They should be seen as complementary to hybridization methods and efficient agricultural practices. The success of biotechnologies in the developing countries will depend to a large extent on

their being closely associated with classical methods of crossing and improving plants, with agricultural training programmes, the establishment of remunerative farm prices and the existence of a good marketing network for agro-food products.

Fourthly, the choice of appropriate biotechnologies does not mean that we should resign ourselves to accepting an international division of biotechnologies: high tech for the technologically advanced countries, outworn technologies for the developing countries. A range of biotechnologies, of varying degrees of sophistication and complexity, should exist in each specific situation. Every national scientific and technological community should take into account international developments in biotechnology when considering local needs, and be able to use the most advanced techniques or adapt them to development projects.

Whatever options for the development of biotechnologies are chosen, education and training are bound to play an essential role. Standing as they do at the crossroads of several disciplines of the life sciences (genetics, biochemistry, physiology and microbiology), and of engineering (fermentation technology, automization of production techniques, chemical and industrial microbiology), biotechnologies call for interdisciplinary training programmes and an integrated approach.

There is a chronic lack of specialists and biotechnology technicians in the developing countries. According to one survey, in 1983 there were 23,000 researchers in this field in the USA, 12,000 in the USSR, 8,000 in Japan, 3,400 in the rest of Asia, 1,900 in Latin America and 400 in Africa.

International and regional co-operation undoubtedly has a major role to play in encouraging the transfer of biotechnologies and the fulfilment of their promise in the developing world, as well as helping to solve the ethical problems involved. It should be possible for countries within a given region to carry out joint research projects into matters of common concern and to obtain results which can be applied in several countries. Efforts must be made to encourage co-operation between developing and industrialized countries, including private sector institutions in these countries. Examples of such co-operation already exist. They include the production of vaccines against foot and mouth disease in Botswana with the co-operation of Rhône-Mérieux in France; biogas production from wastes through co-operation between India, China and several developing countries; and the cloning of the oil palm and the creation of new oil palm plantations in Côte d'Ivoire, Malaysia and Indonesia in co-operation with the French Office of Scientific and Technical Research Overseas (ORSTOM) and the French Research Institute for Oils and Oil-Producing Substances (IRHO).

The role of international intergovernmental organizations is important in helping to provide governments with consultative services with a view to the formulation of national policies and programmes in biotechnology; to encourage joint research projects and other joint activities between developing and industrialized countries; to encourage researchers and technicians from all countries to take part in these activities, and to strengthen national research and training capacities.

Ever since its early days, UNESCO has laid great stress in its scientific programmes on international co-operation in research and training in the life sciences, and at an early stage drew attention to the importance of research into micro-organisms and embarked on a programme in applied microbiology. In 1962 UNESCO sponsored the creation of the International Cell Research Organization (ICRO), and in 1972 joined with ICRO and the United Nations Environment Programme (UNEP) in launching a world programme to safeguard the genetic heritage of microbial resources and to make this heritage accessible to developing countries. Then, in 1975, UNESCO began to create the world network of Microbiological Resources Centres (MIRCEN).

Following the adoption of UNESCO's second Medium-Term Plan (1984-1989), activities relating to training, research and international co-operation in applied microbiology were strengthened and further extended into the field of biotechnologies. Today, in close collaboration with FAO, the United Nations Industrial Development Organization (UNIDO), the World Health Organization (WHO) and other specialized institutions of the United Nations system and with international non-governmental organizations, UNESCO continues this work as part of the broader effort to enable the developing countries to contribute to and benefit from advances in scientific knowledge.

Pesticides

There is worldwide concern over several recent accidents that have occured during production and handling of pesticides. The January 1987 issue of the International Development Research Centre's Reports, notes that interest in the pesticide problem in the Third World is relatively recent. It quotes Dr. J. Jeyaratnam, a physician with the Department of Social Medicine and Public Health at the National University of Singapore:

"People talk about malaria or infectious diseases, but in Sri Lanka, malaria did not cause a single death in 1978, the same year that 1,000 people died from pesticide poisoning.

"... If the Sri Lankan study were applied [worldwide], the numbers would be absolutely horrific - 2.9 million cases expected annually in the developing world, resulting in 220,000 deaths."

UK trade unionists have launched a campaign to reduce the toll of ill health and poisoning suffered by workers using agricultural chemicals. The unions claim that official statistics underestimate the risks, and their concern echoes that of the National Poisons Unit. The campaign coincides with the news that the use of UK's biggest-selling fungicide - Bayleton CF, is being restricted because one of its ingredients, captafol, is carcinogenic. The UK Government is now proposing a mandatory scheme that will require much greater monitoring of residue levels than now exists.

In the United States, a study by the General Accounting Office concludes that over half of the pesticide residues that may be present in domestically produced food are not detected by multiresidue tests. Eight of the nine most dangerous pesticides used are not detected by these standard tests. The most disturbing discovery of the report is the U.S. Food and Drug Administration's record in preventing the sale of adulterated food and in prosecuting wrongdoers. In 107 out of 179 cases in which illegal residues were found, the food had already been sold by the time the results came through. This does not mean that the consumers are often being poisoned. Illegal residues may simply be pesticides applied to the wrong crop or may exceed approved tolerances by a small amount.

Pesticide poisoning is quite properly considered a new Third World disease; while these countries use only 20 per cent of all pesticides, they account for 99 per cent of the deaths resulting from poisoning.

In 1985, the Pesticide Action Network International (PAN) launched a worldwide public education effort known as the "Dirty Dozen Campaign". A handbook describes the activities of people around the world working to reduce the dependence on chemical pesticides. PAN has over 350 member organizations on all continents and can be contacted through the following addresses:

AFRICA
Environmental Liaison Centre
P. O. Box 72461
Nairobi, KENYA

LATIN AMERICA
Fundacion Natura
Casilla 243
Quito, ECUADOR

ASIA/PACIFIC
International Organization of
Consumers Unions
P. O. Box 1045
Penang, MALAYSIA

NORTH AMERICA
Friends of the Earth
1045 Sansome Street
San Francisco, CA 94111, USA

EUROPE
OXFAM
274 Banbury Road
Oxford, OX2 7DZ, UK

The World Health Organization (WHO) has recently initiated a project to study the impact of agrochemicals on public health with particular reference to the general population in developing countries. A limited number of selected countries will be studied in detail, implying, in essence, a literature survey. A working group has agreed to draft a report that will be sent to WHO member nations and others for comments before publication. The report will then be made final at an international meeting during November 1987. Additional information may be obtained from Dr. Tord Kjellstrom, EHE/PEP, World Health Organization, 1211 Geneva 27, Switzerland.

Another study, headed by Dr. Jeyaratnam, began in 1984 and is collecting data in Malaysia, Thailand, Sri Lanka, and Indonesia. It is operated by the Asian Association of Occupational Health and was funded by the International Development Research Centre.

WHO has recently issued a new document in its series on Environmental Health Criteria; Organophosphorus Insecticides: A General Introduction includes chapters on sources of human and environmental exposure, environmental transport and distribution, and exposure levels; metabolism and mode of action; effects on organisms in the environment; and effects on animals and effects on man.

The new International Code of Conduct on the Distribution and Use of Pesticides, which was adopted by the Food and Agriculture Organization (FAO) about a year ago, is intended to "increase international confidence in availability, regulation, marketing, and the use of pesticides in the improvement of agriculture, public health, and personal comfort". The full text of the code is available from all regional FAO offices. (Source: BOSTID Developments, Vol. 7, No. 2, Summer 1987)

Why the world needs population biology to solve its problems

During the past months, pressure from Washington-based groups has led the World bank to withdraw support from African cattle-ranching projects that would cause long-term economic harm and the Agency for International Development to publish lists of its own projects that stress short-term economic benefit at the expense of the environment. Now the Club of Earth, a pressure group of senior academic ecologists, have issued a statement stressing that support for population biology makes economic sense. The club, whose members are drawn from the National Academy of Sciences, points out that it is population biology that solves "practical questions about maximum sustainable yields for fisheries, control of agricultural pests, containment of epidemics..." and that basic research is needed to keep the environment in shape just as much "as basic research in molecular biology is needed for treating human ills".

Financial support for biomedical research in the United States is more than two orders of magnitude higher than support for population biology. The major funding agency for population biology (taken to include ecology, ecosystem studies and systematic biology) is the National Science Foundation, which spends approximately $60 million a year. Jared Diamond, a Club of Earth member from the University of California at Los Angeles, points out that most ecology graduate students have to leave the field and that any job opening will attract around 300 applicants.

Better knowledge of population biology could have helped avoid the collapse of the Peruvian fishery industry and the Californian sardine fishery industry, according to the Club of Earth. The former alone lost the world fishmeal worth $1,000 million a year.

The evolution of malarial resistance, the seriousness of the AIDS (acquired immune deficiency syndrome) epidemic and the likely impact of genetically engineered organisms on the environment are all areas where failure to support population biology is preventing serious answers from emerging. Lack of taxonomists prevents the cataloguing of potentially valuable species, particularly in the tropics. Failure to research the chemical interactions of plants, animals and fungi is slowing the development of more intelligent methods of pest control and will, in the long run, harm agriculture.

There ought to be an acceleration in the changes that are now occurring in political organizations such as the World Bank alongside a wider recognition of what population biology could contribute. To achieve that will require skilful management of Washington's complex political ecosystem - a fair intellectual challenge for the club's academics. (Source: Nature, Vol. 329, 3 September 1987)

BIOTECH '87 focuses on biosensors and environmental biotechnology

The International Conference and Exhibition for Bio- and Gene Technology (Biotech '87) was held at the conference centre in Düsseldorf, FRG, from 17 through 19 March 1987, focused on two areas of biotechnology research, namely, biosensors and environmental biotechnology. The topics covered under the biosensors section were:

- Development and application of novel biosensors
- Biosensors based on thermistors and semiconductors
- Gaseous-media biosensors
- Trends in biosensor technology
- Development of DNA probes for clinical diagnostics

- Biosensor systems for food analysis
- Enzyme electrodes in bioprocessing
- Electric monitoring of cell behaviour in culture.

The section on environmental biotechnology included the following topics:

- Aeration systems for aerobic wastewater treatment
- Development of novel catabolic pathways
- Degradation of halogenated hydrocarbons
- Anaerobic treatment of wastewater from the pulp and paper industry
- Fluidized bed reactors in anaerobic wastewater treatment
- High solids anaerobic digestion
- Microbial degradation of problematic exhaust air components
- Technical systems for biological treatment of exhaust air
- Biosorbent material for metal recovery.

A summary of selected topics presented at this conference emphasizing primarily research on biosensors is presented in this report.

Biosensors: The future has already started

Biosensors have gradually emerged from science fiction fantasy and come to market reality. Especially Japanese and US as well as some European companies are developing, producing, or already marketing biosensors; those marketing biosensors include Amersham International, Cambridge Life Sciences, and Harwell in the UK and the Pharmacia affiliate, Biosensor, in Sweden.

Application of these sensors ranges from the detection of substances in blood serum (tumour antigens or glucose, for example) or the analysis of food components to fermentation control or environmental monitoring. Biosensors have been developed for the determination of urea, penicillin, amino acids, glucose, lactate, galactose, sucrose, alcohol, and others. In particular, biosensors will be involved in human health care and veterinary medicine where metabolites, hormones, drugs, or toxins will be detected or physiological functions monitored. The pharmaceutical industry will probably apply biosensors in production process control or as an alternative for animal uses in testing. The biosensors will be used in agriculture for the detection of pesticides as well as for quality control. Detection of the pesticides will also be important in environmental protection in addition to detection of other contaminants.

The advantages of biosensors are their high selectivity combined with high sensitivity plus the fact that they work without reagents and even in turbid media. In addition, biosensors exhibit great potential for miniaturization and computer compatibility, thereby facilitating process control and data analysis.

It is evident from the presentations at this conference that biosensors have emerged as a marketable product. Their high selectivity and sensitivity make biosensors an important and useful new detection system with numerous applications not only in human healthcare and veterinary fields but also in their use for process control and data analysis. There is still much work to be done in miniaturization and computer compatibility. However, the progress that has been made in the development of the present generation of biosensors is an indication that further improvements will be made and new types of biosensors will be available in the near future. (Extracted from European Science News, August 1987)

Biotechnology consortium at Wisconsin

Promotion of advanced training and research in bioprocess and metabolic engineering is the goal of a new university-industry consortium at the University of Wisconsin, Madison. The consortium consists of faculty, students, and member companies, with each firm contributing an annual fee of between $2,500 and $10,000. It will concentrate on designing systems to produce, recover, and purify biochemical products, with an emphasis on the genetic engineering of cells to yield industrial enzymes and proteins with novel catalytic properties. Also, researchers will study ways to make cells grow and release their biochemical products more efficiently. (Source: Chemical and Engineering News, 21 September 1987)

Biomedical research centre established

The University of Cincinnati has established a biomedical chemistry research centre. The goal of the centre is to enhance interdisciplinary, collaborative research in biomedical chemistry among faculty members from various colleges and departments. The centre's director is Edward A. Deutsch, professor of chemistry and radiology. Among the research interests of the centre's members are preparation of biologically active natural products; chemistry of technetium and other transition metals as applied to nuclear medicine; glycoprotein structure and function; bioanalytical chemistry, and drug metabolism. (Source: Chemical and Engineering News, 21 September 1987)

Glossary

Aerobic. Living or acting only in the presence of oxygen.

Allogamy. Cross-fertilization in flowering plants.

Amylolytic. Capable of converting starch into sugar.

Anaerobic. Living or acting only in the absence of oxygen.

Autogamy. Self-fertilization in flowering plants.

Biomass. All organic matter that grows by the photosynthetic conversion of solar energy.

Biotechnology. Techniques that use living organisms, or substances from those organisms, to make or modify a product, and including techniques used for the improvement of the characteristics of economically important plants and animals and for the development of micro-organisms to act on the environment.

Callus. An undifferentiated cluster of plant cells that is a first step in regeneration of plants from tissue culture.

Cell. The smallest structural unit of living matter capable of functioning independently; a microscopic mass of protoplasm surrounded by a semi-permeable membrane, usually including one or more nuclei and various non-living products, capable,

either alone or by interacting with other cells, of performing all the fundamental functions of life.

Cell culture. The in vitro growth of cells isolated from multi-cellular organisms. These cells are usually of one type.

Cell fusion. Formation of a single hybrid cell with nuclei and cytoplasm from different cells.

Chromosomes. The rodlike structures of a cell's nucleus that store and transmit genetic information; the physical structure that contains genes. Chromosomes are composed mostly of DNA and protein and contain most of the cell's DNA. Each species has a characteristic number of chromosomes.

Clone. A group of genetically identical cells or organisms produced asexually from a common ancestor.

Culture medium. Any nutrient system for the artificial cultivation of bacteria or other cells; usually a complex mixture of organic and inorganic materials.

Cytoplasm. The "liquid" portion of a cell outside and surrounding the nucleus.

Deoxyribonucleic acid (DNA). The genetic material found in all living organisms. Every inherited characteristic has its origin somewhere in the code of each individual's DNA.

Fermentation. An anaerobic bioprocess. Fermentation is used in various industrial processes for the manufacture of products such as alcohols, acids and cheese by the action of yeasts, moulds and bacteria.

Gene. The basic unit of heredity; an ordered sequence of nucleotide bases, comprising a segment of DNA.

Genome. The genetic endowment of an organism or individual.

Genotype. The genetic makeup of a given organism.

Germ cell. The male and female reproductive cells; egg and sperm.

Germplasm. The total genetic variability available to a species.

Hybrid. The offspring of genetically dissimilar parents (e.g. a new variety of plant or animal that results from cross-breeding two different existing varieties, a cell derived from two different cultured cell lines that have fused).

In vitro. Literally, in glass; pertaining to a biological reaction taking place in an artifical apparatus; sometimes used to include the growth of cells from multicellular organisms under cell culture conditions.

Meristem. The undifferentiated plant tissue from which new cells arise.

Metabolism. The physical and chemical processes by which foodstuffs are synthesized into complex elements, complex substances are transformed into simple ones and energy is made available for use by an organism.

Molecule. A group of atoms held together by chemical forces; the smallest unit of matter which can exist by itself and retain its chemical identity.

Mutagenesis. The induction of mutation in the genetic material of an organism; researchers may use physical or chemical means to cause mutations that improve the production capabilities of organisms.

Nitrogen fixation. The conversion of atmospheric nitrogen gas to a chemically combined form, ammonia (NH_3) which is essential to growth. Only a limited number of micro-organisms can fix nitrogen.

Nodule. The anatomical part of a plant root in which nitrogen-fixing bacteria are maintained in a symbiotic relationship with the plant.

Nucleus. A relatively large spherical body inside a cell that contains the chromosomes.

Pathogen. A disease-producing agent, usually restricted to a living agent such as a bacterium or virus.

Protoplast fusion. The joining of two cells in the laboratory.

Recombinant DNA. The hybrid DNA produced by joining together in vitro pieces of DNA from different organisms.

Somaclonal variation. Genetic variation produced from the culture of plant cells from a pure breeding strain; the source of variation is not known.

Species. A taxonomic subdivision of genus. A group of closely related, morphologically similar individuals which actually or potentially interbreed.

Totipotency. The capacity of a higher organism cell to differentiate into an entire organism. A totipotent cell contains all the genetic information necessary for complete development.

Vector. DNA molecule used to introduce foreign DNA into host cells. Vectors include plasmids, bacteriophages (viruses), and other forms of DNA. A vector must be capable of replicating autonomously and must have cloning sites for the introduction of foreign DNA.

Vegetative propagation. Reproduction of plants other than by seeds; that is, division of part of the plant body. New plants are genetically identical to parent plant.

(Definitions included in this section have been largely taken from a glossary published in ATAS Bulletin (1 November 1984), a publication prepared by the Centre for Science and Technology for Development, United Nations, New York.)

B. COUNTRY NEWS

Austria

New biological filters

At the Agricultural University of Vienna a team under the leadership of Professor Uwe Sleytr has developed and patented novel biological "ultrafilters" which will be marketed with the help of venture capital. These ultrafilters are produced by accumulating bacteria on commercially available microfilters. The bacteria form an extremely fine and even pore distribution with high permeability and an extremely homogenous structure. These ultrafilters are intended for use in immunology, the pharmaceutical industry, and in gas separation. (Extracted from VDI Nachrichten, 27 March 1987)

Brazil

Brazilian-Argentine biotechnology centre established

The Brazilian-Argentine Biotechnology Centre in Brasilia was officially opened in April. For the first time in Latin America two countries have joined together to create a bi-national centre for promotion and co-ordination of scientific research and business investments in the field of biotechnology. Participating in the project are public agencies, universities, research centres, and business firms of both countries, interested in studying new products in the fields of pharmaceuticals, staple foods and alternative energy sources.

The Brazilian-Argentine Biotechnology Centre has an initial appropriation of $4 million, $2 million from each country.

As part of the Brazilian-Argentine biotechnology programme, the Bi-national School of Biotechnology is being created, similar to the one established two years ago (EBAI, the Brazilian-Argentine School of Computer Science), its purpose being to train intermediate and high-level specialists. The first two-week course at the Brazilian-Argentine School of Biotechnology will be held in February 1988 in Curitiba.

In the energy field, the centre will be required to conduct studies on waste treatment and the use of sugar cane waste to produce energy. Also planned is the creation of enzymes, as well as other biological components to produce antibiotics.

Consisting of a bi-national deliberative council (comprised of eight representatives from the two countries), the centre has a higher decision-making body, responsible for the establishment of its policies, priorities and lines of action. The executive secretary of the Argentine National Biotechnology Programme, Jose de la Torre, was appointed general director of the centre. Two deputy directors were also assigned: the Brazilian, Edmundo Reichman, and the Argentine, Rodolfo Ertola. The general director's position will rotate every two years. (Extracted from Brasil Ciencia, 11 April 1987)

Biological pest control plant not yet operational

A year ago, the first biological insecticide plant in Latin America, intended to produce insecticides for combating the sugar cane borer was opened, but it has not operated to date. It lacks raw material, that is, a daily supply of 400 kilograms of the very caterpillar that the insecticide combats.

Established in Jaguariuna, 120 kilometers from Sao Paulo, the plant (actually a pilot mill) uses a technology developed on the basis of the UNICAP (State University of Campinas) genetics professor, Octavio Henrique Pavan, head of the biological insecticide plant project research. It consists of soaking caterpillars (which attack sugar cane) in a virus that is their natural enemy: the baculovirus anticarsia. After the soaking, a liquid with a large concentration of the virus is extracted, the liquid is converted into a powder, and the latter is later diluted in water to be sprinkled on the plantations, where it contaminates and kills new caterpillars that appear. Thus, it is a natural insecticide, replacing chemical insecticides.

According to Octavio Pavan, three specialized technicians are sufficient to put the plant into operation, but this has not happened to date because the entomology section of Planalsucar (research centre of the Sugar and Alcohol Institute located in Araras, Sao Paulo) has not been receiving the necessary funds from the agencies involved in the project to raise and transport the caterpillars that are to be processed at Jaguariuna.

Its daily production could supply 20,000 hectares of sugar cane. Therefore, in 250 days the plant, operating at full capacity would have produced natural insecticide for use on 5 million hectares; because a single spraying protects the entire crop. Pavan adds: "And with all the advantages offered by biological insecticides, which combat specific pests without collateral reactions."

Recommended by the IAA (Sugar and Alcohol Institute) to all of the country's sugar mill owners as an ideal method for controlling the sugar cane borer, this cheap and apparently simple formula stems from one of the most fascinating experiments in the field of insect virology. Pavan selected the sugar cane caterpillar virus which was unknown to the world scientific community when he was still a post-doctoral student at the University of Texas. This micro-organism, deadly to the insect, had not yet attacked the caterpillars that were infesting Brazilian sugar cane plantations, and the scientist "imported it" to Brazil on one of his trips.

Continuing the experiments at UNICAMP, Pavan started feeding the virus to the caterpillars that were two weeks old (in their larval phase). Then he discovered that, for every 100 particles of the virus ingested, before dying the caterpillars were reproducing a billion of those micro-organisms, which remained in their shells. Grinding the contaminated caterpillar shells and purifying them to eliminate other viruses and also undesirable bacteria (which could, possibly, harm humans), he thereby created an insecticide. The experiment showed 80 per cent efficiency for the method of combating the borer. (Extracted from Jornal do Brasil, 28 May 1987)

Canada

New biochemistry institute in Canada

A research institute for molecular biology and biochemistry is being established at Simon Fraser University, Barnaby, British Columbia. The new institute will co-ordinate research of faculty members in both the departments of chemistry and of biological sciences, as well as graduate programmes in molecular biology and biochemistry. According to George Ivany, vice president for academic affairs and acting director of the new institute, the institute was first proposed about four years ago but put on hold during a period of budgetary restraint. Although the major focus will be on basic research, Ivany says, it's expected that the institute will evolve a master's degree programme in biotechnology that will be useful to researchers in applied fields such as forestry. The school has a good reputation for applied research, particularly in biological sciences, Ivany adds, and grants professional master's degrees in several areas, most notably in pest management. (Source: Chemical and Engineering News, 20 July 1987, p. 40)

Culture collection started at University of Toronto

The University of Toronto has created a culture collection (UTCC) of bacteria, microalgae and higher plant cells chosen for their usefulness in environmental and biotechnology research. The collection will be maintained by the department of botany and the Institute for Environmental Studies. Over the next five years, the organizers hope to gather at least 1,000 separate isolates of bacteria, algae and higher plant cell and suspension cultures.

The collection is intended to be available to researchers in universities, government and commercial laboratories anywhere in the world. Requests have been received from some universities and one industrial firm, and interest has been shown by the Ministry of the Environment and the Canadian Centre for Inland Waters. In addition to the organism collection, the UTCC will also be a repository for DNA clone banks from photosynthetic organisms. (Extracted from Canadian Research/Biotechnology Canada, July 1987)

Canadian/Japanese collaboration

Allelix Inc. of Canada and Mitsui Petrochemical Industries Ltd. of Japan have agreed to joint research and later commercialization of two widely prescribed anti-cancer drugs - vincristine and vinblastine. The agreement represents an unusual alliance, being one of the first times a Japanese company has funded biopharmaceutical research in Canada.

Under the agreement, Mitsui will collaborate with Allelix and fund the further development of its proprietary plant cell fermentation process for manufacturing high-value therapeutics. The advanced process, which involves growing plant cells in fermentors, eliminates the costly need to extract active ingredients of drugs from plants. Allelix operates North America's largest plant cell fermentation facility at its Mississauga location.

According to Graham Strachan, President of the biochemicals division, once research is complete, Mitsui and Allelix will collaborate further on what will be the first commercial use of the technology to produce high-value therapeutics. The products, vincristine and vinblastine, have a current worldwide market value in excess of $100 million.

Research in the area was partly funded by the National Research Council. It involved input by two other leading Canadian research groups - the Plant Biotechnology Institute in Saskatoon and the University of British Columbia.

The process is just one of many being developed by Allelix Biochemicals using modern biotechnologies to develop human health care products. Another proprietary process - a genetically-engineered fungal system useful in the production of new and improved therapeutic drugs - won a 1986 Canada Award for Business Excellence in a competition conducted by the Canadian Government. Allelix Biochemicals believes its protein production systems are among the most advanced in the world.

Mitsui Petrochemical Industries Ltd. is Japan's leading integrated petrochemicals manufacturer, with a major strategic commitment to diversify into pharmaceutical and agrichemical markets through biotechnology. (Source: Company News Release, 5 August 1987)

Czechoslovakia

New biotechnology centres

A new biotechnology centre, which was set up at the Prague Institute of Crop Protection in Czechoslovakia earlier this year, is to concentrate on biological crop protection methods to limit the use of pesticides. The Institute has already developed a product, Polygandron, based on the fungus, Pythium oligandrum, for the protection of young sugar beet plants. Polygandron, which is considered suitable for large-scale production, has also been tested in the protection of potato tubers.

Meanwhile, construction of the South Bohemian Biological Centre at Ceske Budejovice has entered phase two. This will involve the construction of the Experimental Botany Institute, new buildings for the Soil Biology Institute, libraries, a centre for scientific and technical information, lecture halls, and a mathematics centre. Preparations are under way for phase three. Phase one of construction was completed in 1985.

At that time a new, modern facility of the Czechoslovak Academy of Sciences opened housing the Entomology Institute, the Parasitology Institute, the Territorial Ecology Institute, and the newly organized Soil Biology Institute, in addition to the Centre. The facility also houses joint laboratories, equipped with up-to-date equipment for the use of all the participating entities. (Extracted from Rude Pravo, 23 February 1987)

Denmark

Danes seek plant test in U.K.

De Danske Sukkerfabrikker (Danish Sugar Group), here is considering switching its field trials of gene-enhanced rape-seed plants from Denmark to the U.K. A request to plant the seeds outdoors was filed with the environmental authorities in January. The Sugar Group received no answer, and it is already too late to plant this year. The hybrid plant contains a male sterility gene introduced from wild mustard via protoplast fusion, which is considered gene-splicing under Danish genetic-engineering law. (Source: McGraw-Hill's Biotechnology Newswatch, 15 June 1987)

EEC

EEC directives delayed

Plans by the European Commission to introduce a series of directives regulating biotechnology by the end of this summer are unlikely to be introduced until the end of this year.

Officials within the environment directorate, DGXI, are preparing the final draft of the directive designed to regulate the deliberate release of genetically engineered organisms.

The Commission now has to decide whether the latest draft needs further consideration by experts in Member States or to send it straight to the Council of Ministers. The first option is probably the most likely course of action as the commission is seeking as many opinions from interested parties as possible.

DGXI is also putting together its proposal for a directive regulating waste control and accident prevention, however this draft is unlikely to be ready until the end of this year. The containment guidelines directive from DGIII and the occupational safety directive from DGV are likely to be delayed even further. (Extracted from European Chemical News, 21 September 1987)

Finland

Finnish/French biotechnology joint venture formed

Finnish Sugar, Finland's largest agrofood concern and la Cellulose Du Pin, the wood and paper branch of France's Saint-Gobain have set up a biotechnology joint venture, Biopulp International to develop and market enzymatic applications in wood processing and paper manufacture. The venture has received EUREKA status for a research and development programme covering the degradation and modification of wood lignin. (Extracted from European Chemical News, 28 September 1987)

Federal Republic of Germany

BMFT plans gene safety projects

The Federal Republic of Germany's Federal Ministry for Research and Technology (BMFT) plans to sponsor projects aimed at improving safety standards in research or industrial production with genetically altered organisms. The major focus will be human and environmental risk assessment.

BMFT is to award funds for projects dealing with basic research into formation and manipulation of pathogens; safety in research with animal cell cultures; research into the biology of viruses; safe handling of altered materials in production; and threats to the environment from deliberate release.

Parallel to this, criteria for releasing such organisms are to be drawn up. Earlier this year the parliamentary committee examining the risks associated with recombinant DNA technologies recommended a five-year moratorium on deliberate release but did provide for exceptions. BMFT has set up a working group to advise on permit applications. (Source: European Chemical News, 3 August 1987)

Biotechnology funds to increase

A status evaluation of the biotechnology programme of the Federal Ministry of Research found that the FRG's scientific capabilities in this area are now available. This progress is due in part to the seven genetic engineering centres now in operation and to the promotion of basic research projects in conjunction with universities and industry, such as the institutional promotion of, above all, the Society for Biotechnological Research.

Funds for biotechnology almost doubled from 1984 to 1987 - to DM 213 million. A double-digit growth rate is also projected for 1988. In addition to the institutional funding of DM 69 million in 1987 (1986: DM 59 million) and the expenditures for the gene centres, which remain unchanged at DM 26 million, major funding is being supplied in the following areas: microbial research and genetic engineering at DM 16 (1986: 17) million, cell culture and fusion at DM 16 (12) million, bioprocessing engineering and enzyme technology at DM 22 (12) million, as well as regenerative raw materials at DM 14 (11) million. Almost as much funding is now being supplied for the development of alternative methods to animal experimentation as for plans for animal experimentation itself; combined with the expenditures for biological safety, the total for this area is DM 20 million for this year (1986: DM 17 million).

The slightly more than DM 11 million spent from April to December 1986 for the new, indirect-specific promotion programme "Biotechnology for Small and Medium-sized Businesses", for which DM 100 million have been earmarked for a five-year period, have been met with another DM 20 million from the businesses themselves. This particularly applies to apparatus and equipment engineering, the development of bioreactors and the preparation and reprocessing of products, as well as to biochemical laboratory procedures. (Source: VDI Nachrichten, 29 May 1987)

FRG firm expects first stage approval of gene-spliced human insulin

Two FRG companies are poised to receive key approvals from the federal health authorities for gene splicing projects. Hoechst is hoping to win approval for the first stage of its gene-spliced human insulin process while Boehringer Ingelheim is expecting to receive marketing approval for tissue plasminogen activator within the next few weeks.

Officials from the central commission for biological safety (ZKBS) are to look at Hoechst's plant this week. The whole process for the production of gene-spliced human insulin can be split into three distinct sections: the fermentation step, a chemical purification of pro-insulin and a final step to convert the protein precursors to the insulin itself.

The ZKBS officials are expected to grant approval for the first phase involving the fermentation of gene-spliced bacteria and the associated killing of the micro-organisms. The other two phases are still to be investigated.

Hoechst is unlikely to seek approval for the insultech (third) stage until the other two stages have been cleared. The FRG company currently has a one to one pilot plant but expects to have an industrial scale plant with up to three times existing capacity once all test phases are complete.

The plant includes more safety provisions than required by the commission's rules. These rules only regulate State funded research products but private industry has committed itself to these rules until the federal government introduces its own specific regulations.

Total cost for the project is put at about DM 70 million. Behringwerke, the Hoechst subsidiary, is conducting clinical trials for the gene-spliced human insulin but the product is not a key component of the chemical giant's drugs portfolio. (Source: European Chemical News, 28 September 1987)

West Berlin to be site of new AIDS centre

West Berlin will be the site of the new FRG AIDS (acquired immune deficiency syndrome) centre, which will open officially next January. The FRG Federal Health Office (BGA) says that the centre will serve as a clearinghouse for information about the spread of the disease as well as a research institute.

The new centre will be housed in the Robert Koch Institute, itself a division of the BGA, but will operate independently. Its main tasks will include collecting data on AIDS epidemiology, standardizing diagnostic tests for HIV (human immunodeficiency virus), managing research groups already established in the FRG and conducting basic research into both the 'natural history' of the disease and into its psychosocial effects. Perhaps most importantly, the centre will be given the task of assessing AIDS policy in the various states and making recommendations to the FRG Government on how to proceed. The institute is expected to need roughly DM 5 million in start-up costs in 1988. (Extracted from Nature, Vol. 328, 13 August 1987)

'DESY' Synchrotron used for protein study

Synchrotron radiation, once only energy-dragging waste in high-energy physics, has recently proven to be a valuable resource in biological structure research. The high intensity and special quality of the X-ray light provided by the synchrotron makes it possible to rapidly and at the same time safely resolve the refined structure of complex biomolecules, even down to the atomic level. In addition, it can be used to record dynamic processes, such as "contact" and reaction between an enzyme molecule and its substrate molecule, in individual photographs. In order to use and extend these potential applications, the Max-Planck-Gesellschaft in Hamburg has recently set up three study groups for structural molecular

biology. The "source of light" for these groups, which are working closely with the University of Hamburg, the Hamburg Synchrotron Radiation Laboratory (HASYLAB) and the European Laboratory for Molecular Biology (EMBL) is the DORIS storage ring at the German Electron Synchrotron - DESY for short.

For the scientists in the three study groups for structural molecular biology, the high intensity of synchrotron radiation is of primary importance, because they are interested in the structural analysis of protein molecules. To this end, the molecules, which are either ordered crystals or in solution, are "illuminated" with X-rays of the appropriate wavelength; these rays are then diffracted in the molecules, depending on their structure, and fanned out into numerous single rays. From the intensity and direction of the individual partial rays, which are measurable using appropriate detectors, conclusions can be drawn about the structure of the proteins.

Because proteins yield only weak X-ray contrasts, analyses such as these using traditional X-ray tubes require very lengthy measurement times, of several hours up to several days. This is because in order to get the complete space structure of a molecule, diffraction patterns of it must be taken from many different directions. However, many proteins are too unstable and sensitive to stand up to such a tedious process; they change or decompose under the continual effect of high-energy X-rays.

This is the decisive advantage of the synchrotron: Its radiation, one hundred to one thousand times more intensive than that of an X-ray tube, reduces the measurement time to several minutes. Structural analyses can in this way be made of especially "sensitive" proteins rapidly, and thus at the same time safely. In addition, special experimental tricks can be used to record rapid reactions by a protein.

The three Hamburg study groups are working closely with various Max Planck institutes where the relationship between the structure and the function of biomolecules is being studied. One group, led by Professor Ada Yonath, is working with the Max Planck Institute for Molecular Genetics on elucidating the structure of ribosomes - the "protein factories" of cells in which all cell-specific proteins are produced, according to genetic information.

A second group, led by Dr. Hans Bartunik, which is co-operating with the department headed by Professor Robert Huber and Professor Dieter Oesterhelt at the Max Planck Institute for Biochemistry in Martinsried, near Munich, is concerned with dynamic aspects of protein structures, i.e., structural changes that turn up in certain proteins in the course of biological reactions. This includes proteinase, which reacts with other proteins - their respective "substrates" - something like a digestive enzyme, splitting and decomposing them.

The third study group, led by Dr. Eckhard Mandelkow and Dr. Eva-Maria Mandelkow, comes from the Max Planck Institute for Medical Research in Heidelberg. The Department for Biophysics there, led by Professor Kenneth C. Holmes, first conducted structural analyses using synchrotron radiation more than 10 years ago. At that time, it was a pioneering project that showed the value of the synchrotron as a resource in molecular biology through work on muscle fibres.

Mandelkow and his colleagues are also working on a special type of fibrous proteins, the microtubules. Components of the so-called cell skeleton, these are hollow, cylindrical strings whose walls consist of single, parallel-positioned and spirally wound tubuline molecules. (Extracted from Biotechnologie, May 1987)

Institute to focus on bio-information processing

Within the framework of new tasks for the nuclear research installation in Juelich (KFA), the former Institute for Neurobiology is being renamed the "Institute for Biological Information Processing" (IBI). It will conduct research in the area of information processing in biological systems.

Based on previous work done at the Institute regarding signal reception and signal transformation in photoreceptor cells, future research projects will be increasingly concerned with the explanation of secondary processes in cells, particularly signal amplification, signal transmission and integration, and adaptation and adjustment of cell-specific rhythmic activities. These problems will be researched in simple and easily accessible experimental objects, such as bacteria or cells which are specialized for one function only.

The capabilities of the human brain are among the most mysterious in nature, and science is still far from understanding them. At present, neurobiology offers the promising prospect of reaching conclusions regarding the functioning of neural circuits from the analysis of relatively simple neural networks in snails and crayfish.

Another approach to the use of biological mechanisms is through the analysis of signal paths in the cell. Receptor molecules from sensory cells can be combined with semiconductor elements to form artificial "sensors" which can be used for medical diagnostics and the control of foodstuffs. The change of state in certain proteins between two conformations is being discussed as a possibility for a "molecular switch". Interacting enzymes also may be used as building blocks in "bioelectronics". The basic research at IBI could make such future applications possible. (Source: Technologie Nachrichten, No. 454, 24 April 1987)

Information on Japanese biotechnology available via new data base

German enterprises and research facilities in the future will have direct access to current information concerning new developments in biotechnology in more than 2,500 Japanese research facilities. This will be accomplished through the new database BIJANCA at the Association for Biotechnological Research mbH (GBF) in Braunschweig. The database will be available at the end of 1987 for research work.

At present, according to the observations of the Federal Research Ministry, the Japanese are making considerable efforts to become stronger in modern bio-engineering. According to the estimates of the Japanese Biotechnology Development Corporation (BIDEC), the proportion of biotechnologies in the gross national product will presumably increase from the present 4 per cent to 10 per cent by the year 2000. Approximately 200 large and medium businesses from pharmacology, chemistry and the foodstuff industry have for years been preparing the construction of biotechnical business branches or have already put new products on the market. Even the Japanese steel industry and breweries are intensely interested in biotechnology.

The Ministry for International Trade and Industry (MITI) presented a corresponding "Technopolis Concept" for 18 developmental areas, already in 1980. Furthermore, in the meantime, 36 of the 46 prefectures have established biotechnical development associations to prepare the local medium and small industry for the new working methods. Improvements in fruit, vegetable, and flower cultivation by biotechnically derived, virus-free seed material as well as improvements in the embryo transfer technique for

quality enhancement of meat and egg production, and new methods of fish production are being emphasized. (Extracted from Frankfurter Zeitung, 5 February 1987)

France

AIDS campaign launched

A long-awaited national campaign to combat the spread of AIDS (acquired immune deficiency syndrome) in France was outlined by health minister Michèle Barzach at a cabinet meeting on 24 June.

The Minister has based her proposals on a report commissioned by her ministry last December and published at the beginning of June, from a multidisciplinary working party headed by social services minister Jean Choussat. The four-point national campaign embraces prevention, care, research and international co-operation.

The government's proposals also follow the working party's recommendations in emphasizing that there will be no programme of compulsory screening for HIV antibodies. Rather than a national screening campaign, which, it is argued, would be prohibitively expensive as well as ineffective, Barzach plans to make free, voluntary and anonymous screening widely available at special centres throughout France. There will also be a concerted information campaign, directed especially at young people and health workers, which will be launched in the cinema, on television, through posters and with 24 million brochures distributed to everyone on the electoral list.

Other preventive measures include the systematic, anonymous screening of blood whenever a sample is taken from a patient, the supply of syringes without prescription and freedom for manufacturers to advertize condoms.

With the search for an AIDS vaccine declared a cause "of national importance" to which the public is invited to donate, Barzach intends to provide an extra FF 100 million (£10 million) for research into new methods of treatment and diagnosis and the development of a vaccine. Meanwhile, eleven centres will be opened in October in Paris and other French cities for the care and monitoring of AIDS patients. In addition, it is intended that general hospitals should create small AIDS units, with up to 20 beds and with an emphasis on day-care where possible. (Extracted from Nature, Vol. 328, 2 July 1987)

Joint AIDS project set up

Institut Mérieux is joining forces with Cambridge Bioscience, the Worcester, Massachusetts-based biotechnology concern to jointly develop an AIDS vaccine.

Cambridge Bioscience is expected to spend between $2-3 million on retrovirus research and development this year. The company is currently investigating the use of an adjuvant from the plant, Quillaja saponica, to stimulate the immune system prior to vaccination in feline leukaemia therapy, a disease caused by a retrovirus.

The US biotechnology firm is not restricting its research effort to one approach. The project will look at recombinant vaccines, conventional vaccines, synthetic subunits of noninfective viral proteins and anti idiotypes (antibodies synthesized in response to AIDS antibodies). (Source: European Chemical News, 10/17 August 1987)

Hungary

DNA 'super-chain' developed

The world's longest artificial DNA-chain is said to have been generated at the Hungarian Academy of Sciences' genetic research institute at Szeged.

Scientists there have reportedly developed a chemical and enzyme method which makes it possible to put together a chain of 1,800 units. The Institute says that transplanted into a bacterium or other living bodies, the new DNA can generate protein which in turn can be used in human therapy.

With previous artificial gene-synthesizing methods only short DNA chains could be generated and the attachment of the parts needed a lengthy purifying process. The new method is claimed to reduce the time of the chemical synthesis by half.

The Institute has also announced the setting up of a joint Hungarian-Soviet research team in biotechnology. The Szeged Institute is to house the research projects in which seven Soviet bodies will participate. (Source: Manufacturing Chemist, September 1987)

Ireland

Guide to recombinant DNA regulations published

The National Board for Science and Technology (NBST) has published the National Recombinant DNA Committee of Ireland's booklet, Guide to Recombinant DNA Regulations in Ireland. The guide outlines the practices and procedures developed by the Committee since it was set up in 1981. It uses the US National Institutes of Health (NIH) DNA research guidelines as its model. Details from: Mary Gillick, secretary, Recombinant DNA Committee, NBST, Shelbourne House, Dublin 4, Ireland or on Dublin 683311. (Source: Biotechnology Bulletin, Vol. 6, No. 7, August 1987)

Re-equipped biotechnology plant opened

At a reception to mark the extended production facilities in Dublin, Jeremy Cook, Director of The International Biochemicals Group, said that the Group was now firmly established as, technically, the most advanced and experienced company in the field of industrial applied biotechnology.

The plant was opened by the Minister for Science and Technology, Ireland, Dr. Sean McCarthy T.D. following completion of an expansion plan that included the purchase and installation of some of the most sophisticated fermentation equipment currently available. This will enable the Group to triple its output of freeze-dried microbial products. The expansion has involved the strengthening of the research and development facilities and the recruitment of a number of additional specialist scientists.

International Biochemicals is committed to the development, manufacture and marketing of high-performance biotechnology products which provide environmentally safe solutions to problems currently being treated by less acceptable methods. Their products include systems that deal with harmful industrial wastes that are responsible for the contamination and pollution of rivers and seas.

The automatic fermenters and specially designed freeze-drier systems which allow micro-organisms to survive in suspended animation for up to two years,

make the laboratories into the most advanced facilities of their type in the world and give the Group a leading position in the field of applied biotechnology. (Source: Company News Release, 25 August 1987)

Israel

New test for rapid identification of bacteria being developed

Finding the appropriate antibiotic treatment for a given ailment depends on the rapid identification of bacteria in clinical specimens. But available test methods are tedious and often require long periods of incubation.

According to a Tel Aviv University news release, Drs. Eli Sahar and Raphael Lamed of the University's department of biotechnology are now working on a rapid, automated method that can quickly identify, enumerate, and analyse the antibiotic sensitivity of bacterial micro-organisms. It works by passing the bacteria through a focused laser beam that probes their optical properties.

Research has so far demonstrated the validity of the concept; testing has been done on a model system of urine infected with controlled numbers of E. coli. The determination of their antibiotic sensitivity has been accomplished in less than an hour. Identification of Streptococcus Pyogenes, common in throat infections, has also been done.

The new system will enable the physician to determine:

- The level of bacterial contamination in the analysed sample;
- The category of bacteria present;
- The presence and number of leucocytes in the urine.

In addition, the physician will be able to perform, in approximately half an hour, a complete antibiotic sensitivity test in order to determine the best drug for those patients whose urine was found to contain pathogenic bacteria.

Future research will seek to apply the new system to many additional areas of microbial analysis:

- Bacterial identification of clinical specimens of saliva, blood, and cerebrospinal fluids;
- Identification of bacteria in dairy and meat products;
- Environmental bacteriological control of drinking water, sewage, and other infected wastes;
- Quality control in the pharmaceutical and cosmetic industries.

The project will require approximately two more years of pre-industrial research and clinical testing, for which funds are currently being sought. (Source: European Science News, August 1987)

India

India carries out large-scale tests of anti-leprosy vaccine

India entered the race to develop an anti-leprosy vaccine last February when large-scale clinical trials of the indigenously developed ICRC vaccine began in the state of Maharashtra. Already, 2,500 healthy household contacts of leprosy patients have been vaccinated, and the figure will reach 40,000 by 1990.

The vaccine was developed in 1979 by Dr. Madhav Deo and his colleagues at the Cancer Research Institute (CRI), in co-operation with the Acworth Leprosy Hospital, G.S. Medical College and The Haffkine Institute, all in Bombay. The project is financed by the Indian Council of Medical Research in New Delhi.

The vaccine contains gamma-ray-inactivated ICRC bacilli, named after the Indian Cancer Research Centre (ICRC), the previous name of CRI. The bacilli are a group of leprosy-derived slow-growing mycobacteria that have been cultivated repeatedly from human lepromata for the past 20 years. Although the exact taxonomical position of the ICRC bacilli is somewhat uncertain, they supposedly belong to the Mycobacterium avium intracellular complex. The fact that the bacilli exhibit antigenic cross-reactivity with M. leprae, especially with reference to T-cell immunity, the dominant host defence against the leprosy germs, forms the scientific basis for the use of ICRC bacilli in the preparation of an anti-leprosy vaccine.

Since 1979, the vaccine has been administered in phase 1 and phase 2 clinical trials to patients with lepromatous leprosy and to healthy subjects in an endemic area. The vaccine enhanced immunity in both patients and healthy subjects. It was cleared for large-scale clinical trial by the Drug Controller of India for both immunotherapy and immunoprophylaxis in October 1984.

A pilot project conducted during the past three years on about 200 healthy household contacts of leprosy patients shows that the vaccine has no untoward side-effects. Fears that lepromin-positive healthy contacts may develop hypersensitivity to leprosy antigens resulting in nerve damage have been set to rest.

The Maharashtra trial is the first ever large-scale clinical trial of a vaccine containing cultivable leprosy-derived mycobacteria. The vaccine is important for India, which accounts for one-third of the 12 million cases of leprosy world-wide. (Source: Nature, Vol. 328, 20 August 1987)

Cheaper loans for biotechnology projects

Banks and financial institutions (FIs) are likely to provide credit at cheaper rates for biotechnology projects.

This was indicated by Mr. M. U. Kini, Executive Director, Union Bank of India, at a news conference in New Delhi.

Mr. Kini said that for pre-commercial expenses on research, finance could be provided from the Venture Capital Fund which involved a service charge of 1 per cent. However, for commercial application of biotechnology, new norms for lending on softer terms would have to be worked out since it was a new area.

The Union Bank held a one-day seminar on productive harnessing of biotechnology. The objective of the seminar is to create an awareness among banks and FIs about the vast potential that modern biotechnology holds for development.

Mr. Kini said the banks could consider financing seedling and such projects based on biotechnology which offered vast scope in health care, food industry, animal husbandry and horticulture and agriculture. (Source: Financial Express, 28 July 1987)

Industry told to transfer biotechnology to farmers

The Agriculture Minister, Dr. G.S. Dhillon, has called upon the industrial and commercial enterprises interested in agriculture to carry biotechnology to the real users - the farmers. They should co-operate with scientists in concerned research organizations and undertake developmental activities like faster multiplication and spread of proven technology into the fields, he has said.

Dr. Dhillon said the Government attached high priority to research in biotechnology. It had set up a separate department of biotechnology. The facilities required for further research in this field were being created in the leading institutes to bridge certain technological gaps with particular reference to oilseeds, pulses and coarse grains.

Biotechnology in agriculture, the Minister said, was of special relevance to India where about 67 per cent of the cultivated areas was under rain-fed conditions. The high-yield potential and drought tolerance for the crops grown could be combined by the application of biotechnology. Modern tools of biotechnology could also create a wide genetic base for resistance to diseases and pests. It could also play a vital role in biological nitrogen fixation. (Source: Financial Express, 28 July 1987)

Uniform import duties sought on R&D items

In an attempt to improve the growth of the domestic biotechnology industry the Government will increase the upper limit for duty-free import of materials required for research and development. The new limit will be Rs 5 lakhs, up from Rs 1 lakh, according to Dr. S. Ramachandran, Secretary in the Department of Biotechnology.

In his keynote address at a seminar on biotechnology in New Delhi, Dr. Ramachandran said that the Department had asked the Finance Ministry to apply uniform import duties on capital equipment for research and development activities. A flat rate of 85 per cent has been suggested and further concessions are expected.

The seminar, organized by Union Bank of India aims to establish a working relationship between entrepreneurs and scientists on the one hand and financial institutions on the other.

Dr. Ramachandran said that it was now to private industry in the country to assume a major role in the fast growing field of biotechnology. Fifteen business houses at present were examining product lines to invest in. However, he said the major obstacle, both the Government and the industry faced was the lack of competent manpower.

The Government's effort in the next few years will be aimed at building links between the research institutions and industry.

According to a background paper prepared for the seminar, there are 60 research institutions in the country engaged in the field of biotechnology. However participants said there was a need for a centralized research facility. (Source: Times of India, 29 July 1987)

Italy

Italy joins international gene mapping study

Dr. Renato Dulbecco will direct the Italian part of the gene mapping project and co-ordinate U.S. participation.

At present Italy is expected to allocate 1.5 billion lire to this project. This National Research Council (CNR) strategic project will then require re-financing if research is to be carried out in depth. The 23 pairs of chromosomes will be divided among the various countries. Italy will work on chromosome 22. Despite its small size, chromosome 22 contains some interesting genes, including a DNA segment in which translocation of an oncogene occurs, producing chronic myeloid leukaemia; the gene of the light chain of haemoglobin and another gene which is believed to be responsible for the development of the Ewing tumour, which occurs in children. Professor Alberto Albertini, director of the Department of Chemistry at Brescia University and in charge of the strategic projects on advanced technologies at the CNR, explains: "This project will involve a number of subgroups, and the plan is for one of these subgroups to work on traditional genetic techniques and chromosome sorting. The latter procedure enables us to isolate and purify large quantities of chromosomes". Expertise in this technique has been acquired in Italy by the Bologna Institute of Cytomorphology.

A second subgroup will deal with DNA analysis techniques, the most important part of the programme. The work in this field will be done by the laboratories of Rome, Naples, Pavia and Milan, which represent the leading CNR research areas. Data management and sorting constitutes another vital point of the programme. In this connection the researchers will be able to count on the flow of information from Los Alamos and Heidelberg (FRG), which are the major data banks, providing the whole world with information on DNA. The operating units involved will be those of Turin and Milan and the Bari CNR Centre. The National Institute for Cancer Research in Genoa directed by Professor Leonardo Santi represents another area of expertise. Finally, in addition to the U.S., Japan and Canada, EMBO (European Molecular Biology Organization) also directs a European initiative for the co-ordination of the EEC countries along with Israel and Switzerland. (Extracted from Italia Oggi, 22 May 1987)

Japan

Harmonization of biotechnology regulations

Two Japanese government ministries are expected to standardize approval policies for the use of genetic engineering technology by the end of this year. Currently the Ministry of Health and Welfare is responsible for granting permission to drug firms while the Ministry of International Trade and Industry processes applications from the chemical industry to use the technology.

In those cases where the technology involves products that can be used by both sectors the approval needs to be granted by both Ministries. The two Ministries are planning to standardize the criteria for approval to help promote the fledgling genetic engineering sector. (Source: European Chemical News, 10/17 August 1987)

Protein bank

Thirty-five Japanese petrochemical companies and MITI - the Ministry of International Trade and Industry - have established a non-profit high technology organization known as the International Chemical Industry Promotion Organisation (ICIPO), to promote the exchange of international high-technology information and protein banking services.

The centre will accommodate a broad spectrum of projects, including pharmaceuticals, specialty

chemicals, agrochemicals, pulp and paper, and biotechnology, in addition to petrochemicals.

The banking programme is designed to form deposits of high-quality proteins that are looked upon as indispensable in chemical R&D. These proteins are expected to help develop not just enzymes and drugs but other advanced products including decomposable plastics, parts of electronics components and sensors.

The proteins will be lent to ICIPO member companies in order to enable them to cut down on R&D costs. MITI will urge both Japanese and foreign concerns to expand the new organisation as far beyond the original 35 member firms as possible. (Source: Manufacturing Chemist, September 1987)

Japanese firms plan seed group

Following a revision to Japan's main crop seed law, private companies are joining forces to establish an organization to register new grain varieties developed using biotechnology. About 60 firms, belonging to the Japanese Association for the Protection and Development of Plant Varieties, have asked that the plan receive sanction.

Under the revised law local self governing bodies have full authority to select and designate new seed varieties and encourage farmers to use them. In reality, however, it is expected that private firms will have problems competing with the Government.

Private firms are planning to establish the new organization to overcome this barrier. (Source: European Chemical News, 24 August 1987)

Heat resisting biosensor

A research group at Kyoto University of Industrial Art and Te tiles has developed a heat resisting biosensor capable of working at temperatures of around 60°C. The university group raised the sensor's heat resistance by penetrating the membrane for immobilizing the enzyme with plasma gas. (Source: European Chemical News, 27 July 1987)

The Netherlands

MIP delays bourse launch

Bio-MIP, the investment fund of the Netherlands' Maatschappij voor Industriele Projecten (MIP), which has biotechnology interests, is delaying its listing on the Amsterdam stock exchange's parallel market until spring 1988 at the earliest.

The MIP now has 12 partners from US high-tech companies, most of them in electronics, computers and biotechnology. By delaying the introduction of Bio-MIP to the bourse, MIP will be able to add more biotechnology companies to the fund, thus making it more attractive to investors. MIP plans to expand its American high-tech company portfolio from 12 to 17 by spring 1988, with several of its new participants being biotechnology firms. (Extracted from European Chemical News, 21 September 1987)

Shell, Gist Brocade joint venture

Dutch biotechnology group Gist Brocades hopes to complete negotiations in the summer to set up a joint venture with Shell Petroleum. The venture, for which negotiations were announced last December, will produce fine biochemicals, biopolymers and industrial enzymes in a 50/50 deal with the Royal Dutch/Shell subsidiary. The new company is expected to have a turnover of 300 million guilders and affect 800 workers. Gist Brocade has said it was struggling with an increased overcapacity of 30 per cent, due to cancellation of orders for dry yeast from African countries. It said first quarter figures had confirmed predictions that cyclical market conditions, lower profit margins and currency fluctuations would continue to affect company results negatively. (Source: ANP News Bulletin, 24 April 1987)

Sweden

Recombinant-DNA regulations

Sweden will not establish a special control panel or licensing agency for recombinant-DNA technology. Moreover, the Government is taking steps to eliminate existing regulations requiring special permission to launch gene-splicing R&D and production.

The ruling, which has already received the approval of Parliament, is in line with recommendations of a special commission established by the law-makers in 1984 to investigate the need for tighter controls of recombinant-DNA activities. The Government concluded that existing licensing, controlling legislation and agencies - Occupational Health and Safety Board (OHSB) and Environmental Protection Board - are sufficient to cover these activities. An existing recombinant-DNA advisory board within OHSB will function as a "warning signal" to Government for ethical and humanitarian questions. (Source: McGraw-Hill's Biotechnology Newswatch, 15 June 1987)

Protein structures studied at BMC

With the help of powerful computers, it is now possible to "look into" molecules that form proteins, viruses, and other structures.

Pictures of the molecules are used in gene technology and for the efficient production of pharmaceuticals.

BMC in Uppsala is one of the leading centres in Europe for studying the structure of proteins.

The possibility of studying the relative position of atoms in molecules such as proteins, nucleic acids, and virus particles has increased dramatically in recent years. Developments in the field of computers are primarily responsible for creating these possibilities, since the process involves enormous quantities of information that must be processed.

Along with modern gene technology, this research can also be applied in protein engineering and pharmaceutical design.

Professors Bror Strandberg and Carl-Ivar Branden of the Department of Molecular Biology, BMC, Uppsala, have both worked in structural research for more than two decades. They have watched this research develop from purely academic research to research of great industrial interest.

The large pharmaceutical companies of the world have already established their own structural research laboratories with expertise in X-ray crystallography and computer graphics. The pharmaceutical industry in Sweden wants to acquire this same experience and, for reason, want Swedish expertise in this field of biotechnology to keep pace with developments abroad.

For the structural research groups in Uppsala, this means purchasing their own interactive mini-supercomputer and more effective equipment for data collection (purchase of a surface detector). However, one bottleneck in this work is a lack of crystals for X-ray crystallography. Extremely high crystal is required. In the future, it may be possible to produce these crystals at zero gravity in

space. Another helpful tool may be crystallization robots, capable of conducting thousands of experiments each day.

The research itself will probably proceed from the study of individual molecules to large molecular complexes. These are often found in cell membranes and perform important functions in the regulation of passage through the membrane.

Industrial interest is so great today that commercialization of the achievements in this field may be expected within the foreseeable future, perhaps within a decade. (Extracted from Teknik i Tiden, No. 1, 1987)

United Kingdom

New centre to identify UK research targets

A centre for Exploitable Areas of Science and Technology is to be set up in the UK to try to help identify areas of research which can be developed commercially. The Centre is the first fruit of over three years' deliberation by the Advisory Council for Applied Research and Development (ACARD) on how the UK can best capitalize on its research effort.

Last year, ACARD said that the UK was in urgent need of a means of collecting statistics on R&D and of targetting industrial funding for service. Now, fifteen companies have been persuaded to support the new centre. The centre is likely to be based at one of the university science parks, probably at Warwick, and much of the initial funding is expected to be used to establish a database, which would be prepared along the lines of those found in the USA and Japan and include as many detailed statistics as possible on R&D in companies, the universities and at Research Council institutions.

Details of the centre, which will be independent of Government, are to be decided over the summer by a steering committee comprising the industrial companies, financial institutions and government departments which have provided finance for it. The committee will be chaired by Sir Robin Nicholson, technical director and former chief scientific adviser to Mrs. Margaret Thatcher.

The main objectives of the centre will be to monitor scientific developments in world markets and to find ways of forging better links between scientists, manufacturers and commerce. It is also expected that it will suggest which areas of research hold out the best promise of commercial exploitation. (Extracted from Chemistry & Industry, 20 July 1987)

Biotechnology Advisory Group to co-ordinate research

The Biotechnology Advisory Group, chaired by Professor Roger Whittenbury of the University of Warwick, plans to achieve greater co-ordination between Britain's research councils in the biotechnology field. Its members include representatives from the research councils, universities and such industrial companies as ICI and Glaxo. Early topics for discussion are likely to include the future of protein engineering, industrial safety and the deliberate release of recombinant organisms, and the use of biotechnology in the food industry. (Source: Biotechnology Bulletin, Vol. 6, No. 6, July 1987)

New guidelines

The Health and Safety Commission (HSC) has recently approved Advisory Committee on Genetic Manipulation (ACGM) guidelines on the large-scale use of genetically manipulated organisms. These have been drafted in response to the recommendations of the OECD's international study on safety aspects of genetic manipulation.

The new guidelines, in accordance with the OECD report's suggested approach, establish a minimum of containment known as Good Large-Scale Practice (GLSP). Criteria are given for low-risk organisms for which GLSP is appropriate. The guidelines also set out risk assessment principles for higher risk organisms, together with suitable forms of containment. They continue to require notification of all such work to the Health and Safety Executive on a case-by-case basis. Copies of the new guidelines are available from: ACGM Secretariat, Health and Safety Commission, 1 Chepstow Place, London W2 4TF or on 01 229 3456 ext. 6113/6148. (Source: Biotechnology Bulletin, Vol. 6, No. 6, July 1987)

DTI unit will nurture UK's biotechnology plant industry

The UK's Department of Trade and Industry has set up a Biotechnology Equipment Unit to foster the development of British process plant and instrumentation. The unit, part of the Department's Mechanical Engineering and Manufacturing Technology (MMT) division, is headed by Dr. Christopher Bowden, formerly of the DTI's Warren Spring Laboratory.

Encouraging the development of a healthy UK equipment supply industry is said to be the main objective of the unit during the next three to five years as new biotechnological processes move from the research stage, through pilot scale to production. The unit will make available to industry and research organizations market information to assist in defining technical needs and business opportunities, and guidance on the use of DTI services for developing exports and for improved overseas marketing. (Source: Manufacturing Chemist, September 1987)

New biotechnology unit opens

A biotechnology laboratory with a capacity for fermentation of up to 150 litres has been opened by Professor Heinz Wolff at South Bank Polytechnic, part of the London Centre for Biotechnology. Although the facility is aimed primarily at students, the biotechnology department will also encourage its use by representatives from industry, commerce and government institutions to carry out training, product/process development, and small-scale manufacture.

The London Centre for Biotechnology is a collaboration set up in 1984 between South Bank, Central London, and Thames Polytechnics. The new facility at South Bank complements the others in the consortium, and includes 'state-of-the-art' fermentation equipment as well as an integral effluent handling plant, believed by SBP to be the most sophisticated unit in the UK outside the Water Research Centre. (Source: Manufacturing Chemist, August 1987)

Unilever purchases plant breeding interests

In a move aimed at extending its growing agricultural interests, Unilever, the Anglo-Dutch consumer conglomerate, is to pay the British Government £66 million for the plant breeding assets of the Plant Breeding Institute (PBI) and the National Seed Development Organization (NSDO), which markets new varieties produced by PBI.

The plant science activities of PBI were not included in the package, but will be retained by the Agricultural and Food Research Council (AFRC) and

relocated in 1990 to the new Institute of Plant Science Research.

Unilever intends to allow PBI (to be renamed PBI Plant Breeding) to retain a degree of autonomy and will move its own pea- and bean-breeding programmes to PBI's Cambridge site. PBI's breeding programmes, for wheat, barley, potatoes and field beans, will be retained.

Most of Unilever's plant science research is carried out at Colworth in Bedfordshire, where it is best known for its work on cloning oil palms. Its current agricultural activities focus largely on plantation crops. The Colworth laboratory is also carrying out research on the genetic manipulation of oilseed rape. Although PBI has a rapidly expanding oilseed rape breeding programme, this was not included in the sale. Instead it will go to the Agricultural Genetics Company (AGC) in settlement of various claims that AGC has on PBI. AGC, set up in 1983, was given first option to exploit biotechnological discoveries made by AFRC. (Extracted from Nature, Vol. 328, 13 August 1987)

Drug company buys Biogen's Swiss research facilities

Glaxo, the UK's biggest drug company, has bought Biogen's Swiss research facilities for a performance-related sum which could be as much as $50 million - but could be worth much less. Glaxo acquired rights to two of Biogen's most interesting new drugs, interleukin-2 (IL-2) and granulocyte macrophage colony stimulating factor (GMCSF). Glaxo said the purchase was a strategic move, enabling it to leapfrog the three to four years it would have taken to build up Biogen's expertise. The facility will be renamed the Glaxo Institute for Molecular Biology. (Extracted from Biotechnology Bulletin, Vol. 6, No. 7, August 1987)

Scientists form British Bio-technology Ltd

When Monsanto (St. Louis, MO) bought up and then closed down the High Wycombe research laboratories of G. D. Searle, a group of senior staff raised $4 million of venture capital in London and then started British Bio-technology Limited (BBL) in Oxford. Still in its first year, the company has already exploited a discovery that may result in new or improved vaccines. It also has its first products on the market, a range of synthetic genes, and its first contract with SmithKline Beckman (Philadelphia, PA) covering thrombolytic agents.

The vaccine project is designed to overcome some of the problems of presenting antigens to the immune system in a way that provokes an adequate immune response. It is based on fundamental research on yeast molecular genetics that has been going on in Oxford's department of biochemistry under Susan and Alan Kingsman.

Vaccine development was not at the front of BBL's mind when it set up shop. More central to the aims of BBL then, as now, was the development of new therapeutic agents, particularly for diseases of bone and connective tissues. Research is being carried out on both small active-site inhibitors of enzymes and biologically active polypeptides with the emphasis on second-generation products, particularly polypeptides with fused or hybrid functional domains, selected with the aid of molecular modeling. (Extracted from Bio/Technology, Vol. 5, 1987)

New research centre

Twyford International will open a $10 million plant molecular biology research centre in Cambridge in February 1988. Over 30 scientists will work on plant biology and plant tissue culture research programmes related to developing agronomically better agricultural and horticultural crops with such features as disease and insect pest resistance, better yield and plant products modification. The development of virus resistance in such crops as cotton, melon and sugar beet will be tried. Genetic factors bringing longer shelf life of fresh green and root vegetables and tropical fruit will also be studied. This will involve identifying resistance genes to microbial pathogens that cause rot and spoilage by invading plant material injured during transport or storage. (Source: Technology Update, 13 July 1987)

Biotechnology project folds

The Scottish Development Agency has withdrawn from a joint project with Damon Biotech to start-up a biotechnology plant at Livingston, near Edinburgh.

The project began in 1984 and a plant to manufacture monoclonal antibodies should have come on-stream this Autumn. The bulk of the original £40 million cost was to have come from the SDA and institutional investors.

However, changes in forecasts for antibodies demand halted the project last Summer, and now the SDA has said it must look for an alternative occupier of the factory. Damon had talked of producing tpA at the plant, instead of monoclonal antibodies, but the SDA has decided against the change because of the ever-lengthening period the factory would be empty. (Source: Manufacturing Chemist, July 1987)

United States of America

All field-test permits now under US 'national' system

Regulations promulgated on 14 June are the US Department of Agriculture's way of "trying to establish a national system that utilizes expertise in each state's department of agriculture, but has a uniform structure".

Environmental-release requests will get a preliminary study by USDA within 30 days, then be passed to state agricultural authorities, who will report back to USDA with findings and questions. Final decisions will come down within 120 days of application. Because of data requirements, companies "will probably apply for sequential permits, first for survival, then yield, then multiple states". USDA will consult other agencies when necessary. (Source: McGraw-Hill's Biotechnology Newswatch, 20 July 1987)

OSHA to press AIDS safety for health workers

For the first time, the US Government will begin enforcing measures to protect workers against occupational exposure to biological hazards such as viruses. After 10 months of intensive internal debate, the Occupational Safety & Health Administration has adopted a broad-based plan to protect five million health care workers - from clinical chemists to emergency room staff - against workplace exposure to blood-borne infectious diseases.

The three-part programme, developed in co-operation with the Department of Health & Human Services, was outlined to a House Government Operations subcommittee.

The programme includes:

- Instituting an extensive education, training and information campaign to ensure employer and employee knowledge of and compliance with

non-mandatory guidelines on AIDS and Hepatitis B issued in recent years by OSHA and the Centers for Disease Control.

- Enforcing those guidelines under existing general OSHA powers, including development of targeted inspection plans for hospitals and other health care facilities, with employers liable to fines of up to $10,000 for each violation.

- Placing adoption of a permanent standard for blood-borne diseases "on a fast track", leading to approval in 18 to 24 months.

OSHA's action comes in response to health workers' increased concern over their risk of exposure to AIDS.

CDC recommends AIDS prevention precautions

The Centers for Disease Control recommends the following precautions to protect health care workers from workplace exposure to the AIDS virus:

- Careful handling of needles, scalpel blades, and other sharp items.

- Disposal of needles, syringes, scalpel blades, and other sharp items in puncture-resistant containers; no recapping, bending, breaking, or other hand manipulation of needles.

- Use of personal protective equipment, such as gloves, gowns, masks, and eye-coverings, when exposure is possible to blood or body fluids; thorough, immediate washing of hands if contaminated by blood.

- Use of mouth pieces, resuscitation bags, or other ventilation devices to avoid mouth-to-mouth resuscitation.

- Educating all health workers, especially pregnant women, on steps to prevent virus transmission.

- Strict adherence to infection control rules on sterilization, disinfection, housekeeping, and waste disposal.

(Abstracted with permission from Chemical and Engineering News, 3 August 1987. Copyright (1987) American Chemical Society)

No AIDS in Antarctica

Anyone intending to spend the entire winter at any of the US National Service Foundation-supported Antarctic stations must be tested for the presence of antibodies to HIV, the virus causing AIDS. Those testing positive will not be allowed to spend the winter. That policy was announced in a letter from the director of the Division of Polar Programmes. The new policy does not apply to summer-time investigators. It takes effect in the 1988 austral winter. (Source: Nature, Vol. 328, 20 August 1987)

Presidential Commission on AIDS set up

President Ronald Reagan has announced the membership of the commission that will advise him on "a full-fledged strategy for battling AIDS (acquired immune deficiency syndrome)" at the end of July. The commission will make its first report to the President in 90 days, with a final report within one year. The panel's brief is comprehensive. It will make recommendations on research, treatment, ethics and international participation.

Called the US Presidential Commission on the HIV Epidemic, named after the virus that causes AIDS (acquired immune deficiency syndrome), the panel at its first meeting in September, heard how the Public Health Service and other federal agencies are combating the AIDS pandemic, but they also listened to testimony suggesting that the Government is not doing enough to counter the crisis, and that federal efforts are disjointed and suffer from credibility problems.

The commission has much to do before it prepares its preliminary report in December, and its final recommendations to the President by next September. The commission is chaired by chairman Eugene Mayberry, head of the Mayo Foundation. The commission is scheduled to meet in New York, San Francisco and Nashville during the next year. (Extracted from Nature, Vol. 328, 30 July 1987 and Vol. 329, 17 September 1987)

Genetic engineering gets confidence vote

A report prepared by a panel of five top scientists for the US National Academy of Sciences, concluded that the risks of releasing genetically engineered organisms into the environment are no greater than the risks of releasing organisms altered by conventional techniques.

It recommended that genetic engineering be regulated on the basis of the organism and the environment into which it will be introduced, rather than the process by which it was produced.

"There is no evidence that unique hazards exist either in the use of recombinant DNA techniques or in the movement of genes between unrelated organisms", the report stated.

The panel noted the technology used in genetic engineering has been used in "hundreds of laboratories for more than a decade". While the technology has resulted in many gene transfers between different kinds of organisms, "no hazard peculiar to the use of recombinant techniques has yet surfaced, and there is a broad consensus among biologists that the techniques are safe", the report said.

Opponents are concerned that the new genes in the altered plants and bacteria will have unpredictable effects in the changed organisms and could allow it to spread out of control or cause disease.

But the panel scientists said such an occurrence was unlikely because an organism's ability to spread rapidly or cause disease involves a number of genetic traits, each determined by many genes.

Genetic engineers can only transfer a small number of genes, which are predictable and well understood from laboratory studies, the panel said. The degree of regulatory caution in controlling releases should depend on the ecology of the unaltered organisms, the panel added.

The biotechnology industry, which has been pushing for less restrictive regulation, gave the report a favourable review. (Extracted from Chemical Marketing Reporter, 24 August 1987)

New York launches test programme for AIDS virus

New York, the US state with the second highest incidence of acquired immune deficiency syndrome (AIDS), will be the first to take steps on its own to assess the spread of the AIDS virus within its borders. Governor Mario M. Cuomo announced that the New York state health department will screen 100,000 blood samples selected randomly from routine

specimens taken at state hospitals for antibodies to human immunodeficiency virus (HIV), the virus causing AIDS.

The study will give public health officials an indication of how far the virus has spread through different sub-populations and regions of the state. This will allow them to assess the burden the disease will place upon health care and insurance systems, and help to target preventive educational campaigns.

The tests will be anonymous, and patients will not be notified of the results. The samples used in the study will be accompanied only by clinical information that will enable researchers to determine if the donor fell into a high-risk group, such as homosexuals or intravenous drug abusers. Testing will begin in October, and is expected to take six months to a year to complete.

The New York study will be one of the first nonmilitary sampling programmes in the US. The Department of Defense has been screening its personnel since 1986. But HIV frequency in the military is unlikely to be representative of the population at large.

The protocol for the nationwide random survey for HIV, announced by Secretary of Health and Human Services Otis Bowen at the Third International Conference on AIDS in June, is still being developed. The national survey is intended to test the blood of 45,000 people in order to estimate the number who are infected with the virus in the United States. (Source: Nature, Vol. 328, 13 August 1987)

AIDS education programme

Plans for a co-ordinated, multi-agency education campaign aimed at slowing the spread of AIDS (acquired immune deficiency syndrome) are a bit confused. Public service announcements await approval, publicity for the campaign has been muted and a national mailing of an information brochure has been abandoned, but the Centers for Disease Control (CDC) are pushing for an "AIDS Prevention Month", despite conflicting signals on how to proceed from the highest levels of government.

The CDC campaign's theme is "America responds to AIDS", and will involve government agencies working in partnership with state, local and private groups already coping with the AIDS pandemic. CDC is also sponsoring forums to discuss how to make these efforts more successful. Five cities will receive a heightened level of attention, including underwriting for television programmes, information desks in pharmacies and more intensive public relations campaigns. (Extracted from Nature, Vol. 329, 17 September 1987)

California court forces closure of biology laboratory

Legal precedent was set earlier this month when the state Court of Appeal ordered research to be halted at the pharmacology school of the University of California at San Francisco. It is believed to be the first time that a court has shut down a major university facility to allay public fears over the dangers of research in molecular biology.

The action is the second of two unexpected defeats for the University in a long-running battle with a neighbourhood association opposing the opening of a laboratory at Laurel Heights in San Francisco. In July the Court of Appeal ruled that the University's environmental impact report was inadequate. In August this was followed by an injunction to close the laboratory for 90 days. Only rapid action by the state Supreme Court saved the research programme from destruction. Two days into the shutdown the court granted the University temporary emergency relief from the injunction but followed this with a decision barring the laboratory from using radioisotopes.

To restart its plans, the University must now win state Supreme Court appeals on both the injunction and the adequacy of the environmental impact report. The court has 60 days to decide whether to hear the appeals or simply to let the lower court decision stand. (Extracted from Nature, Vol. 328, 20 August 1987)

New centres to study human genome

Two of the US Department of Energy's national laboratories, Los Alamos National Laboratory and Lawrence Berkeley Laboratory, are setting up research centres to study the human genome. The research will focus on physical mapping of genes, cloning, and eventually full sequencing of the genome. The laboratories will also explore possibilities of co-operative research programmes with the private sector to develop commercial applications of human genome research. The Department of Energy says that this research effort stems from the department's mission to evaluate the health effects of energy systems. The Los Alamos laboratory is currently the home of GENBANK, a computerized DNA database. (Reprinted with permission from Chemical & Engineering News, 14 September 1987. Copyright (1987) American Chemical Society)

Bioscience centre established at Lehigh

A Center for Molecular Bioscience & Biotechnology has been established at Lehigh University. An interdisciplinary unit, the Centre will draw on 26 scientists in biology, chemistry, chemical engineering, psychology, and civil engineering. Arthur E. Humphrey, Theodore L. Diamond, Professor of Biotechnology and executive director of the new Centre, notes that the Centre's activities will be divided into generic research, industrial research partnerships, and specialized academic programmes. Research studies will focus on targeted drug delivery, clinical methods for diagnosing cancer, biosensors for monitoring cellular growth systems, and surface interaction of cells and polymers. (Reprinted with permission from Chemical and Engineering News, 6 July 1987. Copyright (1987) American Chemical Society)

First EPA biotechnology approval for IMC

The US Environmental Protection Agency has granted permission to the International Minerals & Chemical Corp subsidiary, IMCERA Bioproducts, for the manufacture of the genetically engineered micro-organism, Escherichia Coli K-12, in the production of its IGF-I growth factor for cultivating tissues and cells. The company said the action, which followed testing and evaluation through the EPA's pre-manufacturing notice procedure, marked the first time such a biotechnological product has undergone successful review by the federal agency.

The EPA announcement said, "Escherichia Coli K-12 is a non-pathogenic organism commonly used in laboratory operations, well adapted to life in laboratories and industrial fermenters, but not in mammals. Because of these properties it is useful for laboratory studies and commercial fermentations and does not affect humans".

IMCERA Bioproducts, until recently known as IMC's IMCELL Products Division, said it plans to use the micro-organism for commercial production of the

insulin-like growth factor for use in research institutions and pharmaceutical companies in the USA and other countries. (Source: Manufacturing Chemist, July 1987)

French company sets up subsidiary in US

IBF, a biotechnology subsidiary of the French pharmaceutical company, Rhône-Poulenc Santé (RPS), has set up a company in the USA - IBF-Biotechnics - as part of the increasing internationalization of Rhône-Poulenc. IBF specializes in culture techniques and biological purification.

While RPS's aim has been to consolidate in Europe, its American policy has been markedly different (except in the case of US Ethicals), partly on account of the high price of buying USA companies but also because it is the nature of the product which determines the purchase. The presence of active R&D in a company RPS may contemplate buying in the USA is seen as crucial to eventual success in the American market.

Meanwhile, RPS has said it will have completed its restructuring programme by the summer months and the plan will go into operation in September. (Source: Manufacturing Chemist, March 1987)

Escagen, Inc. rises from Chapter-11 ashes of IPRI

On 30 June, the International Plant Research Institute (IPRI) goes back into bankruptcy court in San Francisco with a plan for re-organization, made possible by fresh cash receipts of $2.5 million, plus 1.3 million shares of brand-new Escagen, Inc., also of this city.

With permission of the bankruptcy court, IPRI's officers formed a new corporation, Escagen, to which IPRI transferred all of its assets - but none of its $6.5 million liabilities. On 28 March 1987, Escagen put an initial public offering of two million shares on the American Stock Exchange, underwritten by Prudential-Bache Capital Fund N.Y.

IPRI, a closely held private company, sought Chapter-11 protection on 31 January 1985. It spent the next two years doing contract research to improve food plants by molecular biology and tissue culture. (Source: McGraw-Hill's Biotechnology Newswatch, 15 June 1987)

USSR

AIDS tests compulsory

The Supreme Soviet has taken powers to authorize obligatory tests for AIDS (acquired immune deficiency syndrome , according to a statement by TASS, the Soviet news agency. Tests will be administered to both foreigners and Soviet citizens when there are grounds for believing that people have been infected with the virus. Foreigners and stateless persons refusing to be tested when asked are liable to deportation under the regulations. Anybody deliberately exposing others to the risk of infection may be imprisoned for up to 5-8 years.

According to the president of the Soviet Academy of Medical Science, Dr. Valentin Pokrovskii, on 17 August, there are some 130 people in the Soviet Union infected with AIDS, most of them foreigners. The only Soviet citizen with AIDS (out of 19 carriers) is said to be responding to treatment with two Soviet medications. In Bulgaria, testing for AIDS has been made compulsory for all newly-weds and pregnant women.

The Soviet Union made a disproportionately large contribution - $1 million in 1987 - to the World Health Organization's programme on AIDS. In addition, the Politburo is taking steps to control the spread of the virus within the country's borders.

The Soviet Union is preparing a massive information campaign on AIDS. TASS news agency says that the national programme will provide a network of specialized laboratories for the diagnosis of HIV infection and monitoring the spread of the virus. Until recently, the Soviet Union had to import tests for antibodies to HIV, but researchers have now developed domestic tests.

The Soviet Union has been slow to respond to the problems posed by AIDS in comparison with some East European countries. In Eastern Europe, however, the general pattern now emerging suggests that the theory that AIDS is a disease of capitalist countries no longer applies.

Poland and Hungary have set up "help lines" to answer callers' questions. In a recent interview, Bulgaria's deputy health minister, Mr. Lyubomir Shindarov, admitted that there were no "state, social, racial or religious boundaries for AIDS".

The communist countries still report few cases, mostly involving haemophiliacs and homosexuals. In no East European country have the reported numbers of people with the full-blown disease reached double figures; and Hungary, with 137, has the highest reported number of carriers of the virus. The progress of the disease is surely greater than such figures suggest, although Soviet and East European travel restrictions put in place long before AIDS became a menace, have probably helped to limit its spread. Whatever the true count, governments are worried enough to have dropped their earlier complacency.

Bulgaria introduced rules similar to Russia's last month. The Government intends to test all foreigners who come to Bulgaria for more than a month, as well as all Bulgarians who return after more than a month abroad; newlyweds and pregnant women also face mandatory tests. In all, Bulgaria claims it will test 700,000 people each year, out of a population of 9 million.

Testing, especially of blood-donors, has been stepped up throughout Eastern Europe. Poland says it has tested more than 200,000 people, East Germany nearly one million. Some countries are trying to make provision for voluntary testing for anyone who wants it. (Source: New Scientist, 20 August 1987 and The Economist, 19 September 1987)

New biotechnology plants

The Soviet Union will build biotechnology R&D laboratories and pilot plants at Chemyakin Biotechnology Institute (Moscow) to produce plant and animal growth regulators, monoclonal antibodies, polymers for use in chromatographic separation media and low-molecular weight proteins. An international consortium including Sulzer Biotech Systems has the contract. (Extracted from Chemical Marketing Reporter, 6 July 1987)

C. RESEARCH

Research on human genes

How cells get the message

The idea of cells as social creatures, engaged in constant communication with their environment and with one another, is not new. In the late 1960s and early 1970s, Earl Sutherland laid out the basic steps

involved in cells' responses to hormones, describing a signal discriminator (receptor), which activates a catalytic subunit inside the cell, which in turn activates 3'-5'-cyclic adenosine-5'-monophosphate (cyclic AMP), which through several more metabolic steps results in activation of functional proteins.

However, in the past few years, the techniques of molecular biology, particularly recombinant DNA technology, have enabled cell biologists to probe the communications apparatus of the cell in much greater detail. What they have found proves that the metaphor of the cell as "newsgatherer and interpreter" holds up very well, right down to the most fundamental level.

At a seminar at the National Institutes of Health in Washington, DC,* Allen Spiegel, Michael Gottesman and Robert Adelstein reviewed the mechanics of signal transduction in cells and discussed the latest advances in understanding how cells get the news. The "news" is signals, so-called first messengers, that originate outside the cell. These include many types of substances - hormones, amines, peptides, and glucose and other nutrients - as well as energy, such as photons.

Perhaps the most intriguing - and promising - aspect of how cells get the news is the insight it has provided into cancer. It is fairly well accepted that many, if not all cancers, are initiated by oncogenes, which, when turned on, disrupt the orderly growth of cells. The oncogene alters the DNA blueprint, cutting the cell off from normal communications and allowing it to grow wildly. Scientists are beginning to match the protein products of various oncogenes to the proteins involved in normal signal transduction. Molecular analysis of the Rous avian sarcoma virus, which carries the ras oncogene, reveals that this gene is very similar to the G-proteins. Similarly, other oncogenes have been found to be structurally analogous to certain growth factors, and receptors for growth factors.

Thus, the theory goes, cancer results when the protein product of an oncogene mimics a normal protein involved in the chain of intracellular communication, causing either the wrong kind or too much news to be assimilated. For example, the oncogene erb b is an altered form of the receptor for epidermal growth factor. Unlike the normal receptor, it lacks regulatory sites that allow it to be turned off. A vicious cycle establishes itself: the cell keeps making growth factor, which causes it to grow. The more it grows, the more growth factor it makes, and so becomes a cancer. This view of cancer opens a new field for possible therapies. Substances that inhibit the key enzyme tyrosine kinase, for example, could stop a cancer at its source - a vast improvement over the current approach of blasting cancerous and normal cells alike with highly toxic drugs. However, such a treatment is probably years away. At present, drug companies are more interested in the structure of the G-protein and ways to design drugs that will communicate directly with that protein rather than just clumsily block a particular receptor. (Extracted from New Scientist, 20 August 1987)

Maternal and paternal genes distinguished

Geneticists have known for some time that at least for some mammals, a developing embryo can distinguish whether a particular gene comes to it from its father or its mother. The gene is said to carry an imprint - a distinguishing trait of some sort - that marks which parent it came from. Now a group of researchers from the Department of Molecular Embryology at Cambridge University in England and another group from Ludwig Institute for Cancer Research in Montreal and Mount Sinai Hospital Research Institute in Toronto independently propose that this imprinting occurs through the degree of methylation of the DNA as it is inherited from the parent. Both groups used the same experimental strategy; they inserted extraneous but easily recognized pieces of DNA into the gametes of mice and observed the inheritance of this DNA through several generations. Four of five gene segments studied by the Canadians and one of seven studied by the British group showed significant differences in the degree of methylation of the DNA, depending on which parent the gene segment was inherited from. In both studies, a son who inherited the gene from his mother passed it on in the male form to his offspring, whereas a daughter passed it on in the female form.

Azim Surani and his colleagues at the AFRC Institute of Animal Physiology and Genetics Research at Babraham, Cambridge, have established that the maternal genome is essential for the development of the foetus itself. The paternal genome, on the other hand, is needed to form the extra-embryonic tissues, notably the placenta. Fertilized mouse eggs that have two sets of chromosomes which are both from females fail to thrive, because the placenta does not develop properly.

A rare mischance of human reproduction represents the opposite case. A fertilized egg can sometimes lose the maternal genome and have two sets of paternal chromosomes instead. This entity, known as a hyatiform mole, is a sort of runaway trophoblast, made up of tissues that normally form the placenta. It invades other tissues and may become malignant.

Imprinted genes also function differently in adults, and might have an impact on human genetic diseases. In Huntington's chorea, for instance, symptoms of dementia first appear in adolescence if the father has passed on the defective gene. If the gene is inherited from the mother, symptoms do not appear until middle age.

Genomic imprinting opens up new avenues of research for evolutionary biologists as well. Many animals other than mammals can reproduce asexually, through parthenogenesis. But something has happened to mammals. "It seems that through evolution the functions of the maternal and paternal genomes have become distinct. Thus it may be impossible to get 'virgin birth' in birth in mammals", says Surani. The division of labour may be linked to the evolution of giving birth to live young, nurtured in utero through a placenta. (Source: Chemical and Engineering News, 27 July 1987, p. 24 and New Scientist, 30 July 1987)

Similarities in cell membrane receptors

The structures of two proteins that span nerve cell membranes and regulate the flow of ions in and out are remarkably similar to each other, as well as to a receptor that performs the same function in muscle cells, according to FRG, UK, and US scientists. Researchers from the University of Heidelberg, the University of Cologne, and Max Planck Institute of Biophysical Chemistry deduced the structure of the receptor that binds the neurotransmitter glycine to brain cell membranes. The structure of the protein that binds another neurotransmitter, γ-aminobutyric acid (GABA), was determined by researchers at Genentech, South San Francisco, and at the Laboratory for Molecular Biology, Cambridge. When the neurotransmitters bind to their receptors, they inhibit nervous activity by allowing chloride ions to pass through the membrane into the cells. The receptors have about half of their amino acids in common and share features with the acetylcholine receptor in muscle, whose structure

* How cells Get the News, National Institutes of Health, 24 June 1987.

had been determined previously. (Reprinted with permission from Chemical and Engineering News, 20 July 1987. Copyright (1987) American Chemical Society)

Oncogene alters cell's architecture

A new kind of oncogene that appears to induce cancer by modifying a crucial protein component of the cell's structural scaffolding has been identified by a team of California researchers. The modified protein, called β-actin, is the most abundant structural protein of all replicating cells in the body. The researchers, led by John Leavitt of Linus Pauling Institute of Science & Medicine in Palo Alto, worked with cancerous cells containing a mutant form of the β-actin gene. Using genetic engineering techniques, they retrieved the mutant gene and inserted it into human cells in culture. Several of these previously normal cells then became capable of causing tumours when injected into laboratory mice. The scientists do not fully understand how the protein alteration could lead to uncontrolled cell division and invasive growth, which are the hallmarks of cancer. But Leavitt stresses that the transformation of a normal cell into a cancerous one probably requires several steps, and that a change in the β-actin gene may be just one of those requirements. (Reprinted with permission from Chemical and Engineering News, 20 July 1987. Copyright (1987) American Chemical Society)

Tolerance by process of elimination?

Exactly how the immune system recognizes substances from outside the body as foreign is a mystery immunologists would like to solve. Scientists have hypothesized that groups of T cells potentially capable of reacting with substances in the body are either eliminated early in their development or prevented in some way from becoming activated after maturation.

Recent evidence from scientists at the University of Colorado Health Sciences Center and the National Jewish Center for Immunology and Respiratory Medicine in Denver supports the clonal elimination theory. Using monoclonal antibodies, the researchers measured T cell concentrations of surface receptors for a protein crucial in antigen recognition processes. They found that T cells with the receptor are selectively removed from the body's T cell pool early in a process that may take place while the lymphocytes are maturing in the thymus. (Source: Science News, Vol. 131, 16 May 1987)

New Mab discovered

Konishiroku Photo Industry (Japan) has discovered a monoclonal antibody that could be used to treat cancer. It is an antibody to galactose-II, a substance that appears as cancer develops. The company says it has proof that galactose-II is a marker antigen produced by cancerous cells. The monoclonal antibody was used to treat a variety of cancer tissues, and was found to be effective in 50 per cent of the cases. Konishiroku Photo Industry worked in collaboration with researchers at Stanford University in California. (Extracted from Japan Economic Journal, 4 July 1987)

Method of linking substances to Mabs

Cytogen has patented its method of linking drugs or isotopes to antibody molecules aimed at specific disease sites in the body. The monoclonal antibodies, must be attached, or linked, to a payload substance such as a drug or isotope to create a conjugate. The antibody then carries the payload directly to the target tissue or antigen (e.g. a tumour, a blood clot or other diseased cell).

Current first-generation methods of linking substances to monoclonal antibodies coupled the payloads to amino acids situated randomly along the surface of the antibody. When coupling occurs on the amino acids in the antibody's variable region - the region where the antibody attaches itself to the target - the process is defeated. Cytogen's process links the payload to a single carbohydrate on the constant (i.e., non-variable) region of the antibody, far away from the antigen-binding region. Cytogen's linkers are functionally active, so they can either bond the payload permanently to the antibody or release the payload at some specified signal. The released payload can then act on nearby cells. The same process can be used to detect metastases. The patent protects the specific use of the carbohydrate linking site and the releasable linkers. (Extracted from New York Times, 1 July 1987)

Possibilities for gene transplants

A new gene transplantation technique could lead to the development of treatments for otherwise incurable genetic diseases, according to R.S. Kucherlapti of the University of Illinois. A gene can be introduced into a precise location in a cell's complement of chromosomes or modify or inactivate a particular gene. Initially, the method will be used in basic research and in developing laboratory animals bred specifically for gene defects comparable to those of important human hereditary diseases. There are over 3,000 human diseases stemming from one gene that is defective or missing from cells.

The method is based on a well-established process in which part of a cell's DNA may be exchanged with a closely matching piece of DNA to help repair a defect. A piece of transplanted DNA will find a matching piece in a cell's genes because of their close similarity. The efficiency of this method has been increased recently by using enzymes to make specially located cuts in the transplanted DNA, thus activating a cell's natural repair procedures. The technique could eventually be used to put corrective genes in a patient's cells that have been kept alive in the laboratory. The cells could be transplanted back into the patient, and their influence could eliminate symptoms of a disease. (Extracted from New York Times News, 29 July 1987)

Nerve growth factor receptors could be used against tumours

Nerve growth factor receptors on some tumour cells could allow drugs to be targeted to the tumour, greatly reducing side effects, according to researchers at Harvard and Yale Universities. The receptor is present in tumours of certain cells of the peripheral nervous system, skin pigment cells and certain glands. The receptors are not normally present after infancy. Coupling nerve growth factor to lipid spheres containing a cytotoxic drug allows the entire complex to enter the tumour cell, thus killing it.

Researchers at Scripps Clinic have developed bispecific antibodies that link leukaemic white blood cells to T lymphocytes. Bringing the cells into close proximity allows the lymphocytes to attack the leukaemic cells. Just two billionths of a gram of the antibody was sufficient to cause the death of 33 per cent of the tumour cells in laboratory tests. (Extracted from New Scientist, 11 June 1987)

Yeast or human, this gene's the same

In a discovery that could influence laboratory research on human cell growth, scientists in London have cloned human genetic material they say is essentially the same as a gene in yeast that controls

cell reproduction. The gene, called cdc2 in the yeast Schizosaccharomyces pombe, is important in regulating the micro-organism's cell cycle, and its counterpart in humans may play a similar role, say Melanie C. Lee and Paul Nurse of the Cell Cycle Control Laboratory at the Imperial Cancer Research Fund facility.

By inserting segments from a "library" of human DNA into yeast cells lacking active cdc2 genes, the researchers isolated human genetic material that could substitute for cdc2 and initiate cell division in the cdc2-deficient yeast cells. Lee and Nurse report that the human gene has been sequenced, and its structure is very similar to that of the cdc2 gene. The authors say the S. pombe system can be used for isolating other genes that resemble those found in the yeast. (Source: Science News, Vol. 131, 16 May 1987)

GABA receptor genes cloned

Scientists at the Medical Research Council's new Molecular Neurobiology Unit in Cambridge have cloned the DNA from the genes for the GABA receptor, a key molecule in the complex business of transmitting information around the brain. Knowing the gene sequence opens the way for further understanding of the structure of the receptor, how it works, and what happens when it goes wrong. The same molecule is the target of widely used anti-anxiety and anaesthetic drugs, and a structural model of the receptor could help in designing improved versions of such drugs.

GABA, or gamma-aminobutyric acid, is the most important inhibitory neurotransmitter in the brain. When it binds to its receptor, a protein embedded in the cell membrane, it reduces the excitability of that cell. In an effort to gain greater insight into that process, Eric Barnard and his colleagues set out to unravel the molecular structure of the receptor protein. Important contributions were made to this team effort by Peter Schofield and Peter Seeburg, originally at Genentech in the US and now at the University of Heidelberg.

While GABA receptors are ubiquitous in the brain, their concentration is very low, but the chance discovery that certain drugs acted very specifically on the GABA receptor itself helped Barnard's group to isolate a pure form of the protein.

About 10 years ago, groups at the Ferrosan Laboratories in Denmark and at Hoffman La Roche in Switzerland were looking at the binding of radioactively labelled form of the tranquilliser diazepam. At that time, although doctors were issuing anxious patients with millions of prescriptions for such drugs, no one knew how they exerted their tranquillising effects. Both groups found that diazepam bound very strongly to a protein in the cell membranes of brain tissue.

Later experiments showed that these benzodiazepines had an even stronger affinity for the membrane protein if GABA was present; and that they enhanced the effects of GABA on the flow of ions in and out of the cell. It was impossible to avoid the conclusion that GABA and the benzodiazepines were acting on very closely associated receptors, if not the same receptor. The question of whether a single protein was involved could be answered only by isolating it and examining its properties.

The purification of the proteins that act as receptors for neurotransmitters is difficult, for two reasons. The first is that they are not very abundant; the GABA receptor represents between 0.01 to 0.001 per cent of the weight of the total protein in the brain. Secondly, the proteins are tightly enmeshed in the membrane, with part of their structure protruding on either side.

The first task is to detach the proteins from the surrounding membrane. The next step was to isolate the GABA receptor from the hundreds of other proteins in the detergent extracts. This involved exploiting the GABA receptor's propensity to bind to certain molecules. Knowing that the binding site for benzodiazepines was very close to that for GABA, even if it was not on the same molecule, a benzodiazepine was used to trap the elusive receptor. With an isolated protein at last in their grasp, the researchers could demonstrate that just one large protein accounted for the binding and activity of GABA, the benzodiazepines and other drugs that influence GABA's effects.

The researchers next set out to find the gene that encoded the receptor. This involved partially analysing the sequence of the protein and using the protein fragments to construct gene probes to screen libraries of DNA, like the protein itself derived from calf's brain. The probes picked out two types of gene sequence; these turned out to code for the two subunits of the receptor molecule, known as α and β. They had already found that benzodiapines bind to the α subunit, and GABA to the β subunit.

From these genes Barnard's group could deduce the complete sequence of amino acids, the building blocks that make up the protein molecule. From what they already knew about how different amino acids influence the overall structure of the molecule, they were able to develop a model of its appearance in three dimensions.

As a final check that the two genes were really the ones that made the receptor, the researchers used the egg cell of a frog, which normally has no GABA receptors, but which will obligingly make them and put them in its membrane if given messenger RNA from brain tissue. Barnard's team injected messenger RNA prepared from their two DNA clones, and found that as long they injected both types together, the egg cell made GABA receptors that behaved exactly like the ones in real brains.

The isolation, cloning and sequencing of the GABA receptor is important for many reasons. There is, to begin with, the intellectual satisfaction of knowing in ever-increasing detail how the brain regulates its activity. More importantly, we can design more effective drugs once we understand where and how they act. Finally, we have the means to investigate the mechanisms underlying brain disorders involving GABA and its receptor.

One puzzle remains: why should a naturally occurring brain protein, the GABA receptor, have a highly specific binding site for a group of synthetic compounds, the benzodiazepines? The chances are that there is a naturally occurring compound in the brain that has a similar structure (and presumably function) to these tranquillisers. (Extracted from New Scientist, 6 August 1987)

Further clues to the cause of manic depression

Evidence is mounting that, in some cases of manic depression, there is a gene near one tip of the X chromosome that predisposes its bearers to the disorder. Scientists who recently studied five families in Jerusalem used DNA-cutting enzymes to locate two genetic markers - one for colour blindness, the other for a chemical deficiency that causes anaemia - at the end of the long arm of the X chromosome. The markers occurred overwhelmingly among subjects with manic depression or related mood disorders.

Julien Mendlewicz of the Free University of Brussels, Belgium, and his colleagues now report that

there is another manic depression marker in the same area of the X chromosome. DNA was isolated from 89 individuals, 41 of whom had manic depression or severe depression, in 10 families. A genetic marker for a blood coagulation factor located near the colour blindness and anaemia markers occurred mainly among family members with the psychiatric diagnoses.

The genetic link was emphasized by the fact that no fathers and sons shared mood disorders, say the researchers. The 23rd pair of human chromosomes consists of two X chromosomes for females and one X and one Y chromosome for males. The Y chromosome is inherited from the father.

There is probably more than one gene involved in predisposing people in different populations to manic depression, but the investigators suggest that the long arm of the X chromosome may hold special promise for tracking down a predisposing gene. (Source: Science News, Vol. 131, 16 May 1987)

Activation of genes may cause SLE

Systemic lupus erythematosus might be caused by activation of genes for auto-antibodies in normal T cells, according to B.C. Richardson of the University of Michigan (Ann Arbor). Some drugs can induce or exacerbate SLE, and the action of these drugs might help researchers understand the causes of the autoimmune disease. SLE tends to attack the lining of joints and other tissues, and causes a butterfly-shaped facial rash. The disease is often misdiagnosed as fibrositis, skin photosensitivity or psychosomatic illness. There are some 16,000 new cases every year, with women succumbing nine times more often than men. The drugs hydralazine and procainamide, which exacerbate SLE, have now been shown to induce T cells to produce auto-antibodies.

Meanwhile, researchers at the University of California (San Francisco) have used monoclonal antibodies to extend the life of mice with SLE, by retarding the activity of helper T cells. Since the helper T cells may be needed to fight off other infections, however, the researchers hope to suppress only the T cell activity that helps produce auto-antibodies. (Extracted from Science News, 20 June 1987)

HSV-1 as possible vehicle for genes

Herpes simplex virus type 1 (HSV-1) may be used to introduce genes into victims of Lesch-Nyhan syndrome, according to T.D. Palella and W.N. Kelley of the University of Michigan (Ann Arbor). The virus could deliver the gene for hypoxanthine phosphoribosyl-transferase (HPRT) to the central nervous system, unlike RNA viruses. Restoring HPRT levels to just 1 per cent might reduce a patient's compulsive self-mutilation symptoms to symptoms of gout. The herpes virus can also integrate its DNA into that of central nervous system cells even though those cells do not replicate. Researchers would have to rid HSV-1 of its pathogenic properties before using it as a vector to carry the Lesch-Nyhan syndrome gene. Simply altering the viral genome to add the new gene apparently reduced the tendency of rat cells to kill the viral invaders. The work is still very preliminary. (Extracted from Science News, 20 June 1987)

Possible key found to malaria deaths

Scientists have discovered that a natural body protein is a likely major cause of the deadliest complication of malaria, a finding that suggests that blocking the chemical's action might save hundreds of thousands of lives each year.

Studies indicate that tumour necrosis factor (TNF) or cachectin is an essential element in highly fatal cerebral malaria, said researchers with the World Health Organization and the University of Geneva in Switzerland. Blocking the protein's action with antibodies or other agents might be a new way to treat the most fatal complication of malaria, according to a report in the journal Science. Estimates are that cerebral complications account for more than half of all malaria deaths even though the condition develops in less than 1 per cent of cases overall. There are an estimated 100 million estimated new cases of malaria worldwide each year, with one million resulting in death. (Source: International Herald Tribune, 10 September 1987)

False start for Alzheimer's gene

The gene underlying Alzheimer's disease, the most common form of dementia in the elderly, still eludes us. Hopes that the genetic defect lies in the amyloid gene are dashed by new research by scientists in Belgium, FRG, Australia and UK.

Just a few months ago, all the evidence suggested that the gene encoding the amyloid protein, on chromosome 21, was the key to the brain damage in Alzheimer's disease. Amyloid protein, called A4 in its purified form, turns up in the abnormal "plaques" and "tangles" in the brains of people with the disease. Even more intriguing was the apparent link between Alzheimer's and Down's syndrome, caused by inheriting an extra copy of chromosome 21. People with Down's often develop amyloid-rich lesions in their brains as adults and they have too much of the amyloid protein, because they have three copies of the gene, while people with the familial form of Alzheimer's have inherited a mutated version creating a faulty product. In sporadic Alzheimer's, where there is no history of the disease in the family, a chance duplication of the gene brings on the disease in theory.

Progress was rapid once the amyloid gene was cloned by three groups of researchers.

The trouble is, researchers have now found that affected family members do not always share the same allele of amyloid. John Hardy and his colleagues at St. Mary's Hospital in London have found such a family; several members are afflicted with Alzheimer's but they do not all share a common amyloid allele. Christine Van Broeckhoven and her colleagues at the University of Antwerp in Belgium have found another such family. Hence: "a mutation in the amyloid protein gene is not the primary defect causing familial Alzheimer's disease in all cases". In independent research, Mike Conneally of the University of Indiana at Indianapolis and Jim Gusella at the Massachusetts General Hospital in Boston find similar evidence from another family. "We agree that amyloid is not it", says Conneally.

However, a defective gene is somewhere on chromosome 21, but it is not amyloid. (Extracted from New Scientist, 10 September 1987)

Blood clot agent's genes are read

The protein responsible for triggering blood clots in the body has been cloned and its genetic code cracked, researchers report. The new information, they say, could eventually lead to the development of a new class of anticlotting drugs to combat heart attacks and strokes.

The protein, called tissue factor, is one of eight major proteins involved in coagulation, but unlike the other clotting proteins, which circulate in

the blood, tissue factor is bound to cell membranes within blood vessel linings. Because of the difficulties in working with such membrane-bound proteins, and because the protein is present in extremely minute quantities, tissue factor did not succumb easily to genetic analysis.

Whereas other clotting factors rely upon proteolytic activation by blood-borne enzymes, tissue factor triggers coagulation in response to tissue damage. It is the last of the blood clotting proteins to have its genetic sequence completely deduced.

The research was a collaborative effort by scientists at Yale University in New Haven, Conn., and the Mount Sinai School of Medicine in New York City. According to Ronald Bach, who was part of the Mount Sinai team, the work could lead to the development of antibodies or assays to measure tissue factor availability. Such tests might detect early signs of thrombosis - the blocking of blood vessels due to unwanted clots - so as to allow early intervention with clot-dissolving drugs. The research could also facilitate the discovery of natural clot inhibitors capable of blocking coagulation before it even begins. (Extracted from Science News, Vol. 132, 15 August 1987)

Boosting cell numbers in AIDS

A growth hormone that stimulates certain cells in the bone marrow can increase the number of white blood cells circulating in the blood, and perhaps give AIDS patients more "ammunition" with which to fight infection, scientists reported last week.

Using 16 AIDS patients who had decreased white cell counts, a research group from New England Deaconess Hospital and Harvard Medical School in Boston, Sandoz Research Institute in East Hanover, N.J., and the University of California at Los Angeles tested the toxicity and effectiveness of granulocyte-macrophage colony-stimulating factor (GM-CSF). The scientists conclude that GM-CSF is both nontoxic and capable of boosting the number of white cells in the body, suggesting a possible treatment for disorders with depressed white cell counts.

The scientists used a genetically engineered form of the naturally occurring hormone, which is thought to activate bone marrow precursor cells that eventually become various types of white blood cells. A major component of the immune system, white cells can be drastically decreased in immune disorders like AIDS, as well as by irradiation and cancer chemotherapy. Too few white cells (a condition called leukopenia) makes the patient defenseless against a variety of opportunistic, often fatal infections like pneumonia.

In the recent study, the authors report that intravenous infusion with GM-CSF for two weeks produced significant increases in white cells called neutrophils, monocytes and eosinophils. The size of the increase was directly related to the dose given the patient. Cell counts, however, returned to their previous low levels after the treatment was discontinued.

Cells with genes inserted without the use of a virus may be a viable alternative to using virus-infected bone marrow cells, according to researchers at Massachusetts General Hospital. The use of viruses may mask expression of the desired gene or the virus may become active in the new host. Transkaryotic implantation uses clones of cells which have a foreign gene implanted without the use of a virus. The transplant usefulness would be limited by the implant's location, size and compatibility with the recipient. (Extracted from Science News, Vol. 132, 12 September 1987 and 16 May 1987)

Cytotoxic T cells kill AIDS-infected cells

Evidence is mounting that persons infected with human immunodeficiency virus (HIV), which causes AIDS, develop T lymphocytes that specifically kill virus-infected cells. Researchers at Massachusetts General Hospital in Boston and National Institute of Allergy & Infectious Diseases report that they have detected these cytotoxic T cells in persons who have antibodies to the AIDS virus. People not exposed to the virus do not have these on cytotoxic cells, which appear to recognize molecules on the surface of infected cells derived from the virus's envelope gene. In addition, a team of researchers from Pasteur Institute and two Paris hospitals have shown that cytotoxic T cells carrying the CD8 antigen attack HIV-infected cells in the lungs of seropositive patients. But there may be a negative side to this: The French scientists suggest that the cytotoxic response may cause inflammations in the lungs, opening the way to some of the infections from which AIDS patients often die. The two groups' findings may help explain why some HIV-infected people do not develop the overt disease and may point the way to a practical vaccine. ((Reprinted with permission from Chemical and Engineering News, 27 July 1987. Copyright (1987) American Chemical Society)

Pair of genes goes awry in bowel cancer

Walter Bodmer and Ellen Solomon and their colleagues at the Imperial Cancer Research Fund in London have found the gene for familial polyposis coli (FAP), a rare cancer of the colon. The discovery may also help to explain the origins of other forms of colorectal cancer, which together amount to the second most common cancer in Britain after lung cancer. The research suggests that many such cancers develop only if someone loses both copies of a gene that normally suppresses the growth of a tumour.

Researchers at ICRF are searching for clues to the genes that go awry in cancerous cells, and so have focused on cancers known to be inherited, even if they are rare. FAP fits the bill admirably; children are susceptible to the disease if they inherit a defective gene from one parent (it is a dominant gene). By their early teens they develop hundreds or thousands of polyps in their colons. These polyps are increasingly likely to become cancerous as the individual ages.

Last year, a boy with polyposis in Roswell Park Hospital in Buffalo, New York, provided the first clue to the location of the gene. He turned out to have lost a small bit of chromosome 5. The combination of a small deletion, rare in itself, in a person with a rare cancer was unlikely to be a coincidence, the researchers concluded. They immediately began to concentrate their search on chromosome 5.

The next step was to pinpoint the gene on chromosome 5, by finding genetic markers near enough to it to be inherited along with FAP. Fortunately, Peter Scambler of St. Mary's Hospital Medical School in London had already isolated a probe from chromosome 5 that picked up a suitable polymorphism. This probe enabled the researchers to follow the inheritance of specific chromosomes through families, and show that the probe is closely linked to the gene that leads to FAP. The probe turns out to be virtually on top of the gene for FAP. Bodmer and his colleagues clinched the location of the probe by showing that it binds to the area of chromosome 5 that was lost in the patient in New York.

Solomon and Bodmer have gone on to show that this gene on chromosome 5 is involved in at least 20 per cent of cancers of the colon. Most importantly, they have gathered evidence to strengthen the hypothesis, suggested some years ago by Al Knudson

of the Fox Chase Cancer Center in Philadelphia, that cancers develop only after a cell has undergone two genetic changes.

In FAP, it seems that a person who inherits a susceptibility to the disease has one copy of the mutated gene, which knocks out the production of some key protein that would normally suppress the development of polyps in the colon. But for these polyp cells to become cancerous, the cells have to suffer a further mishap - the loss of the other chromosome which carried the normal gene. Cells actively dividing in a polyp are more likely to lose a chromosome than normal cells are.

To test this "two-hit" hypothesis, Solomon and Bodmer looked at cells from tumours of all sorts of colon cancer, not just FAP. At least 20 per cent, and probably as many as 40 per cent, given the difficulty in obtaining samples of tumour cells, had suffered this second step: that is, they had lost one chromosome 5. The researchers at ICRF detected the loss of the chromosome in these cells with another probe, to the tip of chromosome 5, provided by Alec Jeffreys of the University of Leicester.

This newly-discovered gene thus seems to be a "tumour-suppressing" gene or negative growth factor, which can actively transform normal cells to cancerous ones. Other types of cancer may also develop in this fashion. FAP joins retinoblastoma, a tumour of the eye, in this category.

The molecular geneticists now face the difficult task of finding the gene, sequencing it, and determining the role of its product in a cell. (Extracted from New Scientist, 13 August 1987)

Chimeric antibodies

Commercial interest is heating up over a number of techniques aimed at creating the next generation of antibodies. Chimerics are two promising approaches, but the most useful and economical methods of producing these space-age immunoglobins still need to be determined.

Two companies that are pursuing chimerics in different ways are Centocor (Malvern, PA) and Ingene (Santa Monica, CA). Centocor, in collaboration with Sherie Morrison at Columbia University (New York, NY), makes mouse-human antibodies by first cloning genomic DNA fragments coding for the heavy and light chain variable regions of mouse monoclonals. The researchers then insert these sequences into mammalian expression vectors containing genomic DNA segments coding for human constant regions. Scientists believe the resulting chimerics will combine the specificity of the mouse antibody with the lack of immunogenicity of the human antibody. Centocor recently initiated phase I human trials with a chimeric 17-1A antibody that recognizes a glycoprotein surface antigen on human colorectal carcinoma cells.

Hubert Schoemaker, Centocor's president, foresees cloning other usefull properties into recombinant antibodies, such as metal-binding functions to carry drugs for imaging. Another alternative might be to engineer in catalytic activity, such as the clot-lysing ability of tissue-type plasminogen activator (t-PA).

By comparison, Ingene has applied for patents on an approach to recombine cDNA modules that code for mouse variable and human constant immunoglobin regions; the antibody is then produced in lymphoid cells. The researchers have found that these chimeric antibodies bind to human carcinoma cells as effectively as mouse monoclonals do, but that they kill cancer cells at 100 times lower concentrations.

The main advantage of Ingene's system stems from its ease in generating new chimerics. Also, using cDNA clones (which contain no introns), rather than genomic DNA (which does have introns), allows for the possibility of producing the chimerics in yeast or bacteria and any manipulations tend to be easier because the target gene is much smaller.

One of the most important ways that Ingene envisions its chimerics being used in therapy is to enlist the patient's own immune system to clean up metastases. Ingene is working with Oncogen (Seattle, WA) on two specific anti-cancer antibodies. (Extracted from Biotechnology, Vol. 5, September 1987)

Research on animal genes

Gene product induced by seizures

Treating mice with a convulsion-causing drug triggers a temporary build-up in nerve cells of a protein coded for the c-fos gene, according to research at the Roche Research Center in Nutley, N.J. Although the protein's exact role in the body's response to convulsions is not understood, the scientists say it may affect how the brain adapts to repeated seizures. Related to genes found in mouse-cancer viruses, c-fos normally expresses itself in low amounts. However, about 90 minutes after the researchers injected mice with the seizure-inducing drug pentylenetetrazole (Metrazole), levels of c-fos protein were detected in parts of the brain. By four hours after the injection, "essentially all" neurons in the cortex and limbic-system areas of the brain contained the protein. The scientists report that the distribution of these c-fos-containing neurons is similar to that of binding sites for at least one known anti-convulsant drug. As might be expected from these similar distribution patterns, the scientists also found that prior treatment of mice with anti-convulsant drugs blocks the Metrazole-induced production of the c-fos protein. (Source: Science News, Vol. 132, 1 August 1987)

Genetic fingerprinting of animals

Researchers at the University of Liege in Belgium are developing markers for genetic fingerprinting in animals. The researchers are developing the markers from types used in human genetic fingerprinting processes. They plan to develop markers for use in a wide range of domestic animals including cattle, horses, pigs, dogs, chickens and fish. Genetic fingerprinting will permit paternity testing of animals, and will accelerate mapping of the genes which affect economically favourable animal characteristics. (Source: Technology Update, 3 August 1987)

Leaner beef cattle and pigs

University Genetics (Westport, CT) is importing semen from Belgian Blue bulls, a source of lean beef. Unlike traditional beefsteak cattle, Belgian Blues carry a genetic abnormality giving them twice as much muscle. The bulls are so lean that fat makes up only about 7 per cent of their bodyweight - less than 50 per cent the fat content of 'lite' beef, produced by lean feedlot diets. University Genetics, a biotechnology company, has also obtained the marketing rights to semen from what may be the only Belgian Blue bull in the US - a 2,700-lb specimen in South Dakota. Because purebred Belgian Blues don't calve easily, the company is advising breeders to aim for cows that are about 50 per cent Belgian Blue. University Genetics claim that beef from such a cross would contain 7-13 per cent less fat and 33 per cent less cholesterol than conventional beef, about the same as chicken.

In the six years since 1981 scientists have made remarkable progress in genetically altering animals. Over 100 different foreign genes, including human and virus genes, have been successfully transferred to mice, sheep, pigs and rabbits and attempts are now being made on cows. Most of the gene implants are achieved through micro-injection, which was first developed at Ohio University's Biotechnology Center (Athens, OH). The technique involves injecting a sub-microscopic snippet of DNA into a fertilized egg during the early hours of embryo formation. The gene is then incorporated into the animal's total genetic makeup and passed on to future generations. While the painstaking technique is not yet very efficient, scientists hope that once it is perfected they will be able to produce pigs or cattle that produce more lean meat and less fat, or animals that are more resistant to disease. (Source: Business Week, 10 August 1987 and Wall Street Journal, 3 July 1987)

Salmon expresses protein with mammalian promoter; growth hormone is next

Now that their presumably transgenic salmon express a bacterial marker protein, Irish researchers say the next step is to see if they have created fish that contain extra copies of growth-hormone genes. Frank Gannon of University College, Galway and Joseph Sreenan, Irish Agricultural Institute, Belclare, Tuam, County Galway, tell Newswatch that eggs of Atlantic salmon, Salmo saalar, injected with betagalactosidase genes from Escherichia coli, express recombinant enzyme in 25 per cent of the offspring, on average.

Gannon notes that there is no evidence yet that the galactosidase transformation has entered the germ line, and is therefore cautious in claiming a 'transgenic fish'. But Michael Folen, manager of the biotechnology section of the Irish Development Authority, calls the experiment "very successful from a commercial point of view". Folen points out that with mechanized methods of micro-injection, there is no reason for this to prohibit commercial applications, and would have the advantage of "avoiding accusations of species manipulation".

This summer, Gannon and Sreenan are conducting an expanded version of the same experiment, using 1,400 fish, the survivors of an initial 3,400 injected eggs. Approximately one-sixth of these were inoculated with salmon growth-hormone genes.

In the initial experiments, the researchers injected the eggs, a few hours after fertilization, with DNA in which the galactosidase gene had been fused to a mammalian metallothionein promoter, the one by which Richard Palmiter of the University of Washington, Seattle, transformed mice. Using a fluorometric assay, they found, after 14 weeks, increased galactosidase activity in about a quarter of the initial sample.

On the agenda, says Sreenan, is the development of a true piscine promoter, rather than a mammalian one. In spite of a relatively high mortality rate - in the initial experiment, 7 per cent of an original 600 fish eggs reached the final stage after accidental deaths and culling during incubation - the injections produced no increase in mortality. Death rates remained parallel to the normal for artificially fertilized salmon.

The project funded by the European Economic Community's Biotechnology Action Programme, which has provided some $268,000 over three years to Gannon and Sreenan, aims to develop transgenic fish by using peptide hormones at the embryo stage.

French researchers from the University of Lyon and INRA at Jouyen Josas, who are working closely with the Irish group, are introducing the metallothionein promoter into [illegible]. So far, they have detected the inserted bacterial DNA in their experimental fish, but not its expression. (Source: McGraw-Hill's Biotechnology Newswatch, 20 July 1987)

Peptides from frog skin kill microbes

Two peptides isolated from the skin of the African clawed frog, Zenopus Laevis kill a variety of bacteria, fungi, and protozoa in vitro, according to Michael Zasloff of the National Institute of Child Health & Human Development. Zasloff began analysing the chemical components of frog skin after he noticed that frogs he and his colleagues operated on and then returned to the laboratory aquarium healed without developing infections. The peptides, which Zasloff calls magainins after the Hebrew word for shield, are the first chemical defense system separate from the immune system to be found in vertebrate animals. The magainins appear to damage the cell membranes of bacteria and protozoa and work faster than antibiotics. Zasloff and his colleagues have isolated the magainin genes from frogs and will use them to probe for similar genes in humans.

Turning a puzzle into a scientific fact was far from straightforward. Before anything else, the exact location of the anti-bacterial action had to be found. Since the first place Dr. Zasloff looked, the mucus covering the skin, was full of bacteria, he turned his attention to the skin itself. Using a blender, he made a cold frog soup, and tried it out on some bacteria. There was a trace of activity, but no more, so more ingredients were added to the soup. The ones that finally did the trick were chemicals that stop particular cellular enzymes from cutting up all the proteins they come into contact with. When these were added to the broth it showed clear activity.

The magainin peptides he isolated turned out to be 23 amino acids long, which makes them the same sort of size as hormones. To be absolutely sure that they were there, Dr. Zasloff went onto isolate the DNA that describes them in the frog's genes.

Establishing the existence of magainins opened up a whole new set of questions, many of which have yet to be answered. It is not yet clear how many types a frog has, but there are certainly more than the original two. Each type of magainin seems to work against a slightly different range of cells and the whole family provides frogs with protection against protozoa and fungi as well as bacteria. They work by making enemy cells burst, but the mechanism by which they do so is still a mystery.

Some hints may come from the study of another group of peptides, the cecropins, which were discovered in insects at the beginning of the decade, and have been studied by Professor Hans Boman and his colleagues at the University of Stockholm. Cecropins also make cells burst, and can even break up artificial membranes, which have no protein gateways in them. Though they are a bit longer than magainins, the two groups appear to have similar shapes. In both cases, models suggest that the chain of peptides is folded into a helix, with amino acids that readily combine with water arrayed on one side and those which do not like water on the other. This would make them take up a characteristic position on the surface of a cell, with the side that dislikes water pushing in to the membrane, and the other side free to act on the membrane proteins. The way in which the amino acids of the peptides interact with the components of the membrane may eventually lead to an explanation of how the peptides burst the cell.

Whether or not cecropins and magainins work in exactly the same way, both have potential medical value. As alternatives to antibiotics they would be

well-suited to treating patients with wounds or burns that had disrupted the body's natural fences. They might help to kill off the bacteria infest the lungs of sufferers from cystic fibrosis. (Source: Chemical and Engineering News, 3 August 1987, p. 22 and The Economist, 5 September 1987)

Research on plant genes

Improving the potato's resistance to insect attack

A wild Bolivian potato may provide chemical defenses against insects for cultivated potatoes, according to W.M. Tingey of Cornell University (Ithaca, NY). Chemical insecticides cost potato farmers $120 million/year, according to US Department of Agriculture, and some of those chemicals are losing their effectiveness. The Bolivian plant has glandular hairs on its leaves that, when disturbed, secrete a clear chemical that turns sticky, trapping insects. Such a defense could be effective against the Colorado potato beetle and other insects. Breeding the Bolivian plant with cultivated North American potatoes has produced some hybrids with glandular hairs. The hybrids suffer 80 per cent less damage from aphids, 90 per cent less from leafhoppers and 60-80 per cent less from flea beetles. The glue does not entrap the Colorado potato beetle, but it slows it down, forces it to rest more and eat less, and mature more slowly, thus reducing plant damage by about as much as three to four pesticide applications. Unfortunately, the hybrids are not yet commercially acceptable for growing potatoes.

US Department of Agriculture researchers are meanwhile cross-breeding potatoes with Andean potatoes from Argentina and Peru, which produce a potent glycoalkaloid to inhibit feeding by insects. (Extracted from Science News, 4 July 1987)

Dutch biotechnologists create mutant potatoes, rich in amylopectin starch

Farmers in the far-north region of Holland grow potatoes unfit for human consumption. Rather, the locally produced Solanum tuberosum provides two industrial starches, amylose and amylopectin, commercialized by AVEBE, a potato-starch sales co-operative in Veendam.

AVEBE has become an international enterprise, marketing potato-starch derivatives for the chemical, pharmaceutical, food, paper, textile and petroleum industries. A prime competitor as a source of amylopectin is the amylose-free, or "waxy" corn cropped in the USA. Corn yields this multipurpose product more readily than potatoes, but separating it from amylose is a troublesome, uneconomic process.

So geneticist Richard G.F. Visser and his associates at the Groningen Biotechnology Center have irradiated S. tuberosum leaf strips with X-rays to create amylose-minus waxy potatoes, rich in amylopectin only. Potato starch can be used for a wider range of industrial applications than starch from maize, which is not grown in Holland. Amyopectin from potatoes goes into petroleum drilling compounds, for example, where it forms a thinner, cleaner film. One advantage of breeding and mutating the potato is its very large molecule, whose chemical versatility is now being exploited. The waxy candidate for high-amylopectin yield is still being researched and is far from commercialization. (Source: McGraw-Hill's Biotechnology Newswatch, 20 July 1987)

Gene-engineered tobacco resists insects

Tobacco plants carrying a bacterial gene for an insecticidal protein produce enough of the toxin to protect themselves against attack by tobacco hornworm larvae, according to Belgian scientist Marc Van Montagu and his colleagues from Plant Genetic Systems, Ghent, who inserted modified genes from a strain of Bacillus thuringiensis - a bacterium that produces proteins specifically toxic to a variety of insect species - into tobacco plants. In the most successful case, hornworm larvae stopped feeding on the altered plants within a day and died within three days. The bacterial genes are stable within the tobacco plants and are inherited by subsequent generations. (Reprinted with permission from Chemical and Engineering News, 6 July 1987. Copyright (1987) American Chemical Society)

Gene insertion technique

Pellets of tungsten powder coated with genetic material can be used to insert genes into plant cells, according to T.M. Klein of Cornell University. Onion cells pierced by the 4-micron pellets survived and were able to express the inserted genes. It is not yet clear if the genes have been permanently incorporated into the cells, however, but preliminary studies are encouraging. The technique might be useful for genetic engineering of crop plants. (Extracted from Science News, 16 May 1987)

New gene inoculation process

A new genetic process allows genes carrying codes for superior traits to be incorporated into one-seed leaf plants, like corn. Developed by researchers at the University of Toledo, the process involves making a 'wound' in a very young corn seedling, then inoculating the seedling with a virulent strain of a soil bacterium. A portion of the bacterium's genetic code is transferred into the chromosomes of the corn seedling's cells. The transferred genes become traits of the host plant and can be inherited in the regular fashion. The discovery could lead to the development of genetically engineered strains of corn with higher yields, nutritional value and resistance to herbicides. (Extracted from Chemical Week, 20 May 1987)

New catalyst could fix nitrogen from air

Chemists at the unit of nitrogen fixation at the University of Sussex are working on a novel electrochemical reaction that mimics the way nature scavenges nitrogen from the atmosphere. Raymond Richards reports that the reaction could lead to a commercial replacement for the traditional Haber process, which annually supplies about 50 million tonnes of ammonia for fertilizer.

The Haber process relies on an iron catalyst to convert nitrogen and hydrogen into ammonia. Although well established, the reaction has several disadvantages. It requires both high temperatures and pressures, it is expensive and the technology complex. It also relies on a large supply of hydrogen from valuable fossil fuel.

Certain bacteria that live in the soil, or in the root nodules of leguminous plants, such as peas and beans, fix nitrogen from the atmosphere under much gentler conditions. Scientists have been looking at the chemistry of the reaction for some time to see if they can perfect a simpler way of making ammonia. Nitrogen gas, or, more correctly, dinitrogen (N_2), has a very strong triple bond that links the nitrogen atoms. It requires a rather special catalyst to break the bond, and to add on three hydrogen atoms to each nitrogen atom to make ammonia. The bacteria use an enzyme with molybdenum at its heart. It is called nitrogenase. Instead of consuming hydrogen gas, the enzyme relies on a supply of hydrogen ions and electrons.

Chemists have yet to work out the complex structure of nitrogenase, but a simpler chemical model shows that the molybdenum atom plays a key role. It helps to stage what amounts to a "tug of war" on a molecular scale.

The nitrogen molecule attaches itself to the molybdenum atom, which weakens the triple bond by drawing electrons away from it. At the same time, a series of biochemical reactions supplies electrons to the complex. This gives the nitrogen atom furthest from the molybdenum a negative charge. Positive hydrogen ions add on in sequence until the bond between the nitrogen atoms breaks. Hydrogen ions then start to add on to the second nitrogen atom to produce a second molecule of ammonia.

What the Sussex chemists have done is to take a much simpler molecule containing molybdenum or tungsten, that binds nitrogen in a similar way to nitrogenase. A mercury cathode supplies the electrons. The hydrogen ions come from a solution of tosylic acid which surrounds the electrode. The tosylate anion adds on to the molybdenum but comes off at a later stage, while the hydrogen ions attack the nitrogens in a similar way to that in the biological analogue but at a much faster rate.

So far, the chemists have managed to put their catalyst through the reaction cycle only a few times. They say, however, that the reaction looks very promising. (Source: New Scientist, 3 September 1987)

Plant genetic engineering gets a new tool

For several years, plant molecular biologists have been using sections from the DNA of Agrobacterium tumefaciens, as a tool for inserting foreign genes into plant DNA. Now scientists at BioTechnica International, Cambridge, Mass., have shown that bacterial genes can be moved into plants another way. The mechanism that bacteria use to exchange genes among themselves (a process called plasmid conjugation) can be mobilized to transfer genes from bacteria to plants, according to Vicky Buchanan-Wollaston, Joan E. Passiatore, and Frank Cannon. Their research not only provides another tool for genetic engineers, but raises the possibility that bacteria may have influenced the evolution of plants by naturally inserting genes. (Reprinted with permission from Chemical and Engineering News, 13 July 1987. Copyright (1987) American Chemical Society)

RNA satellites confer viral resistance

For the past decade, researchers have been aware of the existence of tiny RNA "satellites" that reside within the cells of certain crops. Little is known about these enigmatic bits of genetic material; they seem to exist in a sort of dormant state in leaf cells, incapable of replicating without the assistance of a fully formed - and often disease-causing - "helper virus". The satellites are of interest to plant pathologists because they can influence the severity of the disease caused by their respective helper viruses.

Bryan D. Harrison and his colleagues at the Scottish Crop Research Institute in Dundee, Scotland, genetically transformed tobacco plants so that the plants themselves, when attacked by a virus, produce a particular RNA satellite within their cells. The plant-produced satellite takes advantage of the disease-causing cucumber mosaic virus (CMV) in order to reproduce itself, but in doing so it suppresses CMV replication.

In similar research, Wayne L. Gerlach and others at CSIRO Division of Plant Industry in Canberra, Australia, successfully inserted the gene for a tobacco-plant RNA satellite that ameliorates the symptoms of infection by tobacco ring-spot virus.

The advantage of the method is that the satellite precursors in the plant are only activated when the virus infects. When challenged by a virus, satellite levels soon build up to very high concentrations. One disadvantage is that similar RNA satellites actually enhance viral infectivity. Scientists need to understand how these differ lest a minor mutation in a virus-resisting satellite leave a plant more - rather than less - vulnerable to infection. (Source: Science News, Vol. 132, 29 August 1987)

Castor oil shares its poison with dysentery bacterium

As poisons go, the protein extracted from the seeds of the castor oil plant - ricin - takes some beating. Just one molecule is sufficient to kill a cell. Scientists have known for a long time that ricin acts by attacking ribosomes, which are part of the cell's essential machinery for synthesizing proteins, but not what it does to the ribosome. Nor have they been able to explain why such a deadly protein could be useful to the plant itself. Researchers from Yamanashi Medical College in Japan have found that ricin is a unique type of enzyme, which is similar to a toxin produced by a bacterium that causes dysentery.

Yaeta Endo and his colleagues report that ricin does not go inside a ribosome and randomly slice up the proteins or nucleic acids there. Rather, the ricin lops off, precisely, an adenine residue from one position in the chain of nucleic acids that makes up a critical molecule within the ribosome, "28S" ribosomal RNA. In doing this, ricin leaves intact the sugar connections along the backbone of the rRNA.

Endo and his colleagues also found that an agent of bacterial dysentery, Shigella dysenteriae, produces a toxin which also lops off adenine-4324. However, these Shiga-type toxins are not as deadly to animals, possibly because cells take them up less efficiently.

For a bacterium and a castor oil plant to share such a bizarre enzyme (one which removes only one particular nucleic acid base from one particular molecule) is puzzling. Sjur Olsnes, an expert on ricin working at the Norwegian Radium Hospital in Oslo, has suggested that Shigella and its allies have hijacked the ricin gene for their own uses, as their toxins have a similar sequence to ricin. (Source: New Scientist, 20 August 1987)

Creating genetic diversity

Traditionally, plant breeders have introduced genetic diversity into desirable plant populations by hybridizing good quality plants with unrelated lines carrying desirable traits. This has proven to be a powerful technique for developing new products, but can now be supplemented by the use of laboratory-generated germplasm. Whether the new germplasm is from an exotic (but natural) source or a laboratory generated novelty, the plant breeder plays a crucial role in reducing the new germplasm to a practical saleable product.

After a series of crosses has been made and advanced to a field nursery, two selection procedures are commonly used to sort the desirable genotypes from the segregating progeny: (1) pedigree selection, in which plants with the desired combination of characters are selected in the F2 generation, and the progeny of each selected plant is reselected in succeeding generations until genetic purity is reached; and (2) bulk population selection, in which

selection is delayed until a later generation, usually the F5 or F6 after hybridization, at which time further segregation will be minimal.

Multiple crossing, a complex method in which 8-16 varieties are systematically crossed, can quickly bring together combinations of genes from several parents. It has been used in the production of new varieties of some self-pollinated crops. This method is also used to produce new, inbred parent lines for hybrid production.

A disadvantage of the system, however, is that many undesirable combinations may be brought together, since such a large number of parent varieties is involved. The possibility of obtaining desirable combinations is enhanced by selection within each progeny before the next cross is made. This can be accomplished both in the laboratory and in the field.

In a backcrossing programme a hybrid is made between a useful, commercial parent lacking some desirable trait and a second parent containing the trait but of low general utility. Beginning with the F1 generation, crosses are made between progeny of the hybrid and the commercial parent. After each backcross, selection is made for the desirable trait present in the second original parent.

The backcrossing technique has been used effectively for many years in creating new plant varieties with specific disease resistances. For example, the pathogen that causes stem rust in wheat has frequently mutated. Breeders have eliminated the potential for an epidemic each time by finding a source of resistance and backcrossing it into currently used varieties. The frustration has been that it takes five or more years to develop the improved variety. Molecular biology will be able to reduce this timeframe substantially. It will also expand the sources of specific genetic material for plant transformation. (Extracted from Biotechnology, Vol. 5, September 1987)

Research on yeast and fungus genes

Linear plasmids

Linear plasmids in four strains of yeast might aid gene transfer among micro-organisms, according to P. L. Bolen of US Department of Agriculture. Linear plasmids might be more efficient as a transfer mechanism than circular plasmids that are now used, since they are surrounded by membranes that are a hindrance. The linear plasmids, by contrast, reproduce and float freely in the yeast cell's cytoplasm. (Extracted from Chemical Week, 8 July 1987)

Researcher tries to curb lumber-staining fungi

A University of Victoria chemist, Dr. Gerald Poultin, is conducting research on a fungicide to combat wood discoloration - a major problem for British Columbia forestry as discoloration makes wood virtually unsaleable.

Dr. Poultin, in collaboration with the Victoria-based company Safer Ltd., is experimenting with compounds from natural sources such as plant oils. Wood samples are either innoculated with fungal spores and mycella first, after which the test mixture of natural compounds is applied; or the test mixture is applied before the fungus is introduced.

Although there are already chemical products on the market which curb sap stain, Dr. Poultin said he knows of none made from natural materials. "The types of compounds we are using in our experiments are already in the human body and diet. They don't pose a health hazard to humans. Also, natural compounds can be broken down more quickly by micro-organisms in the environment", he said.

One product now commercially available is a non-toxic fungicide spray designed to combat powdery mildew. The two fungicides awaiting government approval are combination fungicide/insecticides. Once approved, they should help growers fight mildew and small insects such as aphids. (Extracted from Canadian Research/Biotechnology Canada, July 1987)

Lignin degrading enzyme gene cloned

A molecular biologist and a biochemist at Pennsylvania State University have cloned and sequenced the gene for an enzyme that degrades lignin. This ligninase, as naturally produced by the white-rot fungus, Phanerochaete chrysosporum, takes years to turn a pice of wood into powder. Drs. Ming Tien and David Tu are trying to amplify the gene's expression in yeast cells, by site-directed mutagenesis, so it will overproduce enzymes.

Meanwhile, Repligen Corp., Cambridge, Mass., has filed for patents covering "Novel Enzymes for Degradation of Lignin". (Extracted from McGraw-Hill's Biotechnology Newswatch, 15 June 1987)

Research on bacterial genes

Foreign gene successfully transplanted into BCG

Researchers have successfully transplanted a foreign gene into the bacteria currently used as a tuberculosis vaccine. The bacteria is bacillus Calmette-Guerin, (BCG), which over the last 40 years has been used to vaccinate more than two billion people against tuberculosis. According to B. R. Bloom of the Albert Einstein College of Medicine, who led the research group, the long-range objective is to implant genes from other disease-causing viruses and microbes into BCG to create a vaccine that will guard against several diseases simultaneously. BCG itself enhances the body's immune reaction, a fact that can provide long-term immunity for whomever is vaccinated with it. Other scientists have successfully transplanted genes of disease-causing organisms into the vaccinia virus used as a smallpox vaccine, but vaccinia virus produces strong negative reactions in some patients. According to Bloom, BCG is a hundred times less likely to cause negative reactions. The vehicle used by the Albert Einstein College researchers for gene transplantation was a circular, artificially assembled piece of DNA. The BCG bacteria frequently die after the gene is transplanted, but the researchers are trying to refine their technique so that it will not be damaged. (Extracted from New York Times, 11 June 1987)

Enzyme's gene in bacteria tracks altered microbes

Monsanto has developed a system of using the gene for betagalactosidase enzyme in bacteria to allow tracking of altered microbes. The enzyme allows the bacteria to live on laboratory culture dishes that contain only lactose as a carbon source. If the gene is inserted into bacteria at the same time as other genes are inserted, the gene will allow researchers to determine the spread of the altered microbes in the environment. Monsanto has asked the US Environment Protection Agency for permission to field test the system in autumn of 1987 in Pseudomonas fluorescens bacteria. Tests would be conducted by Clemson University under a $607,000 research agreement. The enzyme would be used to split off an indigo-like chromophore from a lactose analog so the culture dishes containing altered microbes will turn bright blue. The bacteria can be distinguished from other blue cultures because they also fluoresce under ultra-violet light. (Abstracted with permission from

Chemical and Engineering News, 22 June 1987.
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Methane-producing bacteria corrode iron

Anaerobic bacteria that produce methane from carbon dioxide can use either elemental iron or iron in steel as the sole source of electrons in the reduction. Such methanogenic bacteria could play a significant part in the corrosion of buried or submerged metal objects or metal in other oxygen-free environments, according to Lacy Daniels, Negash Belay, and Basavapatna S. Rajagopal from the University of Iowa's microbiology department and Paul J. Wiemer of Du Pont. The researchers find the iron is oxidized by cathodic depolarization, in which electrons from the metal combine with protons from water to produce ferrous ion and hydrogen gas. The bacteria allow the otherwise thermodynamically unfavourable iron oxidation to proceed by continually consuming the hydrogen gas that is released from the metal surface, the scientists think. (Reprinted with permission from Chemical and Engineering News, 3 August 1987. Copyright (1987) American Chemical Society)

Making a meal of iron

Microbiologist Lacy Daniels and colleagues at the University of Iowa in Iowa City report that certain methane-producing micro-organisms are able to extract their energy supply directly from iron in its elemental form.

Methane-generating bacteria, which thrive in an oxygen-free environment, normally produce methane and water by combining hydrogen gas and carbon dioxide. Working with pure cultures of various methane-generating bacteria, Daniels and his group showed that these organisms can also grow and produce methane in the presence of iron. In this case, iron reacts with hydrogen ions to produce iron ions and hydrogen gas. Although thermodynamic calculations show that this reaction is energetically unfavourable, the continual removal of hydrogen by the bacteria keeps the iron reaction going. One result is that the iron is oxidized. The research work suggests that methanogens could contribute significantly to metal corrosion in anaerobic areas. These organisms can be found in sediment at the bottom of almost any lake, pond or stream from the Arctic to the equator. Metal objects buried in soil or sediment, submerged in water or inside containers such as anaerobic digestors would be vulnerable.

The finding is important because researchers interested in bio-corrosion have in the past concentrated their efforts almost exclusively on sulphate-reducing bacteria. Now a second family of bacteria capable of corroding metal has entered the picture. (Extracted from Science News, Vol. 132, 15 August 1987)

Bacteria resistance to antibiotics spread concern

The improper use in health care of powerf l antibiotics called aminoglycosides now carries such risks that the World Health Organization is calling urgently for international guidelines to prevent further damage to patients.

An international study "on the occurrence of bacterial resistance and aminoglycoside consumption patterns" confirms long-suspected fears. The WHO's Global Programme for Appropriate Health Care Technology (ATH), based in Copenhagen, collaborated with the Department of Hospital Epidemiology at University Hospital in Freiburg, FRG, to compile the report which is due to be published shortly.

The report focuses on the spread of single bacteria that acquire simultaneous resistance to many antibiotics. The drugs are less effective or completely useless for growing numbers of patients. The report's data cover 12 countries (involving 34 research institutes drawing on national and local data) including Britain. Samples of bacteria varied in resistance from 2 to 70 per cent. In general, the antibiotics that are used widely created most resistance.

The report concentrated on three bacterial groups that doctors combat with aminoglycosides when patients are infected. Staphylococcus aureus, common on the skin and in the nose, has contributed to the deaths of patients after operations in hospitals. Pseudomonas aeruginosa, found in oxygen and water tubes, even in "sterilized" environments, is a severe threat to victims of burns. Escherichia coli, found in great numbers in the intestines, is associated with gastrointestinal disorders.

The evidence for the increase in multi-resistance appears more striking in general practice than in hospital wards. Where aminoglycosides were used exclusively in hospitals, the proportion of resistant bacteria varied between zero and 1 per cent. When used in hospitals and in general practice, the average rate varied between 2 and 30 per cent.

Resistance varies both geographically and between the groups of bacteria. (Extracted from New Scientist, 27 August 1987)

Discovering microbes with a taste for PCBs

Microbial ecologists and microbiologists are beginning to unearth a startling array of micro-organisms with unexpected abilities to biodegrade some of the toughest and most recalcitrant environmental chemicals. In the past few years they have found entirely new types of bacteria that can carry out reactions previously thought to be impossible. Efforts are now under way to harness those natural abilities and use them in cleaning up toxic chemicals, first by enhancing the performance of non-engineered micro-organisms and later by endowing them with new capabilities through genetic engineering.

Although many questions remain about how to turn these findings into practical, cost-effective systems for pollution control, work is rapidly moving from the laboratory to the field. Exploitation of natural biodegradative processes is not new; indeed, biological approaches have been used for years to treat industrial and municipal waste waters. But most of these applications have occurred above ground, where the processes can be fairly easily controlled. Now the goal is to modify those techniques to work in soil and ground water, often on exceedingly recalcitrant chemicals that are biodegraded only slowly, if at all.

But before these newly found micro-organisms can be harnessed, researchers must first figure out how to make them work in the right place, and at sufficient speed, on the appropriate chemicals. And that, in turn, depends on understanding the "mesmerizing complexity" of microbial ecosystems.

The possibility of manipulating genes to create a "superbug" with new biodegradative abilities illuminated how little is known about what micro-organisms already exist, how they function, and what effect modifying them might have on natural ecosystems. The US National Science Foundation, which until a few years ago did not even have a separate programme in microbial ecology, has dramatically increased its funding. Although genetic engineering applications remain years away, the upsurge in basic research has led to the discovery of these fascinating new microbes, which may not need any engineering at all.

James Tiedje, a microbiologist at Michigan State University, for instance, has isolated an entirely new anaerobic bacterium. It is able to do what was considered impossible only a few years ago: to remove chlorine from aromatic compounds, a key step in breaking down these compounds, which include such major pollutants as PCBs, dioxins, chlorinated phenols, and chlorinated benzenes.

However, although it was known that some compounds can be dechlorinated by micro-organisms, until recently it was believed that aromatic compounds could not. That changed in 1982, when Tiedje observed dechlorination occurring in sewage sludge and realized the reaction was being carried out by indigenous micro-organisms.

Two years later he isolated this micro-organism, which he has dubbed DCB1, that can dechlorinate aromatic compounds - in this case, chlorobenzoate. Since then Tiedje has found that this new organism works in concert with two others, which act in continuous sequence to completely degrade chlorobenzoate. (Chlorobenzoate is not an important pollutant, but it provides a model system for detailed, basic studies.) DCB1 performs only one step: it removes the chlorine from chlorobenzoate to produce benzoate. Then a second organism, a benzoate oxidizer, takes over and transforms benzoate to acetate, hydrogen, and carbon dioxide. Finally a methanogen, a bacterium that produces methane, finishes off the process by converting hydrogen and carbon dioxide to methane.

Tiedje is now probing the details of the interactions of the microbial consortium, and specifically, how the key dechlorination step works at both the genetic and enzymatic levels. Tiedje's eventual goal is to use DCB1 and other dechlorinating micro-organisms, once they are isolated, in a practical system to clean up hazardous waste. But first he needs to determine which pollutants these organisms will transform and how the reactions can be enhanced.

Perry McCarty, a civil engineer at Stanford University, has detected two micro-organisms that can also do the unexpected - in this case, biodegrade trichloroethylene (TCE) and trichloroethane (TCA), which are major ground water contaminants. TCE and TCA belong to the broader class of halogenated aliphatics, which were thought to be completely refractory to biodegradation until McCarty found out otherwise a few years ago.

But, as McCarty's work reveals, adapting either of these micro-organisms for practical use (or for that matter, other micro-organisms yet to be detected) will be tricky.

McCarty wants to use these microbes to treat contaminated ground water in situ, but little is known about microbial processes in ground water and simply gaining access to deep aquifers is a major obstacle. Another problem is toxic intermediates. In some microbial reactions the hazardous chemical is not completely degraded, or mineralized, but is transformed to intermediates. For some chemicals, transformation is sufficient to detoxify them. But for others, it makes the problem worse. For example, methanogens, the anaerobic bacteria McCarty has detected in ground water, transform TCE to organic intermediates, one of which - vinyl chloride - is more harmful to human health than is TCE.

The other TCE degraders McCarty and his colleagues have found, aerobic soil bacteria known as methanotrophs, do mineralize TCE to harmless, inorganic components, which holds great promise for in situ treatment of contaminated soils. But if McCarty is to use methanotrophs in ground water, oxygen would have to be injected into the aquifer along with all the other substances necessary for bacterial growth.

But the biggest obstacle, at least for the compounds McCarty is working with, is a poorly understood process known as co-metabolism. Biodegradation occurs fairly readily, even in ground water, if the micro-organism can use the hazardous chemical as its primary energy source. But for many if not all halogenated aliphatics, this is not the case. Instead, the micro-organism requires a second compound as its energy source and, in the process of metabolizing that energy source, degrades the "target" compound in a fortuitous reaction. This biochemical piggy-backing is known as co-metabolism.

Researchers at the Environmental Protection Agency's Gulf Breeze laboratory in Florida are also encountering problems with co-metabolism. Michael Nelson and his colleagues recently isolated another new bacterium, which they call strain G4, that also degrades TCE. The catch is that its energy source is phenol, a highly toxic aromatic compound.

What co-metabolism means in a practical sense, McCarty says, is that huge quantities of the energy source must be made available to the micro-organisms. On the basis of preliminary studies, McCarty says, it looks as if the primary energy source must be present in quantities 100 to 1,000 times greater than the hazardous chemical if it is to be transformed. In other words, in order to transform 1 kilogram of TCE you would need to add 100 to 1,000 kilograms of the energy source. In addition, the carbon, nitrogen, and phosphorous needed for cellular growth all must be present and in proper balance for the reaction to proceed.

As these basic studies proceed, other researchers are moving toward application in the field. General Electric's current assault on PCBs is a good example. The company has much at stake in this research, as it was a major user of PCBs for some 50 years and now is faced with a hefty clean-up task. At the drag strip, where PCBs were sprayed to hold down dust, the soil is contaminated with roughly 525 parts per million of Aroclor 1242, one type of PCB, of which there are more than 200 different forms, and what works on one will not necessarily work on another. Ronald Unterman and his colleagues are testing a strain of Pseudomonas putida, LB400, one of two dozen bacterial strains they have isolated that can grow on biphenyls and transform PCBs.

In the laboratory, LB400 works superbly, Unterman says. In what he calls a "shake and bake" procedure, they innoculated soil from the site with LB400, mixed it, and put it into an incubator. Within three days, 51 per cent of the PCBs were transformed. But when they tried it under simulated field conditions - they innoculated a few kilograms of soil with LB400 and left it at ambient temperatures in the laboratory without shaking - nothing happened. Thirty days brought a "hint" of activity, Unterman says, and by 100 days they had achieved 50 per cent degradation.

They are now testing LB400 on a test plot at the drag strip. He expects transformation to occur even more slowly in the field, where the bacterial concentration is more dilute and temperature and moisture content cannot be precisely controlled. At the time of the meeting, 23 days into the test, there was, not unexpectedly, no sign of activity.

In other work, Ronald Crawford of the University of Idaho and Thomas Frick of the University of Minnesota have developed a microbial consortium to degrade pentachlorophenol, a wood preservative and increasingly common ground and surface water

contaminant. In a demonstration project, BioTrol Corporation of Minnesota is using that consortium in bioreactors to clean penta- and creosote-contaminated ground water at Superfund sites. Ecova Corporation of Washington State has used biodegradation in combination with physical processes to clean up contaminated soils at an abandoned refinery on the Gulf Coast. There are obstacles as well. Some industrial discharges and Superfund sites are so toxic that they would "pickle" the organism before it had a chance to degrade them. In addition, bacteria have to be able to work on the chemical as it appears in nature - which usually means in a mixture - rather than in isolation in the laboratory. And if the microbe or microbial consortium does not completely degrade a compound but leaves intermediates, how will those be removed.

Kenneth Timmis of the University of Geneva described his laboratory's efforts to draw on the diverse catabolic abilities scattered among soil and water micro-organisms. Micro-organisms have extraordinary capabilities to evolve pathways to degrade new industrial chemicals, he said. But evolution can be slow, especially when it requires multiple genetic events for which selection pressures are low. (This is especially true for catabolic pathways, which usually require 10 to 15 different enzymes.) Moreover, some chemicals appear to be inherently resistant to biological attack. For those, genetic engineering may be the only approach.

With co-workers Fernando Rojo and Juan Ramos, Timmis is trying to accelerate evolution in the laboratory. They are using two experimental strategies to construct new degradative pathways: restructuring an existing pathway and assembling an entirely new one.

The idea behind the first approach is to modify an existing catabolic pathway so that it will accept a compound that it previously would not, in this case, a model aromatic compound. P. putida, for example, degrades methylbenzoate and 3-ethylbenzoate but not 4-ethylbenzoate. Timmis and his colleagues set out to broaden this pathway by identifying the roadblocks to degradation of 4-ethylbenzoate and then engineering them.

The first obstacle they found is that the protein that stimulates synthesis of the catabolic enzymes in P. putida does not recognize 4-ethylbenzoate. But once they engineered that protein to recognize 4-ethylbenzoate, the organism still did not degrade it. The next roadblock turned out to be an intermediate step in the normal catabolic pathway, in which P. putida produces an enzyme that cleaves the aromatic ring. Timmis found that the enzyme is indeed produced and functions when 4-ethylbenzoate is present, but it is killed during the reaction. (The intermediate of 4-ethylbenzoate is a "suicide substrate" that kills the enzyme.) They selected a mutant enzyme that does work, cloned its gene, and inserted it into P. putida, which now degrades 4-ethylbenzoate in the laboratory.

The second approach comes into play when there is no obvious pathway related to what you want to degrade, Timmis says. The answer, he says, is to "design a new pathway on paper and then go looking in the environment for bacteria that will provide enzymes to construct it."

As their model system, Timmis and his co-workers decided to create a single pathway to degrade two types of aromatic compounds, chloroaromatics and methylaromatics. In nature these are handled by two distinct pathways (an ortho and a meta pathway). Although soil micro-organisms often possess both pathways, only one is usually activated, depending on which substrate is present. When both compounds are present, however, both pathways can be switched on, which results in quite a muddle; intermediates are channeled down the wrong route, and, in the end, neither compound is degraded. Through a series of steps, the Geneva researchers recruited enzymes and assembled a pathway in P. putida that accommodates both. "It works", Timmis says. "It can simultaneously degrade mixtures of both types of compounds in the lab." And that, he says, holds promise for dealing with mixtures of toxic chemicals in the environment. The next step is to try both of these approaches on such major pollutants as PCBs and dioxin.

Such applications for major pollutants are thought to be several years away, however, for both scientific and regulatory reasons. Concern about releasing altered organisms into the environment is certainly one obstacle. (Extracted from Science, Vol. 237, pp. 975-977)

Research on viral genes

Control protein for AIDS virus identified

Gary Nabel and David Baltimore of the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts, have identified a protein, produced only by activated T cells, that turns on the AIDS virus genome, thereby enabling the virus to reproduce in - and kill - infected cells. The researchers identified the regulatory protein by introducing a hybrid gene into Jurkatt cells, a line of leukaemia cells of helper T cell origin. The hybrid gene was constructed by joining a sequence from the AIDS virus genome that contains the viral enhancer and promoter to a gene coding for a bacterial enzyme (called the CAT gene). Enhancers and promoters are regulatory elements needed for the first step of protein synthesis, gene transcription into messenger RNA. The Cambridge workers showed the AIDS virus regulatory sequences only drive the transcription of the CAT gene in Jurkatt cells that were stimulated by two non-specific activators of immune cells.

The researchers then went on to identify a protein that is made in the activated cells, but not in resting cells, and binds to the enhancer sequence of the AIDS virus. This protein turned out to be identical to "nuclear factor-kappa B" (NF-kappa B), another protein that was previously identified by the Baltimore group. NF-kappa B is so called because it is located in the nucleus of antibody-producing B cells where it turns on the expression of the gene coding for the kappa chain of antibody molecules.

The kappa chain enhancer contains a twice-repeated sequence of 11 base pairs in length that is the binding site for NF-kappa B. The AIDS virus enhancer contains a repeated sequence that is almost identical to that of the kappa chain gene and therefore the likely binding site for the protein. When Nabel and Baltimore introduced mutations into that portion of the viral enhancer, the binding of NF-kappa B was abolished. Moreover, a hybrid CAT gene with the mutated enhancer was not turned on in Jurkatt cells when they were activated.

The AIDS virus genome contains at least four genes that participate in regulating the synthesis of the structural proteins of the viral particle. The product of one of these genes, the tat gene, is a potent stimulator of the synthesis of AIDS virus proteins. Nabel and Baltimore have also shown that NF-kappa B works in concert with the tat gene product. The two together stimulate CAT protein synthesis much more than either does alone.

Preventing NF-kappa B synthesis or activity might prevent T cell destruction and the development of a full-blown immune deficiency, even if the virus could not be completely eliminated from the cells of an infected individual. Whether this would have any effect on the development of the neurological symptoms that are often seen in AIDS patients and may be independent of the immune deficiency is unknown, however.

Also unclear is whether shutting off NF-kappa B activities would itself result in a crippling of the immune system. When T cells are activated by immune stimulation they produce a variety of lymphokines, proteins such as the interleukins, that are needed for mounting normal immune responses. If these are also cut off by abolishing NF-kappa B activity, then the patient might still end up seriously immunodeficient. (Extracted from Science, Vol. 236, 24 April 1987)

The search is on for key peptides

Work has begun in Britain to determine which part of the human immunodeficiency virus (HIV) will prove to be a good candidate for a vaccine. Scientists need to identify a component of the virus, probably a protein, which will induce a protective immune response when injected into humans.

Many groups are concentrating on proteins that sit in the viral membrane, the envelope glycoproteins, gp120 and gp41, which are subunits of a protein called gp160. As part of the Medical Research Council's directed programme of research on AIDS, several companies and research teams have received grants to carry out work on the role of these viral molecules in stimulating immunity.

The Medical Research Council (MRC) is paying two companies to produce some of the raw materials that scientists will need in the pursuit of a vaccine. A biotechnology company, Celltech, will supply researchers supported by the Council with quantities of gp160. A second firm, Cambridge Research Biochemicals, is making peptides (short segments) of gp160.

Celltech hopes to begin manufacturing the proteins in bulk by the beginning of next year. The company will grow the proteins in cells taken from the ovaries of Chinese hamsters. The technique involves inserting the genes for the proteins into these cells. The company then grows the cells in bulk in giant fermenters at its factory in Slough.

Peter Lachmann, director of the Mechanisms in Tumour Immunity Unit in Cambridge has already begun to use the peptides manufactured by Cambridge Research Biochemicals. Each of the 86 peptides is 15 amino acids long. The sequences of amino acids of "adjacent" peptides overlap so that every part of the protein is represented twice.

Lachmann says he has already carried out a pilot study with about 10 peptides. If any of the peptides prove to be good candidates for a vaccine, Lachmann adds, the next stage will be to test them on himself and his colleagues to see how good the segments of protein are at raising antibodies in humans. Researchers will then test the most promising peptides on animals, possibly chimpanzees, to see whether they can fight off a deliberate infection with live virus. If they can, this will suggest that the vaccine might work in humans. Clinical trials would be the next step.

Researchers are also looking for a vaccine that causes the host to produce antibodies that help other proteins important in the immune system, called complement proteins, to destroy the virus. It seems that when certain antibodies bind to viruses, other proteins begin to break open the virus so that an important enzyme leaks out. Without this enzyme, called reverse transcriptase, the virus cannot insert its own genetic information into that of the T cell. (Source: New Scientist, 20 August 1987)

AIDS vaccine

Two new studies published in the 6 August Nature go a long way toward sorting out the relationship among the HIV viral varieties. Moreover, they offer hope that AIDS vaccine development may proceed more rapidly than was anticipated.

Researchers at the National Cancer Institute (NCI) report that they have determined the entire 9,264-nucleotide sequence that makes up the genome of an AIDS-like virus found in African green monkeys. The researchers, Genoveffa Franchini, Robert C. Gallo and their colleagues, then compared that sequence to the genetic codes of previously cloned AIDS-related viruses. They found that the newly sequenced STLV-iii AGM virus, although apparently nonpathogenic in green monkeys, is genetically very similar to HIV-2 and is to a lesser extent related to HIV-1.

The new analysis resulted in two important findings. First, the scientists identified genetic variations that may explain why certain strains of AIDS-like viruses do not cause disease. Second, and more important from the standpoint of vaccine development, they found striking similarities within certain genomic regions that code for the production of viral envelopes, or outer skins, of the strains they compared. In almost all cases, for example, the nucleotides that code for the amino acid cysteine are located in exactly the same positions on the genome. This is true even in strains whose genomes otherwise vary by as much as 25 per cent.

In related research, Pierre Tiollais and others at the Institut Pasteur in Paris say they have cloned and sequenced the entire genome of a virus that causes an AIDS-like disease in macaque monkeys. The virus, STLV-III MAC, is the only virus that is known to share most of the properties of human AIDS-causing viruses and that actually causes an AIDS-like disease in animals. The accomplishment opens the door to preliminary tests of recombinant vaccines on animals.

Animal models are considered essential for testing potential vaccines, but until now scientists have been frustrated by the lack of an appropriate animal to work with. Although the STLV-III MAC virus differs somewhat from human AIDS-causing viruses, it has several genetically conserved regions identical to some regions in HIV 1 and HIV-2. Scientists hope to test a variety of STLV-III MAC antigens as potential vaccines in macaques, and then - by referring to the newly created nucleotide map - test analogous HIV antigens in humans. (Extracted from Science News, Vol. 132, 8 August 1987)

Second virus in Europe

There are at least 70 known cases of AIDS in Europe caused by the second human immunodeficiency virus, HIV-2. Luc Montagnier of the Pasteur Institute in Paris said that he knows of 35 cases in France, 20 in Portugal, two in FRG, two in Sweden and one in Norway.

All of the cases in Europe, he said, are people who "are African or have lived in Africa or had contact with Africa". The Pasteur Institute first detected HIV-2 18 months ago, after doctors in Portugal sent blood from an African patient to Paris for analysis.

Montagnier said that the time between infection and the development of AIDS may be far longer for HIV-2 than for HIV-1. He added, conceivably that thousands of people in Europe could already be infected with this virus without being aware of it. (Source: New Scientist, 3 September 1987)

Revised AIDS definition

A new definition for AIDS has come into effect. In the US, and possibly in Britain, the result could be an increase of 10 or 15 per cent in the numbers of new cases of AIDS that doctors report.

The new definition, published by the Centers for Disease Control (CDC) in Atlanta, Georgia, is wider than the old one. It includes for the first time conditions such as dementia and severe loss of weight caused by infection with the human immunodeficiency virus (HIV). In addition, the revised definition relies more heavily on diagnoses made by doctors without the help of laboratory tests, as long as these patients have had a positive result to a test for antibodies to HIV.

The CDC says that the revision should help to identify more effectively the extent of severely disabling disease associated with HIV. The CDC also wanted to be consistent with current diagnostic practices, which often bypass the need for laboratory analysis of certain infections associated with AIDS.

These infections - called "opportunistic" because they take advantage of the body's immune suppression in HIV infection - used to be rare in young people. But as doctors caring for people with AIDS have become more experienced, they can often diagnose certain conditions on the basis of the patient's symptoms, without micro-biological tests.

The inclusion of dementia (AIDS encephalopathy) and HIV wasting syndrome (severe loss of weight, diarrhoea and/or fever) might also cause a bigger increase in reported cases initially.

Spence Galbraith, head of the Communicable Disease Surveillance Centre in Colindale, North London, said that the Centre would be reprinting its reporting forms with the new definition on the back. He thought it might be some time before a rise in the numbers of reported cases became apparent because "it will take some time for the message to get around".

The CDC has also published new guidelines for counselling and antibody testing. The Centre says that counselling and testing people who are infected or at risk is an important method of preventing the spread of HIV. (Source: New Scientist, 3 September 1987)

Mutant enzymes slow the AIDS virus

Researchers are now a little closer to understanding the operation of an enzyme that is crucial to the replication of the human immunodeficiency virus (HIV). A team at the Wellcome Research Laboratories in Beckenham, Kent, has managed to alter the activity of the enzyme, reverse transcriptase, by substituting certain amino acids along its length.

Reverse transcriptase plays an important role in transcribing the RNA of the virus into double-stranded DNA. This DNA then becomes incorporated into the genome of the host cell.

The group at Wellcome concentrated on substituting amino acids in regions of the molecule which are similar in related enzymes, such as reverse transcriptase in other viruses. They believed that if a sequence remained similar in several enzymes, it was likely to be important in the enzyme's action.

On this basis, they concentrated on six regions. One of these contained a sequence of amino acids which is very common in this group of enzymes and which may be important in binding the enzyme to its RNA template. The team found that the three mutations that they introduced in this region produced interesting results. One amino acid substitution completely destroyed the activity of the reverse transcriptase, while two other changes in this region significantly reduced it.

The group then went on to see if the drugs azidothymidine (AZT) and phosphonoformic acid inhibited the mutant enzymes in the usual way. Phosphorylation plays an important part in the action of these drugs. In the case of AZT, for example, cellular enzymes phosphorylate the drug to form AZT-triphosphate. The reverse transcriptase then incorporates AZT into the growing strand of DNA, blocking any further elongation of the molecule.

In these experiments, substituting amino acids in two further sites made the enzyme less sensitive to inhibition by AZT-triphosphate. Still other mutants were less sensitive to inhibition by phosphonoformic acid.

The significance of this work is two-fold. First, it tells scientists something about which parts of the molecule are important in the function of the enzyme and in drug binding. However, to use this kind of information in designing new drugs, it is necessary to know the three-dimensional configuration of the enzyme as well. Scientists have yet to determine this structure. Secondly, further work along these lines will allow researchers to predict what the likelihood is of HIV mutating and so developing resistance to drugs such as AZT.

Scientists have carried out similar work to see if mutant versions of herpes viruses are less sensitive to the drug acyclovir. They found that, in general, any herpes virus that is resistant to acyclovir appears to be attenuated, or weakened.

The team is now going to put the mutant genes for reverse transcriptase into infectious virus to find out how these affect the growth of the virus. The researchers also intend to analyse some of the mutant enzymes that have impaired activity to find out how their biochemistry differs from the parent molecule. (Source: New Scientist, 9 July 1987)

Hybrid particle mimics AIDS virus

By exploiting peripatetic pieces of yeast's genetic material called retrotransposons, British scientists are hoping to hasten the development of effective AIDS vaccines. "Transposable elements" - DNA segments that readily move from one location on a chromosome to another - were first discovered in maize more than 30 years ago, and later in fruit flies and bacteria. When researchers found several years ago that these restless chunks of DNA can transfer traits like antibiotic resistance between bacteria, they began using them as carriers of foreign DNA in genetic experiments.

Scientists at the Oxford-based British Bio-technology ltd., the University of Oxford and the University of Kent in Canterbury used similar technology in their experiments with yeast retrotransposons. The retrotransposons code for a group of yeast proteins that assemble themselves into harmless "virus-like particles" - which the researchers have tricked into accepting segments from the HIV viruses causing AIDS.

These hybrid faux-virus particles may be useful in developing both AIDS vaccines and diagnostic tests to detect the HIV viruses, say the scientists.

Noting that the hybrid particles are simple to construct and then purify, the scientists also report that rabbits injected with the recombinant particles develop antibodies against the HIV component of the particles, suggesting a "new approach to vaccine production". (Source: Science News, Vol. 132, 5 September 1987)

Engineering cells to destroy viruses

Several research groups are developing a way to protect cells from viral infection by injecting them with genes that will stop viral replication. Enzo Biochem has obtained an exclusive licence for such technology from the State University of New York's Research Foundation. Enzo will initially use the technology to develop an AIDS treatment. It also wants to develop plants resistant to tobacco mosaic virus and other common viruses, and cattle resistant to foot-and-mouth disease.

The technology is based on blocking the production of viral protein. Enzo's technique uses antisense genes that are complementary to the viral genes. The antisense genes are inserted into the infected cell, where they become part of the human genes. They produce a type of messenger RNA called antisense RNA that is complementary to the viral RNA. When the antisense RNA binds to the viral RNA, production of viral proteins is blocked. Antisense genes can also be used to prevent infection. Enzo's AIDS therapy will use bone marrow cells treated with antisense genes. The bone marrow cells, when returned to the patient, will produce protected T-cells that will keep the patient from developing AIDS. This technique would not remove the AIDS virus from the body, and would leave brain cells untreated. Another problem is the fact that there is no efficient way to inject foreign genes into human cells. (Extracted from Chemical Week, 29 July 1987)

Cytotoxic T cells kill AIDS-infected cells

Evidence is mounting that persons infected with human immunodeficiency virus (HIV), which causes AIDS, develop T lymphocytes that specifically kill virus-infected cells. Researchers at Massachusetts General Hospital in Boston and National Institute of Allergy and Infectious Diseases report that they have detected these cytotoxic T cells in persons who have antibodies to the AIDS virus. People not exposed to the virus do not have these cytotoxic cells, which appear to recognize molecules on the surface of infected cells derived from the virus's envelope gene. In addition, a team of researchers from Pasteur Institute and two Paris hospitals have shown that cytotoxic T cells carrying the CD8 antigen attack HIV-infected cells in the lungs of seropositive patients. However, the French scientists suggest that the cytotoxic response may cause inflammations in the lungs, opening the way to some of the infections from which AIDS patients often die. The two groups' findings may help explain why some HIV-infected people do not develop the overt disease and may point the way to a practical vaccine. (Reprinted with permission from Chemical and Engineering News, 27 July 1987. Copyright (1987) American Chemical Society)

AIDS virus envelope protein is neurotoxic

US National Institutes of Health researchers have discovered that gp120, the glycoprotein that coats the AIDS virus, is a potent neurotoxin. This finding may help explain why patients with acquired immune deficiency syndrome often suffer neurological symptoms ranging from confusion to dementia. The neurotoxic effects of gp120 were studied in cells cultured from the brain and spinal cord of foetal mice. A gp120 concentration of 10^{-12}M killed most of the neurons, according to neuropharmacologist Douglas Brenneman of the National Institute of Child Health and Human Development. He announced his group's findings last week at an AIDS drug workshop at NIH. The AIDS virus is known to shed gp120, and some of the neurological disorders caused by the deadly virus may stem from the gp120 molecule itself, although he does not know what the mechanism is. The gp120 molecule has previously been reported to be toxic to T4 lymphocytes, key cells of the immune system. Brenneman finds that gp120's neurotoxicity can be prevented in cell culture by administering analogs of peptide T, which has been shown to prevent infection by the AIDS virus. (Reprinted with permission from Chemical and Engineering News, 6 July 1987. Copyright (1987) American Chemical Society)

Company clones key AIDS gene

Moving another step towards a potential new treatment for AIDS, scientists at Hoffman-La Roche have successfully cloned one of the key viral genes which codes for an enzyme involved in assembling the virus particle.

Dr. Michael Hall, head of chemotherapy at Roche Products' laboratory in Welwyn Garden City, UK said that the latest development, achieved only a few weeks ago by company scientists in New Jersey, would help them to find an inhibitor for the enzyme. In theory at least, such an inhibitor could block the action of the virus.

The enzyme is an aspartyl protease that divides separate proteins produced as a combined 'polyproteins' from the viral genes. Hall said it had been cloned by insertion of the protease gene into a plasmid carried in Escherichia coli bacteria. These genetically-engineered bacteria can now simply be cultured indefinitely to provide a supply of the enzyme for screening studies of possible inhibitors.

Protease inhibitors are only one of the approaches being used by Roche and other companies to find therapies for AIDS. One of the main goals has been the development of inhibitors of reverse transcriptase, which transcribes viral RNA into DNA that is then incorporated into the human chromosomes. AZT, the Wellcome AIDS drug already on the market, works this way.

Earlier this year, Roche acquired the rights to one of the most promising reverse transcriptase inhibitors from the US Commerce Department. Called dideoxycytidine (DDC), its anti-AIDS activity was discovered at the US National Cancer Institute last year, and its potency in vitro found to be ten times that of AZT.

Some 60 people have now been treated in clinical trials in the USA with DDC, though this first phase of testing has not been completed because of observed side effects. Hall said the clinical results were 'encouraging', but that as well as skin rashes and falls in blood-platelet count (both transient), the drug produces a peripheral neuropathy - tingling sensations in the limbs, especially feet - after 6-8 weeks of continuous treatment.

This observation has delayed the drug's development. Hall said it would be some three years before DDC could be widely available as a treatment, assuming the neuropathy problem is solved.

Meanwhile, the Wellcome Foundation, which says it also tried to get the rights to DDC when the US Government put them out for tender, has applied for a

patent for the drug in countries around the world. (Source: Chemistry and Industry, 7 September 1987)

Attention turns to diet and exercise

Researchers are devoting a great deal of effort to the search for a vaccine or antiviral drugs to combat the human immunodeficiency virus (HIV). Yet anecdotal evidence suggests that factors such as diet and exercise may be important in determining whether someone with HIV infection progresses to AIDS. If researchers could substantiate some of these theories, it might mean that people infected with HIV could minimize their chances of developing AIDS by modifying their lifestyle.

So far, investigations into such "secondary prevention" have been few and far between. However, researchers at St. Mary's Hospital, in Paddington, London, have begun to study some of these factors. Adrian Renton, research registrar, says that they are particularly interested in the role of dietary fats because it is well known that lipids can affect the function of the immune system, perhaps by their influence on the viscosity of cell membranes.

The team is also looking at the potential influence of dietary fats on other sexually transmitted diseases. Renton says: he and his colleagues are interested to know whether it is possible to demonstrate scientifically a link between fat intake and events such as a herpes attack, or the development of AIDS in someone infected with HIV.

Renton and his co-workers hope soon to publish the results of a pilot study, which was supported by the charities Immunity and the Jefferis Research Wing Trust. (Source: New Scientist, 6 August 1987)

Time from infection to AIDS computed

Based on data from patients who acquired AIDS from blood transfusions, British scientists reported that children under the age of 5 at the time of infection develop their first symptoms of AIDS about two years after transfusion - more than four times earlier than the average eight-year "incubation time" seen in patients between the ages of 5 and 59. The statistical analysis, based on figures from 297 US cases, also found that patients 60 years and older develop AIDS at an average of 5.5 years after transfusion.

Researchers at the University of London analyzed data provided by the Centers for Disease Control (CDC) in Atlanta to determine the average time from infection to development of AIDS. The scientists point out that, although these incubation times may not prove to be identical to those seen among other groups of AIDS patients, knowing the exact date of infection from transfusion makes such studies a unique and valuable resource in understanding AIDS.

David R. Cox of the London group says that the data from the under-5 age group are the most conclusive, and incubation times for older patients may have to be updated as more data become available.

Meanwhile, another group of scientists in the UK have used a computer to construct the probable three-dimensional structure of a protein that may prove significant in developing new drugs against the virus causing AIDS. Laurence H. Pearl of the Institute of Cancer Research in Surrey and William R. Taylor of the University of London report their computed structure for the protease enzyme produced by the AIDS-causing HIV virus in the 24 September issue of Nature. (Extracted from Science News, Vol. 132, 29 August 1987 and 26 September 1987)

Research instrumentation

Laser speeds DNA-sequencer assay

Hitachi Ltd., Tokyo, has developed a prototype DNA base-sequencer analyser that combines the Sanger method with a laser. It eschews radio isotopes, using fluorescein isothiocyanate (FITC) instead. While DNA fragments are on a gel electrophoresis plate, they are marked by FITC, and bombarded by an argon laser at 488 nm, with fluorescence at 515 nm. Images are captured by a TV camera, and processed by computer. The system can handle five fragments simultaneously, and analyse up to 201 DNA base sequences in three to four hours. The Science and Technology Agency is planning to increase funding, so Hitachi can raise the analysis capacity to 600 base sequences over the next three years. A similar system is available from Applied Biosystems Inc., Foster City, California, but it takes up to eight hours to do the same job, say Hitachi researchers. The Tokyo company has yet to formulate a plan for commercial production. (Source: McGraw-Hill's Biotechnology Newswatch, 15 June 1987)

New generation bioreactor

GeDevelop is developing glass fibre matrices with custom-made properties for various applications in biotechnology. This means a new generation of bioreactors for cell cultivation and matrices for separating biological material and isolating proteins.

The technique is patented and is expected to be on the market within a year or so. The company is also developing new types of filters and membranes made of glass fibre.

In bioreactors, cells are immobilized and provided with a nutrient solution and oxygen. This creates a natural environment in which the cells can produce or break down some substance. This may be done to produce antibodies and antibiotics or to break down phenol. Animal cells, fungi, or bacteria may be used in the process.

The cells are usually immobilized by allowing them to attach themselves to the surface or to be incorporated into small spheres. GeDevelop, on the other hand, is offering glass fibre as the immobilizing material. It has several advantages.

Glass fibre is inexpensive. The material has its own bearing capacity and a high porosity. It has a large surface area to which cells can attach themselves - 20 square metres per litre or more.

In addition, the material can withstand high temperatures and can be used in autoclaves for sterilization.

It is also important that the glass fibre material is porous and layered in several planes. This makes it easier to supply oxygen and nutrient solution, thereby making the transport of nutrition to the cells more efficient. This is extremely important for increasing the production scale of the process.

The combination of a large surface area and a high porosity makes the glass fibre matrix suitable for use in separation processes. This is true both of mechanical separations and chemical separations involving materials of biological origin.

Details available from GeDevelop AB, Ideon, Ole Romers vag 12, 223 70 Lund, telephone: 046-16 85 00.

Improved dermatology research with extracellular matrix

Tissue culture dishes coated with extracellular matrix (ECM) may serve to expand the research

possibilities in the field of dermatology. International Biotechnologies (IBT's) organically secreted ECM, which closely resembles the in vivo basement membrane on which cells naturally proliferate, has been shown to promote the attachment, proliferation and subsequent differentiation of guinea pig and human skin keratinocytes. Thus ECM may facilitate the growth of skin for transplants, for evaluating the effect of drugs and cosmetics on skin cells, and for studying a variety of skin diseases.

Because of the unique properties of ECM, cells plated on ECM proliferate as they do in vivo. Transmission electron microscopy of skin keratinocytes cultured on ECM has implied the formation of multi-layered epidermal sheets, hemidesmosomes, keratohyaline granules and cross-linked keratins. It thus may be possible to grow large amounts of human skin keratinocytes which may be used to perform autologous skin transplants. Furthermore, the possibility is created for the preparation of large epidermal sheets to be used in skin transplants vital in cases of severe burns, where the rejection factor of foreign skin is a major problem.

The in vitro-grown human skin may be used in tests concerning the toxicological effects of drugs and cosmetic applications. Results obtained from such tests can be more reliably extrapolated to the human condition. In addition, the ECM model can be used to further investigate a variety of skin diseases involving uncontrolled growth e.g. melanomas, carcinomas, papilomas and psoriasis.

General

Mapping the human genome

Scientists expect the first workable map of genetic markers or chemical signposts to be completed within slightly over one year. A complete map of genetic signposts could lead to major advances against many inherited diseases by enabling the faulty genes to be pinpointed. Many diseases caused by single genetic defects could be diagnosed within weeks after conception, and effective treatments for some disorders could be developed for the first time. Markers have already been found yielding the approximate locations of faulty genes associated with cystic fibrosis, muscular dystrophy and some cases of Alzheimer's disease. A genetic map could also provide information on the hereditary factors linked with heart disease, high blood pressure, diabetes, arthritis and many forms of cancer. Predisposition to these diseases probably involves the complex behaviour of several or many genes. Studies on the heriditary factors associated with these diseases have previously been difficult or impossible, but could be made possible with a complete gene map.

Creation of the genetic marker maps has been made feasible by combining studies of families in which certain genetic diseases have often appeared for several generations with the use of complex chemical techniques to study polymorphisms or natural variations in DNA. The family studies are used to match polymorphisms to the genetic disease. The ultimate gene map would specify the sequence of about three billion subunits that comprise human genetic material in their correct order. This genome sequence map could help scientists identify all genes and might help to aid understanding of the functions of the large amount of DNA in human cells that does not seem to code for any genes. (Extracted from New York Times, 11 August 1987)

D. APPLICATIONS

Pharmaceutical and medical applications

Genetic fingerprinting goes on sale

The first laboratory in the world to offer a service for people wanting to know the genetic relationship between individuals has opened for business. The laboratory uses a technique called "genetic fingerprinting", developed by scientists at the University of Leicester. The technique distinguishes between individuals, whether they are humans or animals, and can determine the parentage of children.

ICI, the company that has bought the rights to the technique, has formed a new company, called Cellmark Diagnostics, to run the laboratory. The laboratory, in Abingdon near Oxford, can test 250 blood samples a week by genetic fingerprinting. ICI says that it will also set up another laboratory in Maryland within the next month to provide the same service in the US.

In genetic fingerprinting, scientists extract genetic material, DNA, from the sample of tissue, whether it is blood, semen, skin, or the root of a hair. They add enzymes to the DNA that chop it into tiny pieces of unequal size. They then put the fragments into a gel, and an electric field separates the larger DNA fragments from the smaller ones.

The scientists then transfer the DNA from the gel to a nylon membrane by a process called Southern blotting - the fragments of DNA move from the gel to the membrane as the solution of DNA is drawn up by capillary forces created by blotting paper placed on top of the nylon membrane. The position of the DNA fragments in the nylon membrane exactly matches their position in the gel.

The next step is to add tiny pieces of DNA that are radioactively labelled. These DNA "probes" are built to identify regions of DNA known as hypervariables. Alex Jeffreys of the University of Leicester found that people are unique in terms of the distribution of hypervariables in their DNA. A child will share some of its hypervariables with its biological mother and some with its biological father.

After washing the nylon membrane, the only radioactivity left will be the probes that have stuck to hypervaribale regions. Put the membrane next to X-ray film, and dark bands will appear where the probes have stuck to these regions. The distribution of the bands is unique to an individual and a child's "genetic fingerprint" will be an amalgam of the fingerprints of its two parents.

The scientists at Cellmark say that they have analysed blood stains that are three years old, and were still able to test for genetic fingerprints. (Source: New Scientist, 23 July 1987)

Malaria vaccine hope

Research on three types of malaria vaccines, aimed at different stages of the parasite's life cycle are showing some promise.

Malarial infection begins with the release of 3000-4000 sporozoites into the blood from a mosquito bite. One type of vaccine being worked on is based on fragments of the protein that forms the coat of the

rod-like sporozoite. Two groups in the USA have had limited success in inducing immune responses in people vaccinated with a fusion product of repeated amino acid sequences from the coat protein and a 'carrier' protein.

This type of vaccine, because it is directed against the parasite stage first entering the body, could prevent infection in an individual that does not appear to be equally effective in different individuals, does not produce the sustained levels of antibodies required for lasting immunity, and does not activate T-cells efficiently.

Another type of vaccine is directed against the asexual stage of the parasite formed once it enters the liver. These have not been tested in humans yet, though trials in monkeys show 'some promise'.

Unfortunately, the antigens on the parasite surface at this stage show considerable variation, which would require there to be a similar variety of vaccines, and the vaccine would require potent adjuvants (those that work in monkeys would be no good for human vaccination).

Finally, a third type of vaccine would block transmission of the sexual stage of the parasite back into the mosquito when it bites already infected people.

While this method would limit the spread of the disease, it would do nothing for an individual vaccinated, since it acts against the parasite after the clinical stage, and could even promote infection. (Source: Chemistry and Industry, 7 September 1987)

Mab's used in medical imaging products

Monoclonal antibody 'magic bullets' have spurred a new wave of medical imaging products. Researchers have dreamed for years about injecting patients with proteins laced with radioactive isotopes that are visible to gamma-ray cameras in order to produce scanning images that can pinpoint blood clots, viruses and tiny cancerous growths. Finally, a few companies have devised ways to eliminate the 'background noise' that has hindered researchers from successfully using monoclonal antibodies - which seek out specific targets in the body - as a scanning tool.

Centocor (Malvern, PA) has developed Myoscint, a monoclonal antibody devised to gauge the severity of heart attacks by providing physicians with a map of dead heart tissue less than 24 hours after it is injected into a patient's bloodstream. Centocor is also in the early stages of testing Fibriscint, an antibody designed to spot blood clots and one that may someday make the painful contrast venography technique obsolete. NeoRx (Seattle, WA) is in the penultimate stages of testing an antibody that pinpoints melanoma, the dreaded skin cancer. Immunomedics (Newark, NJ) uses a combination of two antibodies, injected on consecutive days, to pinpoint colorectal cancer. Neoprobe (Columbus, OH) has devised a new monoclonal antibody that helps surgeons detect cancerous cell pockets that are passed over by CAT scans and X-rays. (Extracted from Wall Street Journal, 14 August 1987)

Possible drug against rheumatoid arthritis

The Thundergod vine may yield a drug effective against rheumatoid arthritis, according to X.L. Tao of Beijing Union Hospital, China. The herb has been used for centuries to treat pains in joints. Patients treated for 12 weeks with Tripterygium wilfordii showed significant improvement to those on placebos in all clinical assessments, including joint pain, morning stiffness, number of swollen joints, grip strength and 15-minute walking time. Joint tenderness scores dropped from a mean of 25.1 to 7.9 after four weeks of therapy. Side effects include skin rash, cheilosis, thinning of skin and nails and pigmentation, but no one dropped out of the study because of side effects. (Extracted from Medical World, 24 August 1987)

BioStar Medical Products Inc. is developing a promising new diagnostic technology that may dramatically cut the costs of a wide range of commonly used medical tests.

The Boulder company's approach to the multibillion dollar diagnostics market is fundamentally different from existing technologies. It employs a unique combination of optics and thin-film techniques that are commonly used in the semiconductor industry.

Existing diagnostic tests use a variety of methods, such as detecting and measuring enzyme reactions, to do their work. By contrast, BioStar's products use a specially treated piece of glass. When a sample such as blood or urine is placed on the glass, it changes colour if the test is positive.

The new technology can save time and money because expensive laboratory processing is unnecessary. Also, it is ideal for doing tests in relatively isolated areas that do not have access to advanced testing facilities. (Extracted from The Denver Post, 21 September 1987)

Windows into the womb

A relatively new technique of diagnosing genetic defects in a foetus early in pregnancy is gaining ground. The World Health Organization says that the new procedure, known as chorionic villus sampling, has been performed on 25,000 women so far. According to Bernadette Modell of the University College Hospital in London, about 10 per cent of all prenatal diagnoses in Europe now use this technique.

In chorionic villus sampling (CVS), clinicians take a sample of foetal cells that will ultimately form part of the placenta. They can test these cells for signs of Down's syndrome, for instance, as early as 10 weeks, enabling a woman to have an early abortion.

The technique thus has a big advantage over aminocentesis, the standard test for chromosomal abnormalities, which uses cells from the amniotic fluid: amniocentesis cannot be performed until the second trimester of pregnancy. Furthermore, CVS gives a result in a few days. It takes about four weeks to obtain a result from aminocentesis, because technicians must first grow the cells in culture.

Chorionic villus sampling also provides enough cells to enable researchers to extract the DNA to diagnose some inherited diseases such as thalassamia, cystic fibrosis and muscular dystrophy. A second test, alpha-fetoprotein screening, is a blood test that is mainly used to detect defects in the neural tube - which forms the spinal column and brain - the most common birth defects in the United States. It can also indicate when a foetus is at greater risk for Down's syndrome. In this test, samples of the woman's blood are taken to measure levels of alpha-fetoprotein, a substance the foetus excretes into the amniotic fluid and that enters the mother's bloodstream.

The test was developed in the UK about 15 years ago, but it was slow to be adopted in the United States, in part because a number of investigators and the FDA feared it would be offered without adequate counselling and follow-up services

such as sonograms and amniocentesis, if necessary. About two years ago, the American College of Obstetricians and Gynaecologists warned physicians that they might be subject to suit if they did not offer a woman the test and she later had a child with a defect.

The test was developed to detect the serious birth defects that occur when the neural t e does not completely close during early development of the foetus. About half the time, the tube is open at the top and the baby is born with a rudimentary brain, or no brain at all. These babies are dead at birth or die soon after.

In the other half of the cases, the opening is along the spine, and a portion of the nerve column of the spine is exposed. These babies, said to have spina bifida, are paralyzed below the portion of open spine. Some of these children also have hydrocephaly, a condition in which fluid accumulates in the head and can result in brain damage. Children with spina bifida may be mentally retarded, and frequently have no bowel or bladder control.

Neural tube defects occur in about one out of every 1,000 babies born.

When a foetus has a neural tube defect, large amounts of alpha-fetoprotein pour out of the open spine or skull into the the amniotic fluid. From there they enter the mother's bloodstream, where they can be detected.

The blood protein test is given at 16 weeks of pregnancy, when there is enough of the protein around to make testing feasible. Those women whose alpha-fetoprotein levels are abnormally high are given sonograms, pictures of the foetus produced by sound waves, to see if there is some other explanation for the finding. If the sonogram reveals no explanation, the woman is given amniocentesis. The amniotic fluid is checked for alpha-fetoprotein and for acetylcholinesterase, a nerve enzyme that is often present when the foetus has a neural tube defect.

In 1984, Dr. Irwin R. Merkatz of the Albert Einstein College of Medicine in the Bronx noticed that just as high levels of the foetal protein in a pregnant woman's blood indicate that her foetus may have a neural tube defect, so low levels may indicate that the foetus has a chromosomal defect, the most common of which is Down's syndrome. The finding was recently confirmed in a two-year study of 34,000 pregnant women in Connecticut directed by Dr. Miriam Schoenfeld DiMaio of the Yale University School of Medicine.

With alpha-fetoprotein screening, it is possible to tell younger women if the foetus they are carrying is at increased risk of having Down's syndrome and to offer them aminocentesis. Not all cases of Down's syndrome will be detected by the blood protein test and most women who have aminocentesis on the basis of the test will not have foetuses with Down's syndrome, but the chance that they will is seen as high enough to warrant the risk of amniocentesis. (Extracted from New Scientist, 9 July 1987 and International Herald Tribune, 24 September 1987)

Gene probes for use in diagnostics

Gene probes and restriction enzymes can be useful and profitable products for medical markets. The US Food and Drug Administration has now approved about seven gene probes for use in diagnostic test kits. Other gene probes are not sold in kits, but are used by laboratories to identify other genetic diseases. Patents have already been awarded on several gene probes, since they are classed as purified substances that have a function they did not have in nature. Closely related gene probes may each be patentable and perform the same function, so restriction enzymes might not be so profitable. On top of all this, doctors might be faced with further lawsuits now that they are able to use the gene probes to diagnose many more diseases in utero. (Extracted from New Scientist, 16 July 1987)

Herpes DNA probe is non-radioactive

DNA probe technology has been used to detect herpes virus for the last five years, and most of these probes use radioactive markers. Now Enzo Biochem (New York City) has received Food and Drug Administration approval to sell a non-radioactive DNA probe for the incurable sexually transmitted disease. The company plans to distribute the probe to clinical laboratories that perform diagnostic tests for hospitals, physicians, and other laboratories.

Like other DNA probes, the Enzo procedure starts with a sample from the infected area. At the testing laboratory this smear is heated to split DNA molecules into their two constituent strands. The probe - a customized single strand of DNA that matches a herpes-infected strand - is then added. If any herpes virus is present in the sample it will link up with the synthetic probe. Most probes use a radioactive marker to identify any linked molecules. Enzo's probe, however, is marked with biotin, one of the B vitamins. To make it visible, the enzyme horseradish peroxidase is bound to the biotin. Hydrogen peroxide and a coloured dye, added in the last step, create a reaction. The dye is oxidized when the enzyme and the hydrogen peroxide interact, turning a reddish-brown colour visible with a microscope. (Source: High Technology, July 1987)

DNA probes for diagnosing cancer

US patent approval has been granted technology covering DNA probes that detect chromosomal translocations associated with the activation of oncogenes, the family of genes whose abnormal expression can cause cancer. Gen-Probe (San Diego) will share a coexclusive license on the technology covered by US patent. Oncogene Science (Manhasset, N.Y.) now has in clinical trials a diagnostic test based on the technology. It identifies a specific chromosomal re-arrangement associated with chronic myelogenous leukaemia. The technology may have application in diagnosing more common cancers, such as those of the lung, breast and colon. (Source: Chemical Week, 29 July 1987)

Cetus tests combined anti-cancer products

A combination of Proleukin (interleukin-2) and tumour necrosis factor (TNF) began human clinical trials last month. According to cetus Corp, they may have a synergistic tumour killing effect when used together. Animal studies showed that this combination approach can be effective on tumours that have not responded, or have responded poorly, to either drug when used alone. (Source: Biotechnology Bulletin, Vol. 6, August 1987)

Gonorrhea test uses mutated gonococcus

A new test for gonorrhea that does not require transport of live bacteria to laboratories and costs about half as much as traditional tests is being marketed to doctors and public health workers by Technology Management & Marketing. The test depends on a strain of Neisseria gonorrheae that has been mutated by a genetic transformation technique to grow only in the presence of gonococcal DNA. Practitioners

will ship swabbed specimens to the Santa Clara, California firm where DNA will be isolated from them and applied to cultures of the mutant organism. Results will be available 24 hours later. The expected cost is $3.00 to $5.00 per test. The new test may be especially useful in areas of the US and in countries that lack easy access to laboratories. For traditional tests, live bacteria must be sent to laboratories in a carbon dioxide-spiked atmosphere at 30 to 40°C. The firm expects to package the test with a similarly based test for sexually transmitted Chlamydia by the end of 1987. (Reprinted with permission from Chemical and Engineering News, 14 September 1987. Copyright (1987) American Chemical Society)

Healing protein

Human tests of a naturally occurring protein that may help wounds heal faster are beginning. US Food and Drug Administration approval for epidermal growth factor (EGF) is expected within two years, and widespread availability of the protein should follow within five years. During that period, EGF may become the preferred treatment for burn victims. Animal trials show that the protein doubles the rate of skin regeneration with no visible side effects; it also aids in cornea regrowth. In a report released earlier this year, the consulting firm of Arthur D. Little said EGF by 1990 will become a standard for healing surgical incisions. If EGF cut one day off the average hospital stay for each of the more than 21 million surgical patients treated annually, savings would total $4 billion. (Extracted from High Technology Business, September 1987)

IL-2 used in cancer recovery

Interleukin-2-stimulated lymphocytes placed in the tumour bed after removing malignant gliomas can aid recovery, according to D.B. Jacques of Hungtington Medical Research Institute (Pasadena, CA). Most of the first 60 patients treated with the procedure have had a positive outcome, and some patients whose original prognosis was that they had 10-14 weeks to live are still alive after over two years. No serious side effects have been noted. The treatment is still highly experimental, but the disease is 100 per cent fatal, so the treatment offers the first hope for such patients. Only patients with high-grade (three or four) gliomas who have failed primary therapy are admitted to the treatment. The tumour is removed as much as possible and IL-2 stimulated autologous lymphocytes are implanted in its place. CT scan follow-ups indicate progressive decreases in tumour size. One patient who had failed two surgeries, radiotherapy and chemotherapy is now free of disease two years after the treatment. It is not known if the disease might still recur. Side effects have been limited to fevers of less than 101°F in 40 per cent of patients, and this may be due to the restriction of fluids to prevent brain swelling. (Extracted from Medical World, 11 May 1987)

Treating cancer with endorphins

The body's own euphoric agents - known as endorphins - may be used to halt cancer growth. So asserts Ian S. Zagon of the Department of Anatomy and Cancer Research at Pennsylvania State University's Milton S. Hershey Medical Center (Hershey, Pa.). Endorphins regulate growth of all human cells, including that of most forms of cancer. Zagon uses two drugs that are approved for treating narcotic addiction - naloxone and naltrexone - to stimulate the body to produce more endorphins. When used for narcotic addiction, the drugs block endorphin receptors throughout the body, thus preventing a narcotic high. However, the drugs also increase production of endorphins and endorphin receptors. When that stronger concentration of endorphins and endorphin reacts with the increased number of endorphin receptors on tumour cells, cancer growth is inhibited, says Zagon. The anticancer activity has been demonstrated in animal trials, as well in vitro on all types of human cancers, Zagon says. He also is studying the use of naloxone and naltrexone to stimulate the body's growth regulators. (Source: Chemical Week, 2 September 1987)

Cetus's monoclonal-aimed r-DNA ricin to be tried on 20 breast-cancer patients

A score of women with untreatable breast cancer are to receive injections of recombinant ricin, steered to the site of their tumours by monoclonal antibodies. They are the first patients in a series of Phase I clinical trials, to see if the targeted toxin can safely kill off malignant mammary cells. This initial test is taking place at the Fox Chase Cancer Center, Philadelphia, using ricin-loaded monoclonals developed at Cetus Corp., Emeryville, California.

Ricin, one of the deadliest cell-destroying toxins known, consists of two amino-acids sequences: the B-chain binds the poison to its target cell; the A-chain is an enzyme that kills cells by disrupting their ribosomes. By cloning and expressing the A-chain alone, in Escherichia coli, the Cetus team was able to generate large amounts of high-purity ricin-A, explains project leader Jonathan C. Raymond. Unlike the native ricin molecule, the recombinant moiety is not glycosylated, so is not swept out of the body by the liver before it has a chance to act.

Guiding this lethal payload to its target is a murine monoclonal antibody raised against a mammary tumour that had metastasized to the liver. Its antigen, reports Raymond, "is a glycoprotein that binds 50 per cent or more of this tumour". In nude mice carrying a transplanted human breast cancer, he states, "the antibody/ricin-A achieved significant inhibition of tumour growth".

It will take six to ten months, Raymond reckons, to complete these Phase-I toxicity trials, which will also be extended to Duke University School of Medicine, and perhaps the US National Cancer Institute. (Source: McGraw-Hill's Biotechnology Newswatch, 15 June 1987)

A combination of recombinant drugs fights cancer

Cetus (Emeryville, California) has entered a combination of genetically engineered analogues of interleukin-2 (IL-2) and tumour necrosis factor (TNF) into clinical trials against a broad range of cancers. When used together, the compounds may have a synergistic effect on a variety of tumours. Preclinical studies have shown that the combination is effective against tumours that have responded poorly to either drug alone. Initial studies will take place at Alta Bates Hospital (Berkeley, California), although Cetus plans additional trials of TNF and IL-2, and trials of TNF with existing chemotherapeutic drugs. (Source: Chemical Week, 29 July 1987)

HA potential in drug delivery

Genzyme has agreed to an initial joint R&D programme with Hoffman La Roche, on using hyaluronic acid (HA) as a drug delivery vehicle.

The companies will engage in research applying Genzyme's proprietary technologies to produce HA based products as a dosage form for injectable formulations for the therapeutic administration of specific biologically active proteins developed by Hoffman La Roche.

Hyaluronic acid is a natural water-retaining and lubricating component of the body's soft tissue. It is also a key component of certain body fluids, including the synovial fluid of the joints and the vitreous humor of the eye. (Source: Manufacturing Chemist, August 1987)

Oral Hepatitis-B vaccine progress

Wyeth Laboratories has made significant progress towards developing an oral vaccine against Hepatitis-B. The current vaccine, available since 1982, costs $115 for a course of three injections and requires refrigeration. These factors have severely limited its use, but an oral vaccine might be much cheaper and easier to handle and administer. Animal tests have shown that adenovirus engineered to include the gene for Hepatitis-B surface antigen can produce antibodies against both adenovirus and Hepatitis-B. The researchers would not predict when such a vaccine might be ready for human clinical trials. The market for an oral hepatitis vaccine would be huge, especially in the Third World, where the ease of administration and the elimination of the risk of spreading other diseases with syringes would give an oral vaccine far better acceptance than the intramuscular vaccine has achieved. (Extracted from Science News, 18 July 1987)

Hepatitis-B vaccine registered and marketed

SmithKline Beckman Corporation says its genetically engineered Hepatitis-B vaccine, "Ngerix-B", has received regulatory approvals in the UK, FRG and the Netherlands. The product of the firm's Belgian-based SmithKline Biologicals unit is now officially registered and marketed in 21 countries. Initial registration came less than a year ago in December 1986 in Belgium. Applications are pending in more than 60 countries. (Source: Chemical Marketing Reporter, 7 September 1987)

Blood substitutes

Northfield Laboratories' polymerized haemoglobin blood substitute will soon begin human trials with US Food and Drug Administration approval. An industry source estimates that 30 firms are working toward commercialization of blood substitutes, but critics are concerned about safety, efficacy and commercial potential of such substitutes. In 1983, Alpha Therapeutics, a Green Cross subsidiary, was denied US Food and Drug Administration approval for its Fluosol perfluorocarbon blood substitute. Now, concerns about the transmission of AIDS via blood transfusions are helping blood substitutes, or oxygen transport materials, move closer to a commercial reality. Blood substitutes, which lack the blood's nutrients and other protective ingredients, can be used for patients who have lost large amounts of blood. They have longer shelf lives than blood, eliminate the need for cross-matching and typing donor blood to a patient's, and are virtually free of viruses (e.g. hepatitis and AIDS).

Problems with fluorochemical substitutes include the need to administer extra oxygen, since they cannot retrieve enough oxygen directly from the air, which could cause oxygen toxicity, damaging tissue. Haemoglobin substitutes, made by modifying the haemoglobin molecule, rely on blood for raw material, supplies of which could become tight if such materials become popular. (Extracted from Chemical Week, 12 August 1987)

Drug against Alzheimer's disease to undergo tests

Warner-Lambert's tetrahydroaminoacridine (THA) will be tested for treatment of Alzheimer's disease by the US National Institute on Aging. The drug may help reduce memory loss in Alzheimer's patients. Researchers from various institutions will take part in the study, which was designed in co-operation with the US Food and Drug Administration. The two-year study is based on preliminary results which showed beneficial effects of THA in 16 of 17 patients. The drug is not expected to stop or reverse the course of the disease, however. THA may act by blocking the breakdown of acetylcholine. The drug will only be beneficial as long as enough brain cells remain alive to produce sufficient acetylcholine. THA will never be a cure for Alzheimer's.

If the results of the clinical trial prove favourable, it is expected that the data will be submitted to the FDA for marketing approval and that the drug will be developed and released to the public. (Extracted from Chemical Marketing Reporter, 10 August 1987)

New antibiotics

Researchers at Abbott Laboratories have designed compounds that may herald the emergence of a new class of antibiotics. The US team has targeted a key bacterial cell-wall enzyme for possible inhibition by the new drugs. This enzyme, CMP-KDO synthetase, is unique to gram negative bacteria.

Peptide prodrugs of the compound, alpha-C-(1,5-anhydro-7-amino-2,7-dideoxy-D-manno-hepto-pyranosyl)-carboxylate, the researchers report, disrupt the formation of the lipopolysaccharide wall.

The current compounds being investigated have very short half lives and an activity spectrum that is not wide enough. However, further research will be carried out in this area. (Source: European Chemical News, 21 September 1987)

A longer-acting TPA heads for clinical trials

Integrated Genetics (Framingham, Mass.) says that it has developed a longer-lasting form of tissue plasminogen activator (TPA), a naturally occurring human protein that is highly effective in dissolving blood clots in heart attack patients. Clinical trials of TPA could begin as early as next year. Using protein engineering techniques, scientists at the company produced TPA by removing a glycosylatin site present in the molecular structure of the natural material, which resulted in a 10-fold increase in the length of time that TPA remains active in the bloodstream. Using this new form, it should be possible to administer the drug in lower doses and in a single injection, rather than in continuous intravenous solution. Longer-acting TPA should also avoid the side effects of reocclusion or reclotting common in patients treated with natural TPA. (Source: Chemical Week, 9 September 1987)

New drugs against Gram-negative bacteria

Astra Alab has developed a new class of drugs against Gram-negative bacteria such as salmonella. The drugs consist of a synthetic enzyme inhibitor coupled to a dipeptide that is a natural nutrient for the bacterium. The microbes thus ingest the poisoned compound. The toxin is released as the bacterium digests the peptide. The toxin is 3-deoxy-beta-D-manno-2-octulopyranosonic acid. It kills the bacteria by inhibiting synthesis of lipopolysaccharide essential for the outer membrane. (Abstracted with permission from Chemical and Engineering News, 13 July 1987. Copyright (1987) American Chemical Society)

Therapeutics to treat central nervous system disorders being developed

Allelix Biochemicals, a division of Allelix, Inc., Canada, and McMaster University of Hamilton, Ontario, have announced a collaborative programme to develop new pharmaceuticals for the treatment of central nervous system disorders including Parkinson's disease, glaucoma and hypertension. The current market for such pharmaceuticals is in the hundreds of millions of US dollars.

The programme is expected to greatly reduce the time, risk and expense traditionally associated with the design of new pharmaceuticals. It builds on the recent advances in the laboratory of Dr. Ram Mishra at McMaster. Dr. Mishra has been able to isolate a specialized structure of the brain - the dopamine receptor - which is known to be the site of action of a number of current drugs. The drugs were developed without an understanding of the receptor and have several undesirable side-effects.

Allelix will apply its expertise in biochemistry and genetic engineering to prepare large quantities of the dopamine receptor or study. In particular, the exact shape and characteristics of the receptor will be determined so that new drugs can be designed to fit precisely into the receptor, thereby reducing their side-effects.

Dr. Brian Underdown, associate dean, research, of McMaster's Faculty of Health Sciences emphasized the advantages of linking McMaster's strength in neuropharmacology with the outstanding ability of Allelix in genetic engineering. "The programme will advance knowledge in brain science and provide opportunities in Canada for the private sector to create jobs and improve health", he said. (Source: Company News Release, 9 July 1987)

Vaccines developed in United States to be tested in India

India will become the testing ground for several new vaccines being developed in the United States, following an Indo-US agreement on a Vaccine Action Programme (VAP) "to develop and test vaccines and diagnostic techniques for major communicable diseases".

The agreement has paved the way for trying out advanced and genetically engineered vaccines in India that might, for practical reasons, be difficult to test in the United States.

India has always been sensitive on the issue of its people being used as guinea-pigs for the trial of drugs and vaccines developed elsewhere, which is one reason for the delay of nearly 18 months in signing the agreement. This difficulty has now been met by the United States, which has associated Indian scientists with the US laboratories where the vaccines are being developed.

Among the vaccines to be tested are those against diarrhoeal diseases (rota-virus, cholera, shigella, E. coli and salmonella), a cellular pertussis vaccine, an oral typhoid vaccine and a recombinant DNA vaccine against Hepatitis-B. The collaboration also provides for the testing of the vaccinia/rabies glycoprotein recombinant vaccine developed at the Wistar Institute and used in a controversial experiment on cattle in Argentina.

The five-year project is estimated to cost $9.6 million, out of which the US Government will contribute $7.6 million. Besides the Department of Biotechnology, the Ministry of Health will implement the project.

Allaying fears that the agreement with the United States will make Indians guinea-pigs, Dr. S. Ramachandran said the rights and welfare of human subjects of research will be protected, taking into account the laws and regulations in both countries. Clearance would be obtained from the drug controller of India before tests of the vaccines.

Whether or not the United States will succeed in testing its vaccines depends on the Indian Council of Medical Research (ICMR), which advises the drug controller whether a vaccine should be tried on humans. Dr. A.S. Paintal, director general of ICMR said he would not allow any vaccine to be used in India unless it was also approved for use in the United States by the Food and Drug Administration.

As for the US motive in collaborating with India, Paintal says it represents only the natural curiosity of scientists to find out the efficacy of their vaccines by testing them in places where the diseases exist. (Source: Nature, Vol. 328, 23 July 1987)

Insulin by genetic engineering

After one year of waiting, the Danish pharmaceutical firm Novo can now begin producing insulin with genetically manipulated yeast. Back in January 1986, Novo announced that it wanted to produce insulin from genetically altered yeast (Saccharomyces cervisie). At that time, it was seen as a breakthrough in biotechnology, but the plans were halted by environmentalist groups that feared the release of genetically manipulated yeast. The storm of public opinion surrounding Novo caused Denmark to pass the world's first law on applied gene technology in June last year. Now the provincial government of West Zealand has given Novo permission to begin production in Kalundborg. The regional authorities who will monitor the application of this law lack expertise of their own. Even the national authorities are uncertain as to how the law on gene technology should be applied. A Novo competitor, Nordisk Gentofte, is having similar problems obtaining permits. Nordisk Gentofte wants to use gene technology produce a growth hormone from E. coli bacteria. (Source: Ny Teknik, 26 February 1987)

A French effort in antithrombosis drugs

A joint venture to develop and produce antithrombotic agents through genetic engineering techniques will be undertaken by a joint venture of French pharmaceutical company Sanofi (Paris) and French biotechnology company Transgène (Strasbourg). As a first goal, the new company, Sotragene, plans to begin industrial production of the protein hirudin, a powerful thrombin inhibitor. In nature, hirudin is secreted by leeches to prevent the coagulation of their victim's blood for better retention. Transgène has developed a high-yield method of synthesizing active and homogenous hirudin molecules, expressed in bacteria and yeast; the product has proved effective in animal tests. Sanofi, a major producer of antithrombosis drugs, will handle clinical trials and international development of hirudin; Transgène will work on new applications. Sanofi and Transgène expect to develop markets in treating thrombosis inhibitor deficiency, in diagnostics, in treating heart condition complications during surgery and in haemodialysis. (Source: Chemical Week, 30 September 1987)

AIDS vaccine test approved

The first human trial of an experimental AIDS vaccine has been approved by the US Food and Drug Administration (FDA). MicroGeneSys of West Haven, Connecticut has been given the go-ahead for human

studies on its vaccine which could begin as early as October.

Volunteers are currently being recruited for the first phase of the programme, designed to test the safety of the vaccine as well as seeing if it produces antibodies to the virus that causes AIDS.

A total of 81 volunteers will be involved, all tested HIV negative and categorized as low risk. The studies will be carried out at the National Institute of Health Clinical Centre at Bethesda, Maryland with the first phase expected to take around six months. Later trials, involving much larger numbers of volunteers will concentrate on testing the efficacy of the vaccine against AIDS. Even if the testing proves successful, MicroGeneSys does not expect to be able to market the vaccine before the mid 1990s.

Genentech and Oncogen/Genetics systems are awaiting approval for human testing of their vaccines whilst Repligen Corp., Merck and Viral Technologies are still at the animal studies stage. (Source: European Chemical News, 31 August 1987)

AIDS trial to control the disease

Plasma from people with high levels of antibodies against AIDS virus will be transfused into AIDS patients in an attempt to control the disease, according to researchers at Westminster and St. Stephen's hospitals (London). A similar trial at Addenbroke's Hospital (Cambridge) had inconclusive results. The new trial will involve about 40 AIDS patients and will last longer than the previous trial. The plasma of people with HIV antibodies may also have antibodies against associated diseases. The plasma will be treated with beta-propiolactone and will be heated to 56°C for 30 minutes to kill any viruses or other pathogens that might be present. A group of patients will receive plasma that does not have the antibodies to serve as a placebo control. (Extracted from New Scientist, 11 June 1987)

A therapeutic role for diphtheria toxin

Diphtheria toxin is one of the deadliest known. A single molecule is enough to kill a cell, and 7.5 micrograms will kill most people. Seragen (Hopkinson, Mass.), a privately held biotechnology company, is developing technology that it hopes will put the diphtheria toxin's deadly force to good use - battling cancers and destroying immune cells that could reject organ transplants.

The technology involves genetically engineered hybrid proteins. Those proteins link a portion of the diphtheria toxin with a receptor that binds specifically to the cancer or immune cell targeted for destruction without harming healthy, non-threatening cells. Seragen plans later this year to enter its hybrid protein in clinical trials against adult T-cell leukaemia, a blood cancer resistant to current therapies.

Diphtheria toxin, produced by Corynebacterium diphtheriae, is made up of two fragments, A and B. Fragment A is the toxic portion of the molecule. It kills a cell by destroying an enzyme called elongation factor 2 that is critical to cell protein synthesis. Fragment B contains the toxin binding site, which allows diphtheria toxin to bind to all eukaryotic cells.

Seragen's technology removes the part of fragment B that contains its binding site. Then the remaining portion of the toxin is attached to a binding site specific for the type of cell marked for destruction.

The IL-2/toxin hybrid is genetically engineered. The gene coding for the shortened diphtheria toxin and the gene for the IL-2 binding site are inserted into the bacterium Escherichia coli, which churns out the hybrid protein.

The advantage of genetic engineering over chemical coupling of the hybrid protein is that the genetically engineered product is consistent and reproducible. In contrast, molecules that are chemically combined can combine in different configurations - resulting in inconsistency and varying efficacies.

Seragen says that another advantage of its hybrid toxin is that when the toxin binds to its target cell, the cell ingests it. As a rule, the binding of diphtheria toxin to a cell receptor causes the receptor to form a vessicle. The vessicle carries the toxin across the cell membrane, depositing the toxin in the cell.

Such cell entry compares favourably to monoclonal antibodies - another potential "magic bullet" that researchers hope will deliver toxic drugs to destroy tumour and other killer cells selectively.

Besides leukaemia, Seragen is targeting malignant melanoma. To combat malignant melanoma, Seragen would combine the toxic portion of the diphtheria toxin with the binding site of melanocyte stimulating hormone (MSH), which binds to the monocytes and spurs them to produce pigment. Seragen hopes to begin MSH/toxin clinical trials next year. (Extracted from Chemical Week, 19 August 1987)

New studies for AZT

Doctors in Britain are planning to carry out trials of the antiviral drug zidovudine (formerly known as azidothymidine or AZT) on patients infected with the human immunodeficiency virus (HIV) but who have not yet developed symptoms. Patients taking part in the trials will be those with signs that predict more rapid progression to AIDS.

Ian Weller, of the academic department of genitourinary medicine at the Middlesex Hospital and Medical School, London, says that the trials will assess zidovudine and other antiviral agents alone and in combination to find out how to make treatment less toxic and more effective. Doctors already know that zidovudine is effective in patients with AIDS-related complex (a condition that precedes full-blown AIDS). So patients in the trial will, if they are not already, receive zidovudine should they progress to AIDS-related complex.

Burroughs-Wellcome reports new medical findings show its AZT drug to have it greatest effect in the early stages of AIDS. These implications bolster the belief that early intervention with antiviral treatments might help cope with the AIDS epidemic.

Expanded use of AZT - or of other antiviral treatments being developed - could broaden the market for makers of AIDS therapies. Ninety per cent of patients with AIDS and AIDS-related complex (ARC) lived after taking AZT for one year, versus a 60 per cent nine-month survival rate among patients receiving a placebo. The reports underscored the fact that the most substantial and lasting improvements with the fewest side-effects occurred in patients with ARC. Based on these findings, a multicentre trial of AZT is now being organized involving 1,500 people who carry the virus but have not manifested any symptoms of disease. In ARC patients, AZT prompted a lasting increase in CD4 cells, key elements of the immune system, but in AIDS patients, these cells were only

temporarily boosted, often declining to pre-treatment levels after 20 weeks of therapy.

Wellcome is also dismantling its limited distribution system to increase the supply of zidovudine (AZT). This means that the drug will now be available to doctors in the US and UK through normal distribution channels.

Increased supply of the key raw material thymidine (derived from herring and salmon sperm) from Pfizer and Wellcome's production capacity increases have allowed the company to shift its strategy. Wellcome now has £17m ($28.2m) of additional capacity in the US and UK on-stream. Also the firm claims to have made improvements to the scaling up of the 16-stage synthesis of zidovudine.

Wellcome is now also in a position to step up clinical trials of the drug in combination with other potential anti-viral compounds such as its herpes treatment, acyclovir and the interferons. Nevertheless, mixing compounds does not necessarily guarantee a summation of effect. Zidovudine loses much of its effectiveness when combined with ribavirin.

Meanwhile, the US Food and Drug Administration is being urged to give fast track approval to granulocyte macrophage colony stimulating factor (Gmcsf) as an AIDS therapy. Researchers from the New England Deaconess Hospital and the University of California in Los Angeles have reported that Gmcsf increases the numbers of several critical kinds of immune cells in 16 AIDS patients.

Gmcsf acts on bone marrow cells in an early stage of development to stimulate production of white blood cells. The drug also boosts the T-cells in some patients although the effect has not been explained. (Extracted from New Scientist, 23 July 1987, Wall Street Journal, 23 July 1987 and European Chemical News, 21 September 1987)

Race for patents on relatives of AZT

The American Government is pressing the pharmaceuticals industry to manufacture and test a new drug for AIDS which is related to azidothymidine (AZT). No one has yet tested the new compound, cyanodideoxythymidine, on animals. Yet researchers say that it is effective against human immunodeficiency virus (HIV) in the test tube, even in very small quantities.

The National Cancer Institute in Bethesda, Maryland, recently invited bids from companies to manufacture cyanodideoxythymidine under exclusive licence so that researchers can begin testing the drug on animals and patients. A spokesman for the institute says that several dozen companies have shown interest.

Currently, the only drug to have approval for widespread treatment of AIDS and AIDS-related complex, which usually precedes the full-blown disease, is AZT, which should now be known by its approved generic name, zidovudine. Like zidovudine, cyanodideoxythymidine (tentatively called CNT) is a nucleoside analogue, a type of drug developed originally to treat cancer.

Researchers are still experimenting in the laboratory with the newest nucleoside analogue, CNT. They exposed lymphocytes to the virus and then cultured these cells with CNT. Even in very small quantities, CNT prevented virus from killing the cells. Milligram for milligram, says Eddie Reed, co-ordinator of preclinical drug development at the AIDS office of the National Cancer Institute, CNT is more effective than zidovudine.

Burroughs-Wellcome, the American subsidiary of the British pharmaceuticals company, the Wellcome Foundation, owns the rights to zidovudine, but a fight for ownership of the other nucleoside analogues could soon unfold. The first researchers to synthesize and test CNT on lymphocytes (white blood cells) infected with HIV were Samuel Broder and Hiroaki Mitsuya of the National Cancer Institute and Jerome Horwitz and Eduardo Palomino of the Michigan Cancer Foundation. Both they, the Government and Burroughs-Wellcome have applied for a patent on CNT. (Extracted from New Scientist, 23 July 1987)

Toxic effects end trial of AIDS drug

Initial trials of a new drug to combat the human immunodeficiency virus (HIV), which causes AIDS, have come to a halt. Doctors in the US have suspended the studies because the drug, dideoxycytidine (DDC), seems to be too toxic.

Lowell Young, director of the Kuzell Institute for Arthritis and Infectious Diseases, in San Francisco, said that DDC appears to be much more toxic than an alternative drug, zidovudine (formerly known as AZT). Young told the first international conference of the Hospital Infection Society, in London, that the results of the initial studies had delayed the start of clinical trials, which doctors had planned for later this year.

DDC, like zidovudine, works by preventing HIV from slotting its own genetic material into the genes of its host. In the laboratory, DDC halts the replication of HIV at about one-tenth of the dose required with zidovudine.

Zidovudine poisons the bone marrow and can cause anaemia. Researchers had hoped that a drug such as DDC, which appeared to be effective in lower doses, would be less toxic. However, it exerts its toxicity elsewhere, through its effects on peripheral nerves. (Extracted from New Scientist, 10 September 1987)

Safer AIDS test uses saliva, not blood

The UK Department of Health and Social Security is seeking an industrial partner to help in bringing a new AIDS test to market. Unlike existing tests which analyse blood samples, the test developed by virologists at the Virus Reference Laboratory in Colindale, North London, can identify the presence of the AIDS virus in saliva, cutting the risk of medical staff being cross-infected. There is also the advantage that saliva is readily obtainable, without the need to use a needle. The test is extremely sensitive, and uses a virus probe with enzyme-mediated colour changes to identify the AIDS virus. (Source: Biotechnology Bulletin, Vol. 6, No. 6, July 1987)

New test detects viral activity

A new type of test for the human immunodeficiency virus (HIV) may make it possible to determine when the infection is active, and whether antiviral drugs are working effectively. The test, produced by a biotechnology company based in Massachusetts called Integrated Genetics, relies on the detection of viral messenger RNA.

A spokeswoman for Integrated Genetics said that the test may help in determining the best timing for antiviral therapy. There is a lag between production of the RNA, and the appearance of the first clinical symptoms in the patient. Most drugs for the treatment of AIDS inhibit replication of the virus. They are of no use during the latent stage, when there is no viral replication, but it would probably be best to start treatment when replication begins.

The test from Integrated Genetics, which gives results in 18 hours, can detect replication before massive amounts of viral RNA flood the patient's system. The test can also determine which HIV carriers are actively shedding virus into their blood.

The test makes use of DNA to find the viral RNA. The first step is to separate out the lymphocytes in the blood sample. The lymphocytes are then lysed - the cell membranes are dissolved, exposing the nucleus - by a patented process which makes the RNA accessible. The operator then introduces a DNA probe, a short length of DNA that hybridizes to (matches up with) the RNA. Hybridization takes about 12 hours. The solution is then filtered, and a second, radioactively labelled "capture probe" in the filter causes the DNA particles to adhere to it. To read the test, the operator places the filter on an X-ray film, which is then developed.

The firm is now working on improving the test, so that it gives faster results and can be used in a doctor's surgery. (Source: New Scientist, 23 July 1987)

Finding two diseases with one blood test

Eastman Kodak (Rochester, N.Y.) and Cellular Products (Buffalo) say they will soon be filing for Food and Drug Administration approval to begin clinical studies of a new test that can simultaneously detect both HIV and HTLV-1. If it is approved, Cellular Products, which developed the test and has applied for a patent, would manufacture the test system; Kodak would market it as part of its business relationship with Cetus (Emeryville, Calif.). (Source: Chemical Week, 9 September 1987)

Rapid tests could fall into the wrong hands

Instant tests to determine whether someone has been exposed to the human immunodeficiency virus (HIV) will soon be with us. Many of them, such as the one which the American company Du Pont hopes to sell in Britain by early 1988 will need no special expertise to carry out or to read.

This new generation of tests raises the issue, however, of how closely regulated their use and distribution should be. British guidelines on tests for HIV were laid down at a time when tests needed a significant quantity of blood, and specialist equipment or technical knowledge to carry them out.

By contrast, Du Pont's test needs only one drop of diluted blood added to the well in the centre. The colour then changes according to whether antibodies to HIV are present or not.

Du Pont's kit, and several others produced in the US and Japan, are so simple that doctors could offer tests at their surgeries. Such use would be very difficult to regulate, however.

William Burns, of Du Pont, says that the company wants to be sure that people who receive supplies of such tests would be able to comply with the guidelines issued by the Department of Health and Social Security. These specify that: the patient must give informed consent before having the test; there must be a clinical reason for the test; if the first result is positive, a confirmatory test must take place; and there must be adequate access to counselling both before and after the test.

Du Pont says that it has already refused to supply other products to diagnose HIV infection to certain private clinics and laboratories, mainly on the grounds that suitable counselling was not available. But it would be difficult, if not impossible, for a company to vet thoroughly every organization that placed an order.

A further problem with the new type of test is that people could use it to test themselves. Medical Advisory Services for Travellers Abroad (MASTA), an organization based at the London School of Hygiene and Tropical Medicine, had planned to include Du Pont's test in kits that people who are going abroad can buy, to reduce the risk of catching blood-borne viral diseases should they need a blood transfusion.

Du Pont will be able to sell its test in Britain only if it receives approval from the Food and Drug Administration in the US. The Food and Drug Administration licenses all tests because blood is considered a pharmaceutical product in the US.

In Britain, a similar regulatory system controls the distribution of pharmaceutical products. But a spokesman for the Department of Health and Social Security said that there are no plans to set up such a framework for tests. All new tests are evaluated by the Public Health Laboratory Service. (Extracted from New Scientist, 6 August 1987)

Another rapid test

Kyowa Medex (Japan) and Murex (US) are developing a substance that detects the AIDS virus within 10 minutes. Conventional detection methods take over one hour. The new substance causes the blood plasma of the patient to change colour if he or she is infected. Kyowa Medex and Murex have agreed that their product will be produced in the US, and will seek FDA approval in September. Kyowa Medex will apply with the Japanese Ministry of Health & Welfare for permission to import the substance by the end of the year. (Extracted from Asian Wall Street Journal, 13 July 1987)

Pharmacia plans entry into AIDS test market

Pharmacia, the Swedish biotechnology and Pharmaceuticals group, is planning to launch two third-generation AIDS tests. Originally developed by Syntello, a Gothenburg-based research group, one test is specific to the HIV-1 virus and the other to the HIV-2 virus, both of which can cause AIDS.

These third-generation tests are based on a peptide sequence of the virus coat belonging to a stable region which is specific to the particular virus. These properties reduce the risk of false positive reactions which can occur if the test traps other antibodies.

Pharmacia has recently completed a full evaluation of the peptide technology and claims that no false positive reactions were recorded and that the increased sensitivity reduces the risk of false negative reactions. First-generation tests were based on the actual viral coat proteins with the second generation coming from recombinant coat proteins.

Both Pharmacia and Syntello are now planning to scale-up production of the tests and if it proceeds smoothly, market introduction in some West European countries could take place by next year. Pharmacia obtained access to the technology when it bought global marketing rights from Syntello's financial backer, Virovahl.

Pharmacia is encouraged that the tests identified antibodies to the HIV-1 virus at an earlier stage in the disease than existing products. (Extracted from European Chemical News, 7 September 1987)

Search for AIDS-retarding drugs

A "magic bullet" to cure acquired immune deficiency syndrome (AIDS) is nowhere in sight. But scientists all over the world are experimenting with a bewildering assortment of more than 80 chemical substances, seeking agents that, at the very least, can retard the virus that causes AIDS and bolster the ravaged immune system of its victims.

So far only one drug, 3'-azido-3'-deoxythymidine, popularly known as AZT, has been approved for treating certain AIDS patients, but it is a palliative, not a cure.

The drug-development pipeline, though, is full of candidates, many of which have revealed some promise in inhibiting the AIDS infective agent - human immunodeficiency virus, or HIV. Some drugs have already fallen by the wayside, but other candidates continue to look good in clinical trials.

The process by which HIV infects cells and replicates is a complicated one. One of the virus's key activities in its replication is reverse transcription, in which it stitches together a DNA copy of its RNA under the supervision of the enzyme reverse transcriptase. Scientists believe AZT interferes in this process by masquerading as a legitimate nucleoside building block for the DNA chain under construction. The enzyme is fooled into incorporating the false building block into the chain, which lacks the proper substituent (hydroxyl) at the 3' position to allow additional nucleosides to be added. Chain building is terminated and no new virus particle emerges.

This same strategy is believed to be the key to the antiviral effects of 2',3'-dideoxycytidine and 2',3'-dideoxyadenosine, two relatives of AZT that are also under study. Dideoxycytidine is expected to be a more effective version of AZT that may lack AZT's harsh side effects.

Another potential weapon against AIDS is the use of natural biological substances such as α-interferon, a glycoprotein that can be produced in quantity through recombinant DNA technology. α-Interferon has shown antiretroviral activity in laboratory studies. It also has been shown to shrink tumours in 20 to 50 per cent of AIDS patients with Kaposi's sarcoma. Preliminary data from an ongoing study by researchers at the National Institute of Allergy & Infectious Diseases suggest that recombinant α-interferon also can keep HIV at bay in healthy persons who have antibody to the virus but whose immune system is till in good shape.

Once AIDS has wrecked a person's immune system, it may be too late for interferon therapy. A placebo-controlled trial in 54 AIDS patients without Kaposi's sarcoma but with opportunistic infections showed no benefit from recombinant α-interferon.

Scientists also are intrigued by an experimental drug called ampligen that induces cells to produce their own interferons. Ampligen is a mismatched double-stranded RNA polymer manufactured by HEM Research Inc., Rockville, Md. Experiments conducted at Hahnemann School of Medicine, Philadelphia, and Vanderbilt University Medical Center indicate that ampligen is more active against HIV in vitro, than α-, β-, or γ-interferon, alone or combined. Ampligen stimulates the immune system and prevents healthy cells from becoming infected with HIV in vitro.

A recently completed pilot study at Hahnemann suggests that ampligen may help patients in the early stages of immune deficiency.

Credit for ampligen's beneficial effects seems to be due to a lot more than the interferons it induces. Ampligen probably elicits a wider range of biological responses in the body than recombinant interferon can by itself. Recombinant interferon lacks the chemical mediators that the natural protein uses to exert its effects in the body. Furthermore, ampligen appears to have no toxicity or side effects in patients. The reason seems to lie in the drug's very short half-life in the body - about 20 minutes.

When ampligen is administered along with AZT to cells in culture, the dosage of AZT can be reduced fivefold without diminishing AZT's virustatic effect. Thus, scientists expect that ampligen could make it possible to greatly reduce the dosage - and hence the toxicity - of AZT in the treatment of AIDS.

Another drug that seems to hold promise as an immune-system regulator is Imreg-1, a low-molecular-weight peptide derived from healthy human leukocytes. It has been shown to stimulate human cells in culture to produce interferon and interleukin-2, a protein that promotes the growth of T cells. AIDS patients treated with Imreg-1 have shown improvements in immune response and clinical signs, with no observed toxicity. In a recent study at Tulane University medical school, AIDS and ARC patients given Imreg-1 showed weight gains and a clearing of candida infections. The drug also seemed to retard the rate at which their helper T4 cells disappeared; in some patients, the average number of helper T4 cells actually increased.

Imreg-1's ability to bolster the immune system of AIDS and ARC patients is now being studied in 150 patients at seven medical centres. Imreg-1 is a product of Imreg Inc., a biotechnology firm based in New Orleans.

Other investigational drugs may have more specific effects, such as blocking HIV from infecting its target cells. The virus attacks T4 lymphocytes by first binding to T4 (also known as CD4) receptors on the cell surface. The gusto with which HIV binds may be related to the virus's high lipid content and abnormally high ratio of cholesterol to phospholipid, says A.S. Lippa of Praxis Pharmaceuticals, the Beverly Hills, Calif., firm that makes the drug. The viral envelope - a lipid membrane - may play an important role by providing a rigid matrix that enables the attachment proteins to maintain the proper orientation for binding to T4 receptors, he says. The crucial attachment step might be hindered, for instance, by making the membrane less rigid.

This line of reasoning led researchers to test AL 721, a lipid mixture consisting of neutral glycerides, phosphatidylcholine, and phosphatidylethanolamine in a 7:2:1 ratio. The mixture fluidizes the HIV membrane by extracting its cholesterol. As a result, the virus cannot attach itself to its target cell. In early human trials, AL 721 showed no toxicity or adverse effects, and immune function in some LAS patients improved markedly. Larger-scale trials of AL 721 are expected to begin in the near future.

A similar anti-HIV mechanism may be at work with amphotericin B methyl ester (AME), a water-soluble derivative of the polyene macrolide amphotericin B. The antiviral activity of AME has been studied in vitro by researchers at Rutgers University and NCI. They find that the drug effectively inhibits the expression of two virus protein antigens called p24 and p15. According to research AME seems to be capable of a triple action: it inactivates the virus directly, inhibits its replication in virus-infected cells, and makes healthy T4 cells more resistant to

infection by HIV. The drug also seems to block cell-to-cell infection, an important route in the AIDS process. The mechanism of AME's protective effect is not known with certainty.

Moreover, when cells are treated with a combination of AME and AZT, a strong synergism is seen.

A slightly later step in the infection process seems to be the target of a plant alkaloid called castanospermine. Bruce D. Walker of Massachusetts General Hospital presented evidence that castanospermine inhibits HIV in vitro by interfering with the processing of glycoproteins that are present on the virus's envelope. The binding of the virus to the T4 cell receptor is not affected, but a subsequent step in virus entry is. He and his co-workers also found that castanospermine inhibits the fusion of T4 cells, an HIV-induced process that kills the cells and thus weakens the immune system. Whether the compound will turn out to be therapeutically useful remains to be seen. It has not yet been tested in humans.

Another drug being tested is D-penicillamine (3-mer-capto-D-valine), which has been used to treat rheumatoid arthritis. Penicillamine has been shown to suppress HIV replication in seropositive patients with generalized lymphadenopathy. In fact, two patients given the highest of three penicillamine doses are still virus-free almost nine months after treatment was stopped. The drug is thought to inhibit HIV replication by binding to the sulfhydryl-containing proteins, such as HIV's nucleic acid-binding protein. Further studies of penicillamine in AIDS and ARC patients are in progress to ascertain how effective the drug really is. (Reprinted with permission from Chemical and Engineering News, 29 June 1987. Copyright (1987) American Chemical Society)

AIDS fight shifts focus to medicines

Discouraged by initial failures to produce an effective vaccine against AIDS, American scientists have shifted their focus to finding drugs that can halt the progression of the virus. They are urging for an intensified effort to identify chemical compounds that could be used to stop the virus from spreading in the body. They added that the focus of new drug development in the fight against AIDS has switched from wiping the virus out to preventing its growth. As it has become clear that the AIDS virus can lie dormant in the body for years - possibly as long as a decade - efforts to stop its progression have taken on new urgency.

Many researchers use cancer therapy as a model for AIDS treatment. Increasingly, researchers have turned to a mixture of drugs to try to repair the damage AIDS does to the body's immune system.

Largely as a result of advances in the field of recombinent DNA technology, researchers are convinced that therapeutic agents will eventually be developed that can stop the virus from spreading. (Extracted from International Herald Tribune, 2 September 1987)

New drug for AIDS/cancer affects cell wall

A research group working at the Royal Postgraduate Medical School, Hammersmith Hospital, London, and at Bristol University, have discovered a new drug, believed to have great potential in the treatment of cancer and AIDS.

The new drug, called Contracan, has been shown in laboratory and animal trials to inhibit the spread of cancer and progression of AIDS infection by preventing a defect in cell membrane structure, i.e. the desaturation of stearic acid that is associated with viral infection and cancer formation.

The team says that the research has shown there is a high degree of co-relation between the ratio of saturated to unsaturated fats and the stage to which a viral infection or cancer has progressed. In particular, they have demonstrated an increase in the unsaturated oleic acid compared with its saturated precursor, stearic acid, and that by restoring the membrane to what they have identified as the healthy state, the cell could be given some protection against infection and its subsequent advance.

In addition, the team says that an index which they have formulated to measure the ratio between saturated to unsaturated fats will also provide the basis of a prognostic measure for infected patients. (Source: Manufacturing Chemist, July 1987)

Protein peptide T in AIDS trials

The protein peptide T may prevent the AIDS virus from entering cells, according to researchers at the US National Institute of Mental Health (NIMH) and the Karolinska Institute (Stockholm). Peptide T is a short segment of the AIDS virus coat. Three AIDS patients who have followed through with weekly injections of the peptide since late 1986 are all doing well. No toxic side effects have been observed. Peptide T caused pneumonia and skin lesions in the three test patients to regress. The mode of action of the peptide is not known. The Karolinska Institute is starting a placebo-controlled trial of peptide T in 36 patients. FDA has just approved NIMH human trials of a synthetic peptide T. (Extracted from Science News, 13 June 1987)

Human test of AIDS vaccine approved

Federal officials announced this week that they have granted approval for the testing of a potential AIDS vaccine using human volunteers. The preliminary experiments, scheduled to begin within a few months, will be the first testing of an AIDS-vaccine candidate in humans allowed in the United States.

According to the US Food and Drug Administration and the National Institute of Allergy and Infectious Diseases (NIAID), MicroGeneSys of West Haven Conn., received approval to initiate human testing of its proposed vaccine this autumn. Other US companies are seeking similar approval for their own AIDS vaccines, and French scientists announced last March they had injected a possible AIDS vaccine into humans, with promising results.

To make the vaccine, researchers at the biotechnology company concentrated on a viral protein called gp 160, taken from the "envelope" structure surrounding a custom-made AIDS virus supplied by NIAID. They then inserted a gene coding for gp 160 into a baculovirus which infects moths and butterflies. In order to obtain large amounts of gp 160 material, the researchers are growing genetically engineered baculoviruses in cultures containing insect cells.

Human vaccine testing is complicated by the question of whether all AIDS vaccines should first be tested in chimpanzees, apparently the only non-human animals that can be infected by the human AIDS virus. Costly and time-consuming, tests in chimpanzees none the less may provide data essential to the vaccine search.

Cambridge Bioscience will jointly develop an AIDS vaccine with Institut Merieux (France), which will get an exclusive licence for any products that may result. Cambridge Bioscience is focusing on engineered recombinant peptides from the envelope gp 160 protein in the AIDS virus. It is conducting animal tests with the material, and will combine them with vaccine-enhancing substances it has already

developed. It is working on a delivery system - originally developed by Virogenetics using a unique recombinant vaccine vector technology. Merieux sells vaccines in over 150 countries, and has an especially strong presence in Africa, where AIDS has reached epidemic proportions in some areas.

Contradictory signals on AIDS vaccines

Meanwhile, Professor Jonas Salk, who developed the first effective polio vaccine, has surprised many researchers by saying that a post-infection vaccine may well work with AIDS - because the virus generally does not cause the disease for several years.

Even more significantly, perhaps, Salk has filed a US patent on an experimental vaccine, assigning the rights to Immune Response Corp. - a privately held company whose scientific advisory board he chairs. Whereas many AIDS researchers are looking for 'subunit' vaccines, based on fragments of the virus, Salk's new vaccine is made from whole, killed virus. Critics argue that this approach is vulnerable, in that even the killed viruses could still cause infections, although the scale of the problem in the USA may encourage the regulatory agencies to be more open-minded.

Immuno (Austria) may start clinical trials of a prototype AIDS vaccine at the beginning of 1988. It has successfully tested the genetically engineered vaccine, gp 160, on animals. The firm has already started to develop alternative vaccines in case gp 160 shows side-effects that make it unviable for treatment of human beings. (Extracted from European Chemicals, 7 July 1987, Chemical Marketing Reporter, 3 August 1987, Biotechnology Bulletin, Vol. 6, No. 7, August 1987, Business Week, 27 July 1987, Science News, Vol. 132, 22 August 1987)

Array of viral proteins may make a good vaccine

British researchers working on a vaccine against the human immunodeficiency virus (HIV) may be ready to start testing their product on people within a year. By that time, British authorities hope to have developed a set of guidelines - which may eventually be adopted internationally - to ensure that such tests are safe.

The vaccine involved is being developed by William Jarrett, head of the department of veterinary pathology at the University of Glasgow. It relies on a method of mimicking the virus particle.

Jarrett said that researchers are now much more hopeful that it will be possible to develop a vaccine, although some conventional approaches have already been abandoned. None of the vaccines based on modified vaccinia virus (which stimulates immunity to smallpox) has been effective, he said. He is working on ISCOMS (immunostimulatory complexes), small cage-like structures which make it possible to present viral proteins in an array, as they appear on the membrane of the virus.

One of the obstacles to the development of a vaccine against HIV is that although the body produces antibodies against the virus, most of these do not neutralize (inactivate) it. ISCOMS, however, may be able to boost the very low levels of neutralizing antibodies to a point where these provide effective immunity. Researchers may also decide to try "immunizing" people who are already infected. Perhaps if infected people could produce high levels of neutralizing antibodies, these could combat the infection.

Table 1: The US search for an AIDS vaccine

TYPE	DESCRIPTION	DEVELOPER
SUBUNIT VACCINES	These vaccines are genetically engineered copies of tiny parts of the virus that trigger an immune response in patients.	Repligen (with Merck), Chiron (with Ciba-Geigy), MicroGeneSys, Genentech, Viral Technologies, Cambridge BioScience, Johnson & Johnson
MODIFIED VACCINIA	Researchers are trying to modify the virus used in smallpox vaccines so that it produces some of the immune-stimulating proteins from the AIDS virus.	Oncogen, Transgene, National Institute of Allergy & Infectious Diseases, Pierre-et-Marie Curie University
ADENOVIRUS	By modifying the tiny virus that causes colds, scientists hope to produce a safer vaccine than those made from vaccinia.	Biotech Research Laboratories, Wyeth Laboratories
KILLED AIDS VIRUS	Considered by many to be the most risky approach, this vaccine would use the entire AIDS virus after it has been killed.	Immune Response
ANTI-ANTIBODIES	Researchers trick the body into producing antibodies that mimic the receptors that the AIDS virus latches onto in human cells.	Wistar Institute, Otisville BioPharm (with New York's Mt. Sinai School of Medicine)

(Source: Business Week)

The team in Glasgow is concentrating on the viral protein called glycoprotein 120 - gp 120 for short. This protein, which is attached to the viral envelope, is involved in binding to the receptor on the T-helper cell, the type of white blood cell that HIV mainly attacks.

The researchers are growing gp 120 in a "baculovirus expression vector". Baculovirus is a type of virus that attacks insects.

The next step is to make the ISCOMS. These form when mix viral protein with a substance called q[illegible] which comes from the bark of the Amazonian [illegible] presence of a detergent. Under these circumstances, ISCOMS form naturally.

Tests in apes and monkeys over two years have shown that ISCOMS are safe, Jarrett said. Veterinarians have already used the same technique for a vaccine against feline leukaemia virus in cats. This vaccine produces 100 per cent immunity.

Jarrett said that he would not test the vaccine against HIV on himself or his laboratory workers. He said he thought it was desirable to have a national body that would help to determine whether trials were ethical, and would specify what type of volunteers should be allowed to take part in the proposed tests.

Development of such a vaccine may not be as simple as it sounds. Geoffrey Schild, director of the National Institute for Biological Standards and Control (NIBSC), and director designate of the directed programme of research, sounded a cautionary note. He said: "there is no cast-iron evidence that antibodies to the envelope are helpful, and we still have to cope with virus variation".

Schild said that NIBSC will be developing a reference collection of different strains of HIV. The Institute will also provide centralized testing of candidate vaccines and, possibly, antiviral drugs. (Source: New Scientist, 17 September 1987)

Livestock applications

Novel fish-farming method

Researchers at the National Institute for Marine Fishing, (USSR), have applied Pavlovian training methods to trout, and claim to have produced a homing response in the fish. Underwater transmission of a signal brings the fish back to a feeding point, while a second signal, transmitted only when the fish are fully grown, brings them back to a cage. The method could make fish farming feasible in the open sea. (Source: Technology Update 14 September 1987)

Bovine growth hormone

A number of animal growth hormones are likely to reach the market over the next few years. Probably the most controversial is bovine somatotropin - or BST. Rather than being used to boost the size of animals, this product will be used to increase milk production. Not surprisingly, the progress of BST is being watched anxiously by a wide range of pressure groups, including those representing farmers.

1988 will see BST on the market in Europe for the first time. Monsanto Europe is building a production unit in collaboration with an Austrian firm, Biochemie Ges.mbH at Kundl, Tyrol. The unit is thought to be the first commercial-scale BST facility. While it will only be able to meet a small percentage of the anticipated demand for the product, it will also be able to manufacture other polypeptide molecules for similar applications in other animals, including porcine somatotrophin (PST) for pigs.

BST is a naturally occurring protein, whose molecular structure has been known since 1973. All cows secrete BST and those which produce the most milk tend to have elevated natural levels of BST in their blood. In lactating dairy cows, BST directs the flow of energy and feed nutrients into the production of milk. Initially extracted from the pituitary glands of cows for research purposes, the product has been made using recombinant DNA techniques since 1982.

BST has the advantage that it is "species limited", which means that while it is active in cows, it is completely inactive in humans. Despite concerns that BST may lead to health problems in treated cows, Monsanto argues that it is safe if administered over more than one lactation cycle, with no discernible effects on cow health or condition. There is a natural self-regulating process whereby cows receiving supplemental BST reach a more efficient equilibrium between feed energy and milk output, the company says. Longer term responsiveness to BST could become a production parameter for which breeding animals are selected.

Milk from all cows contains a trace quantity of BST: generally less than two parts per billion. To be effective, BST has to be injected. If taken orally, the protein is broken down in the intestine. Milk from cows treated with supplementary BST not only shows the same levels of BST but also exactly the same fat, protein and mineral content. Tests have shown that recombinant BST has no influence on milk when used in fermentation for cheese or yoghurt, or on its heat stability after concentration or its response to renneting.

Monsanto has gone to great pains to stress that BST is a protein, with no functional or structural relationship to the steroid hormone implants banned in a recent EEC directive. As a safeguard, however, the administration of BST will be under the control of vets.

Once administered, the effect of BST is to boost milk yields by 10-15 per cent and feed efficiency by 5-15 per cent, under commercial conditions. The product's impact will depend on the rate at which it is introduced which, in turn, will depend on the numbers of farmers and vets deciding to use BST, the proportion of treated cows in each herd, the length of time during each lactation when the product is administered and the extent to which farmers use BST to make up shortfalls in their milk production quotas.

Details of the BST programme from: Monsanto Europe SA/NV, Animals Sciences Division, Avenue de Tervuren 270-272, B-1150 Brussels, Belgium. (Source: Biotechnology Bulletin, Vol. 6, No. 7, August 1987)

Encapsulating animal antibiotics

A new team has formed to develop liposome-encapsulated drugs for injectable animal antibiotics. Pfizer - the largest supplier of those drugs - has joined with MPS and Microvesicular, two subsidiaries of IGI (Vineland, N.J.). The promise of liposome-encapsulated antibiotics is to cut dosage frequency and decrease tissue irritation at the site of injection. The IGI liposomes are non-phospholipid, which makes them impervious to alkalis, acids and certain enzymes that destroy phospholipid liposomes, says IGI. (Source: Chemical Week, 21 September 1987)

Super salmon

Joe Sreenan of the Agricultural Institute in Galway is trying to produce "transgenic" salmon, which carry a foreign gene. He and his colleagues have injected 4,000 salmon eggs with copies of a gene for growth hormone, in the hope of enhancing the productivity of local fish farms. Farmed salmon in

Ireland grows more slowly than intensively farmed fish in Scandinavia, and Sreenan hopes the new gene will help.

Alongside the growth hormone gene, Sreenan inserted another gene, for beta galactosidase, to act as a marker. He has found signs that this foreign gene was active in the young fry. So it looks as though the genes injected into the eggs did incorporate into the chromosomes. The salmon from injected eggs are now almost a year old, so Sreenan will know soon whether the genetic engineering has made the fish grow faster.

The Japanese company Kyowa Hakko Kogyo and Phillips Petroleum will jointly develop biotechnological methods to produce salmon growth hormone. Phillips already has experience in the use of gene-modified methyltrophic yeast for the production of useful proteins. Kyowa has until now been attempting to produce salmon growth hormone via E. coli. Combining the technologies could raise production efficiency. (Extracted from New Scientist, 17 September 1987 and Japanese Chemistry, 9 July 1987)

USDA, private firm set up testing programme for vaccine

Commercial development of a vaccine against the worst parasitic disease in chickens, coccidiosis, may result from an agreement between the US Department of Agriculture and a private firm. The vaccine will be injected by a new automated system through eggshells into embryos.

Under the agreement, scientists at the research agency will further test "antigens" - bits of the coccidia micro-organism - for use in a potential vaccine. Embrex Inc. of Research Triangle Park, N.C., could then use the best antigens to commercially develop an in-ovo (embryo-injected) vaccine.

In large-scale co-operative tests, the firm's patented egg-injection machine will deliver antigens to thousands of chicken embryos. Coccidiosis costs US producers an estimated $300 million a year.

Agency researchers have had preliminary success in using the antigens to trigger resistance to the disease, but the antigens have not been tried with embryos and the researchers need to identify the most promising antigens for use in an embryo-injected vaccine.

Antiviral and antibacterial vaccines are now administered to about five billion newly-hatched chicks each year.

Alan Herosian, president of Embrex, says the new system could also reduce vaccination stress on newly-hatched chickens. Mr. Herosian says Embrex is developing the egg-injection system for commercial use. The agreement also entitles Embrex to obtain an exclusive licence for making and selling in-ovo coccidiosis vaccine that comes from the research.

Scientists who developed the antigens at the agency's Beltsville, Md., agricultural research centre will provide them to Embrex researchers for further purification and processing. The company will purchase several thousand fertile eggs locally and inject the antigens when the embryos are 17 days old - four days before they are due to hatch. The chicks will be sent to the protozoan diseases laboratory at the Beltsville research centre.

There, the chicks will be raised and infected with coccidiosis parasites to see whether they developed immunity to the disease from the antigen injection. The coccidia parasite infects the chicken's digestive tract and can kill the bird unless treated with drugs routinely given in the feed.

Even with drug treatment, the disease causes weight loss, interferes with the conversion of feed to meat and keeps the birds from having the yellow skin colour that brings growers premium prices in some regions.

Embrex developed its injection system to commercialize a process for injecting vaccines into embryos that was patented by scientists at USDA's regional poultry research laboratory in East Lansing, Michigan.

Embrex is developing several other products for in-ovo delivery. These include vaccines for Marek's and bursal disease, and peptides and other substances to stimulate immunity, protect poultry from diseases and improve hatchability and growth. (Source: Chemical Marketing Reporter, 10 August 1987)

Research into foot and mouth disease vaccine

Wellcome Biotechnology (UK) is developing peptide foot and mouth disease vaccines. The firm has produced a synthetic peptide with 20 amino acids of the FMD virus, which protects against the disease. It is now researching delivery methods for the peptide to maximize immune response. The results to date are particularly promising for use in pigs. The Institute for Animal Physiology & Genetics Research has produced a transgenic chicken from a single cell. The institute has only achieved low success rates to date, but aims to reach 50 per cent success in one year. Transgenic chicken production will enable breeders to genetically dictate chicken characteristics. The institute believes that the additional problems encountered in the development of transgenic processes for chicken production are justified by the tremendous potential of a successful commercial process due to the intensive nature of modern chicken farming. (Extracted from Animal Pharmacology, 10 July 1987)

Cheaper animal feed

Sanraku (Japan), a major producer of alcoholic beverages, has developed a cheap way to mass-produce the amino acid tryptophan via biotechnology. Tryptophan is extremely nutritious and is used in animal feed, but only in limited amounts because of its high cost. Sanraku's new process, which uses recombinant DNA, will reduce the cost considerably. The basic ingredients are anthranylic acid and glucose. However, it is unclear when the Sanraku process will be commercialized. (Extracted from Asian Wall Street Journal, 22 June 1987)

Agricultural applications

Nematodes

Biosis may begin commercial sales of nematodes, a natural pesticide, in 1988. Many types of the microscopic underground worms harm crops, while a small percentage attack underground pests and are harmless to humans and plants. The biotechnology company has developed a way to mass produce the worms and to kill all forms except those in their juvenile life cycle, for that is when they are effective bug killers. In order to package and transport the worms in large quantities, Biosis dries them and stores them in a state of suspended animation. Farmers must then add water to revive the nematodes, which eat 200 types of insects. Biosis must still develop nematodes that feed on above-ground pests and must increase production to 40,000-litre tanks in a $15 million plant that it plans to build. It will concentrate on high-value crops when it begins commercial sales, eventually expanding to termite, cockroach and other

field and garden pest control. (Extracted from Wall Street Journal, 28 August 1987)

Nitrogen fixing experiment

Deshen International is experimenting with the use of electricity to help farm crops fix nitrogen from the air to provide a natural fertilizer. It has long been known that lightning causes nitrogen (79 per cent of the atmosphere) and oxygen (20 per cent) to fuse, thus contributing to soil fertility in the tropics. Deshen believes the use of electrically-generated fertilizer will become economically feasible in the 1990s because present capacity for producing nitrogen fertilizer will not be able to meet increased demand, and because oil prices will have risen sufficiently to make nitrogen fixed from the air cheap enough to compete with nitrogen made from gas and oil. The fertilizer-from-electricity process begins by heating the air with electrical sparks. At about 5,000°C, many of the nitrogen molecules split to make nitrogen oxide, which can then be combined with oxygen molecules to make calcium nitrate. Deshen plans to obtain the required electricity from power utilities during off-peak hours. Hydro-Quebec, the Canadian province's main power supplier, has expressed interest in Deshen's plan and may supply the company with interruptible electricity at less than 2 cents/kilowatt-hour. Deshen still needs about $50 million before its process goes into full production. (Extracted from The Economist, 28 August 1987)

Safety comes before new insecticide

The committee that advises the British Government on genetic engineering is likely to give the go-ahead for the second phase of an experiment to make a new type of biological insecticide. The experiment is to release into the environment a virus that virologists have genetically engineered to self-destruct in ultraviolet radiation. The virologists want to convince the committee that they have taken all the necessary safety precautions before they release genetically engineered viruses that cause the production of toxins which kill insect pests.

The first phase of the experiment, which the Advisory Committee on Genetic Manipulation approved last year, was to release a virus that infects caterpillars feeding on cabbages. The virus had had a piece of DNA inserted into its genetic material so that scientists from the Institute of Virology at Oxford could distinguish the virus carrying the DNA "marker" from naturally occurring viruses that did not.

The virologists, led by the director of the Institute, David Bishop, wanted to find out whether the marker could be used to determine how long the virus persisted after it had killed its host, the larvae of the small mottled willow moth, Spodoptera exigua. The marker showed that the virus could survive for many months on cabbage leaves after the caterpillars had died.

The next step was to make sure that the virus would self-destruct after it had killed its host caterpillars. To do this, Bishop has deleted a gene in the virus. This gene makes sure the virus's outer coat, a polyhedrin protein, protects the sensitive genetic material inside the organism from ultraviolet raidation. Without the gene, the virus should not survive outside the caterpillar it infects.

After the Advisory Committee on Genetic Manipulation makes its decision, the Ministry of Agriculture, Fisheries and Food will also consider the safety implications of the experiment, because Bishop eventually wants to use the virus as a biological insecticide, and the use of insecticides comes under the Ministry's control. Neither organization is likely to stop the next phase of the experiment, however, because Bishop has taken such careful precautions to predict and to control the spread of the engineered virus.

If the second phase proves successful, and the virus does not survive outside the caterpillars, then Bishop will consider altering the genetic material of the virus still further to make the virus kill its insect host more quickly, before the caterpillars have time to damage the crop. One option is to insert the gene that produces the toxin made by Bacillus thuringiensis. The bacterium is well known for its ability to kill insects that infect crops.

Eventually, Bishop would like to try out his techniques on viruses that attack caterpillars of the pine beauty moth, Panolis flammea. The larvae of the moth destroy hundreds of hectares of forests in Scotland, and the Forestry Commission wants to see if there is an alternative to spraying the trees with chemical insecticides. (Extracted from New Scientist, 9 July 1987)

Micro-organisms to degrade herbicides being tested

The US Department of Agriculture's Agricultural Research Service is testing a new method to break down herbicides into harmless by-products. Using micro-organisms the system can break down a number of key herbicides and the ARS is now testing the system with atrazine and alachlor, two of the more commonly used herbicides. (Source: European Chemical News, 21 September 1987)

Company delays field tests

Monitoring problems have forced Biotechnica International to delay plans to field test gene-spliced bacteria. The tests are unlikely to be conducted until next spring although the company had originally planned to conduct the tests last May.

Researchers at the company and officials at the US Environmental Protection Agency believe that monitoring techniques are not adequate enough. The planned tests, which were supposed to enhance alfalfa yields, will be conducted once Biotechnica submits a revised monitoring programme.

The company plans to test a strain of bacteria on a five-acre alfalfa field in Wisconsin. Earlier greenhouse tests demonstrated that the altered microbes raised alfalfa yields by 15 per cent. The regulatory bodies are willing to allow the tests to go ahead once a monitoring system is in place.

Biotechnica has developed a recombinant version of Rhizobium melioti, a nitrogen fixing soil bacterium that symbiotically associates with alfalfa.

The scientists planned to use a streptomycin-resistant strain to monitor the gene-spliced strain. This strain has been used many times before as a marker strain but unfortunately the field to be tested has a very high indigenous streptomycin-resistant population and so could not be used.

Biotechnica now claims to have solved the problem and plans to submit its new plans to the relevant regulatory bodies at the start of next month.

Researchers at the biotechnology firm are also tinkering with the genes of Rhizobium japonicum to enhance nitrogen fixation properties when in close association with soya bean. Tests will probably be carried out for this project within 18 months. (Source: European Chemical News, 21 September 1987)

Biopesticide encapsulation

Development of microbial pesticides is the aim of a multiyear project between Monsanto and Mycogen (San Diego) that will combine Monsanto's micro-encapsulation delivery technology with Mycogen's lead biopesticide candidates. The companies say that product development and testing will begin immediately, with large-scale field trials targeted for 1988. Market entry of a micro-encapsulated biopesticide product is targeted for 1990. (Source: Chemical Week, 21 September 1987)

Direct-effect microbes reported for first time

For the first time, soil bacteria that directly stimulate plant growth have been reported. The organisms, which in tests boosted crop yields by as much as 30 per cent, were developed and are being patented by Allelix Agriculture, a division of Canada's largest biotechnology company, Allelix Inc.

Products based on the microbes will offer a new means for producers to increase returns. Allelix expects to market products as early as 1990. Like the company's hybrid canola programme which focuses on developing superior varieties of the important oilseed crop, the microbes are an example of the successful application of biotechnology to crop agriculture.

"The new products will be useful on a number of key crops including soybeans, canola, wheat and corn", says Dr. Joseph Kloepper, the Allelix scientist who heads research in the area. "They represent only part of our plan to market a range of environmentally-safe microbial products that promote plant growth."

The direct-effect microbes work on their own and thus consistently enhance growth under diverse environmental conditions. That makes them extremely versatile from a marketing standpoint. To achieve full market potential of their products, Allelix Agriculture is seeking to collaborate with an established innoculant or agri-chemical company with complementary strengths in marketing, sales and distribution.

Research on the growth-promoting organisms was partly funded by the Canadian National Research Council. The University of Guelph co-operated with Allelix by conducting extensive field trials. Mode of action research will be pursued in co-operation with Dr. Richard Pharis, of the University of Calgary; Dr. Suzanne Abrams, of the Plant Biotechnology Institute, Saksatoon; Dr. Milton Schroth, University of California, Berkeley; and Dr. Yaacov Okon, Hebrew University of Jerusalem, Israel.

For further information please contact: Dr. Joseph Kloepper, Group Leader, Agricultural Microbiology, Allelix Agriculture, (416) 677-0831. (Source: Company News Release, 21 August 1987)

Canola

Allelix Agriculture is using its genetic crop breeding leadership to accomplish the successful commercial hybridization of canola - already Canada's second most valuable agricultural crop and potentially a major new crop in the United States.

Canola is a type of rapeseed suitable for human and animal consumption. As an edible oilseed, canola is competitive with other oilseeds such as soybeans, sunflowers or cottonseed. Like them, it yields both vegetable oil, used directly in the kitchen and in processed edible products, and a high protein meal, used in animal feed. A particular advantage of canola oil is that it contains only half the saturated fat level of corn or soybean oil, yet it is economical to produce. This reduction in saturates and possible healthcare implications are being highlighted in Procter & Gamble's marketing of its Puritan brand canola oil. In recent years, canola oil has comprised more than 50 per cent of the liquid vegetable oil consumed in Canada and more than 30 per cent of the liquid vegetable oil used in Japan, which imports nearly half of Canada's crop.

Since its introduction in 1974, canola has rapidly gained favour with Canadian farmers, accounting for more than seven million acres in 1987 and providing as much as $1 billion income to farmers each year. The potential market for hybrid seed in Canada could exceed $100 million.

In early 1985, the United States Food and Drug Administration approved canola quality rapeseed oil for GRAS (generally regarded as safe for human consumption) status. Consequently, United States acreage is forecast to expand rapidly beyond the small area currently planted, particularly when suitable high yield hybrids become available.

Rapeseed is the leading oilseed in Europe, with several million acres grown in France, the United Kingdom, the Federal Republic of Germany, Denmark, and Sweden, among others. Although total acreage is about half that of Canada, the value of the seed market is roughly equivalent. Rapeseed is also widely grown in Eastern Bloc countries such as Poland and the German Democratic Republic, and it is increasingly important in the Soviet Union. In Asia, both China and India annually plant more acres than Canada, and Chinese acreage, which has been growing rapidly, now leads the world at more than 10 million.

Through its joint venture with United Grain Growers Limited, Allelix Agriculture has field tested dozens of breeding lines and potential cultivars at multiple locations in western Canada over the past two years. Thousands more lines and potential hybrids are being tested in a vastly expanded programme in 1987. The joint venture has entered seven cultivars into the required government licensing trials, two for the second year.

Allelix researchers are also developing and field testing hybrids for eastern Canada, Europe and the United States. Allelix is the only North American company known to be working in both canola species, Brassica napus and Brassica campestris, and in both spring and winter types. The first field trials of Allelix winter hybrids were harvested in Sweden, the United Kingdom, the Federal Republic of Germany, Ontario and the United States in 1986 and expanded trials have been planted for 1987 harvest.

Allelix Agriculture is working on improved second generation product lines, including hybrids with improved yield and climatic adaptation, lines with tailored fatty acid profiles for both industrial and edible vegetable oil applications, and cultivars with herbicide resistance. In 1987 Allelix signed a research agreement with American Cyanamid to develop canola resistant to Cyanamid's extremely effective family of imidazolinone herbicides. The company's advanced hybrid technology is the subject of patent applications pending in the United States, Canada and several other countries.

In planning for the future, Allelex has launched a number of plant transformation and germplasm development projects involving both tissue culture and recombinant DNA techniques. The company's ability to manipulate both haploid cells and protoplasts in culture has been recognized as state-of-the-art for some time, but in the past year increased emphasis has been placed on molecular biology. Thus, Allelix scientists are currently developing a range of

techniques for splicing individual genes into plants to confer specific characteristics.

Allelix Agriculture is actively developing and field testing both spring and winter cultivars adapted to potential growing areas in the United States and expects to enter this market with direct sales of attractive non-hybrid varieties and a limited number of spring hybrids in 1989, with adapted winter hybrids to follow in 1991. (Source: Company News Release, 20 August 1987)

Synthetic genes make better potatoes

The International Potato Center in Lima, Peru, and at the Department of Biochemistry at Louisiana State University in the US, have developed routine ways of inserting synthetic genes into the potato. The work, funded by the United States Agency for International Development, at first concentrated on improving the nutritional value of the potato. A synthetic gene that prompts the plant to make a protein high in essential amino acids, which people must consume in their diet, was inserted. Now they are trying to create genetically engineered potatoes that are more resistant to a wide range of diseases and pests.

To achieve this goal, either genes taken from other plants or synthetic genes constructed in the laboratory could be transferred. A plant gene, like all other genes, is simply a string of nucleic acid "bases". So it is relatively easy to synthesize them in the laboratory. Researchers made the first gene, consisting of some 200 bases, in 1979. The value of using synthetic genes is twofold. Once inside the host plant, they can produce a protein that has its own intrinsic value, for human nutrition, say. But a foreign synthesized gene can also have a more devious role. All active genes - that is, those whose coded instructions are being translated into protein - produce an intermediate product, messenger RNA. This messenger RNA sometimes plays a regulatory role within a cell, turning other genes on or off.

The researchers are trying to exploit this newly discovered type of gene control, called "micRNA" control (mRNA-interfering complementary RNA). In this process, the messenger RNA produced is not translated into protein. Instead, its sequence of bases is such that it can bind to a gene and inactivate it, removing it from the normal pathway of protein synthesis. This messenger RNA is thus sometimes called "antisense" RNA.

This mode of gene regulation could offer a revolutionary means of stopping potato viruses from replicating within cells that they have infected. Genes can be synthesized to produce messenger RNA that bind to and suppress any viral genes sitting among the genes of infected plants. This binding would prevent the virus from reproducing itself or making viral proteins, and would thus halt the progress of diseases. In this way, a new form of viral resistance could be conferred. Each synthetic gene for a sequence of antisense RNA would be specific to a particular virus. Eventually, perhaps, potato plants could be endowed with a suite of synthetic genes to protect crops from a wide range of viral diseases.

This approach is particularly exciting because of the difficulties of working with genes that confer resistance which occur naturally in potato plants. Certain varieties do indeed contain genes that confer resistance to some viruses. Yet no single variety is resistant to all the viruses that attack potatoes, which is why plant breeders try to move genes for resistance from one variety to another by conventional breeding methods. Sometimes a single dominant gene gives resistance; in other varieties, resistance is genetically more complex and several genes work together. Sadly, researchers cannot yet identify, isolate and purify these "resistance" genes from the plant. Often, breeders cannot even tell which chromosomes carry such genes.

Such genetic engineering may also be a useful way of making potatoes resistant to diseases caused by bacteria. These micro-organisms cause diseases of potatoes such as soft rot and bacterial wilt. Bacteria destroy potatoes in developing countries worth hundreds of millions of dollars a year. The potato is often an important crop in the warm tropics, where the climate makes bacterial diseases worse. Until recently, potato breeders could work with only one source of resistance to bacterial wilt, a particular variety of potato. The scarcity of resistant varieties, coupled to the enormous number of bacterial strains that exist, complicates conventional breeding for resistance to bacteria. Genetic engineering could be an alternative method to confer resistance, perhaps by exploiting a range of bacterial proteins produced in other organisms.

The pupae of the silk moth, for instance, respond to bacterial infections by synthesizing about 15 to 20 new antibacterial proteins. One of these is lysozyme, an antibacterial protein also found in egg white and human tears. Lysozyme effectively limits the growth of a broad spectrum of bacteria, including those that attack potato plants. Moths also make two other classes of antibacterial peptides, called cecropins and attacins.

Fungi also attack potatoes. For instance, the disease known as late blight had a devastating impact on Ireland in the mid-1800s. A million Irish people died of starvation and one-and-a-half million emigrated to North America after this fungal disease destroyed the potato crop. Some bacteria produce substances that limit the growth of fungi. Once researchers analyse these antifungal substances and find the genes that enable bacteria to make them, potatoes may be genetically engineered that are resistant to fungi.

The same strategy could promote a plant's ability to resist attack by insects. Several commercial laboratories are exploring the use of a natural insecticide to protect plants from damage by insects. This natural insecticide, produced by the bacterium Bacillus thuringensis, is a protein that forms a crystal of high molecular weight. These crystals are toxic to the larvae of several butterflies and moths. Research at the International Potato Center is trying to insert the gene for this toxic protein into potato plants and is also looking into the possibility of using an enzyme called chitinase as a natural insecticide. Chitinase will attack the skeleton and gut of the insect, leaving it prey to bacterial infections that eventually kill it.

The collaborative research between the International Potato Center and Louisiana State University offers an innovative method of producing potatoes that are resistant to pests and diseases. The sophisticated technologies of modern biology should ultimately benefit small farmers in the developing world, by providing them with potato plants that are resistant to a large variety of diseases and pests. (Extracted from New Scientist, 17 September 1987)

A new team in genetically engineered plants

Development of insect-resistant corn and cotton plants is the aim of a licensing agreement between Calgene (Davis, Calif.) and Toagosei Chemical Industry (Tokyo). Calgene will have exclusive rights to engineer the plants genetically using genes that Toagosei isolates from Bacillus thuringiensis, a

bacterium widely used in insecticides. Calgene aims to develop plants resistant to primary cotton pests, including the tobacco budworm and cotton bollworm. (Source: Chemical Week, 5 August 1987)

Monsanto system tracks engineered organisms

Monsanto has applied to the Environmental Protection Agency for permission to field test a system to track the distribution and survival of genetically engineered micro-organisms in soil. If the Government approves, Clemson University scientists - working with Monsanto under a research agreement - hope to begin field trials at a university test plot in November.

Monsanto researchers have inserted genes into a soil bacterium that allows engineered organisms to be distinguished from naturally occurring microbes in a sample. The firm believes the marker system will prove to be an accurate way of tracking altered organisms once they have been released into the environment. Eventually, other genes that control beneficial traits might be inserted along with the marker genes.

The marking system consists of two genes from Escherichia coli inserted into Pseudomonas fluorescens. The transferred genes direct the Pseudomonas to produce the β-galactosidase enzyme. That enzyme enables the altered bacteria to metabolize lactose (which bacteria that fluoresce cannot normally do), and thereby grow on laboratory culture dishes that contain only lactose as a carbon source.

Clemson scientists plan to apply the organisms to the soil when they plant wheat at their South Carolina research station in November, then monitor the microbes' growth, distribution, and survival. The researchers will also check untreated wheat in adjacent fields to see if the bacteria migrate there and will monitor how far down in the soil the altered organisms travel. (Abstracted with permission from Chemical and Engineering News, 22 June 1987. Copyright (1987) American Chemical Society)

Bio-pesticide to control nematodes

The first commercially marketable biological control for nematodes is now being manufactured in the Philippines.

The product, called Biocon, was developed by Romulo Davide, associate dean of agriculture and a plant pathologist at the Los Banos campus of the University of the Philippines. It is made from the fungus Paecilomyces lilacinus, which attacks nematodes either by parasitizing the eggs or by infecting adults.

In tests with mung beans, P. lilacinus controlled 50-90 per cent of all nematodes that attack this crop. The fungus also attacks Radopholus similis, one of the major pests in commercial Cavendish bananas. And in potatoes, where the fungus kills the golden potato cyst nematode, the result was a 10-100 per cent increase in yield. Davide is now collaborating with the International Potato Center in Peru to test a Peruvian P. lilacinus isolate in potato field trials. Such screening is necessary because only some varieties attack the nematodes.

A memorandum of agreement signed in August of last year gives Asiatic Technologies Inc. (Manila) the right to manufacture and market Biocon in the Philippines. Although the fungus can be grown on any number of cheap waste products - including rice husks, corn cobs, and water hyacinth - Asiatic Technologies chose coconut water as the substrate because of the ease in removing the spores for the finished product.

Biocon is sold in 10-gram foil pouches (each containing about eight billion spores), which cost 150 pesos ($7.50) each. Planting material can be soaked in a spore suspension before planting, or the spores can be mixed with organic fertilizers like chicken manure for application on the field. One pouch mixed with two litres of water is good for 128 kilograms of potato tubers, or up to a one-half-hectare potato field. (Extracted from Bio/Technology, Vol.5)

New bacteria increase soybean yields dramatically

New strains of bacteria that increase soybean and other legume yields by as much as 30 per cent have been developed by scientists at Allelix Agriculture. Two years of field testing in Canada and the US have confirmed the increases. Products will be available as early as 1990 and are expected to generate a new market for the four-year-old biotechnology company.

The bacteria enhance the nitrogen-fixing process naturally carried out by Rhizobium microbes in the soil. The beneficial effects of Rhizobium have been known and studied for years, and Rhizobium products are routinely applied to legume crops. But until now, scientists have not found practical ways to improve the process by which Rhizobium colonize plant roots and fix nitrogen.

The breakthrough came as part of a broad Allelix programme to develop new and environmentally safe microbial products that promote plant growth.

"The new strains are useful on alfalfa, clover, beans, lentils and peanuts in addition to soybeans", says Dr. Joseph Kloepper, the Allelix scientist who heads research in the area, "and their use is not limited to acres already treated with Rhizobium products. They are equally effective on both naturally-occurring and 'innoculated' or commercially-applied Rhizobium".

Research has been carried out in co-operation with the University of Guelph which conducted extensive field trials. It was partially funded by Canada's National Research Council in a programme designed to assist the transfer of technology between university laboratories and Canadian companies.

Allelix plans to commercialize its products through joint ventures with companies with complementary strengths in marketing and distribution. Commercialization will not be unduly delayed by the extreme regulatory requirements often associated with biotechnology, because the organisms are accepted as indigenous to North America.

For further information, contact Dr. Joseph Kloepper, Group Leader, Agricultural Microbiology, Allelix Agriculture, (416) 677-0831 or (705) 325-2256. (Source: Company News Release, 8 September 1987)

Food production and processing

A faster route to make sake

Batch fermentation to brew sake usually takes 25 days. To maintain constant shipments, modern large-volume sake producers operate hundreds of fermenters. Now, a major Japanese sake house, Ozeki Sake Brewing (Nishinomiya, Hyogo), plans to reduce the production period to two days by continuously brewing with immobilized yeast. The company expects to put out the new product with 12-13 per cent alcohol content. Most brands of sake, a beer often erroneously called a wine, have alcoholic contents of 20 per cent. Ozeki plans to have its new offering on the market next spring and is expecting to install a

$100,000 "bio-sake" system, including a 500-litre fermenter, at Nishinomiya in September. Experimental fermentation is expected to last six months. If everything goes well, Ozeki will use the same facility for commercial operations. With the new equipment, the company will try to determine if it can produce glucose from rice starch and syrup in one day and ferment the syrup in another day. The bio-sake would be stored for a few days before the yeast is recovered in a centrifuge. The yeast life is estimated at six months. The bio-sake's lower alcohol content is not a problem, Ozeki maintains. Its advertising is likely to stress the product's "soft feelings". (Source: Chemical Week, 29 July 1987)

Fructose biopolymer

Igene Biotechnology has introduced Poly-Levulan fructose biopolymer, for use as a thickening agent in foods, a foaming agent in soaps and toiletries, and as a moistening agent in skin creams. A patent is pending for the food uses. Igene will concentrate initially on the biopolymer's use in cosmetics. Full-scale commercial production will begin by the end of the year. (Extracted from Chemical Marketing Reporter, 10 August 1987)

Test detects salmonella in meat

A test that lets consumers, restaurants, and institutional food services detect salmonella contamination in meat has been developed by Diversified Diagnostic Industries, Moraga, California. The test, called Chik Chek, depends on detection of an endopeptidase produced uniquely by salmonella. The user soaks a cotton swab in meat juice to be tested, adds a synthetic substrate of the enzyme, and then applies a reagent that reats with the hydrolysis product. A pink-purple colour indicates presence of salmonella. The $5.00 kit includes instructions on how to cook contaminated meat to ensure killing salmonella. It contains enough materials to do three tests and will be available shortly. (Reprinted with permission from Chemical and Engineering News, 6 July 1987. Copyright (1987) American Chemical Society)

New mycoprotein-based food

Marlow Foods (UK) has developed a mycoprotein-based manufactured protein known as Quorn. The substance, made from a microscopic plant related to such edible fungi as mushrooms and truffles, was developed by accident when Hovis McDougall (UK) scientists discovered organisms that convert starch into protein. Marlow is a joint venture between Ranks Hovis McDougall and Imperial Chemical Industries (UK). ICI makes Quorn in a continuous fermenter, and Marlow Foods collects it daily, flash-freezes it, and ships it to a food processing plant, where the product is transformed into materials simulating beef, ham, or chicken. Mycoprotein emerges from ICI's plant as 2-metre wide yellow sheets; Marlow then subjects it to a mechanical process that makes the substance behave as a fluid. This allows the product to be repeatedly folded and extruded until it acquires the fibrous structure of the food it is simulating. Flavour is also added, and it is then sliced, diced or shredded into pieces appropriate for the food product.

Quorn is currently used in Sainsbury supermarket pies, though distribution has been limited because ICI can currently produce only 0.5-1 million tons/week. However, ICI will soon convert an old fermenter run by its Biological Products unit that was previously used to make Pruteen - a protein that failed to catch on in the market - to make up to 20 million tons/week of Quorn. (Extracted from Financial Times, 13 May 1987)

Vanilla flavour grown in cell culture

Escagen is working to produce vanilla flavour in cell culture. Vanilla harvested from the vanilla orchid that grows only in Madagascar and a few other countries is expensive and in short supply. Artificial vanilla contains only one of the over 150 components of natural vanilla. The new technique should yield a flavouring almost as rich as natural vanilla but at a much lower price. Escagen thinks its flavour will qualify as a natural flavour, but not as natural vanilla. It will market to companies that advertize their products as containing only "natural" ingredients.

Cells are taken from vanilla samples grown in sterile conditions in the laboratory and put into a flask with nutrients and hormones to make them multiply. Cells can be taken from roots or flowers or other growing parts of the plant. The proper genes must be activated to obtain the desired chemical. Vanilla cells are encapsulated in polymer beads and put in a tall column through which nutrients and hormones flow. The cells produce vanilla, which is siphoned off.

Attempts to obtain cocoa butter from tissue culture have largely been abandoned. Some experts say tissue culture will not be able to compete with plants grown in the field because the sun provides free energy. DNA Plant Technology, a biotechnology firm that has a research contract from flavour producer Firmenich (Switzerland), tried tissue culture but switched to breeding and genetic engineering to improve the ability of plants to produce the flavours. (Extracted from New York Times, 24 June 1987)

Lesser-known fermented plant foods

Fermented foods form an important part of the diet of many people in practially all parts of the world and such foods are prepared from plant and animal materials by processes in which micro-organisms play an important role by modifying the material physically, nutritionally and organoleptically.

Most indigenous or traditional fermented foods from cereals, beans, seeds, tubers and vegetables are prepared by processes of solid substrate fermentation in which the substrate is allowed to ferment either naturally/spontaneously (usually African and South American style) or by adding a starter or microbial inoculum (Far East, South and South East Asia).

Products from cereal grains

Ting

Ting is prepared from a maize meal by natural fermentation and is a staple food for a large proportion of the population of Botswana. Moss, Mpuchane and Murphy (1984) made an extensive study on ting fermentation and found that the success of the fermentation depended on a number of factors, amongst which temperature was very important.

In Botswana, the maize meal used for the production of ting is traditionally placed in clay pots and covered with warm water to which an inoculum from a previous fermentation is added. The meal is allowed to ferment for two to four days depending on the ambient temperature. Moss et al. (1984) used Impala maize from southern Africa for ting fermentation and obtained an acceptable product in three days at 30°C. Taste panel studies were also made and details of the methodology were reported by Mpuchane (1983).

Moss et al. (1984) reported that moulds (Fusarium, Aspergillus and Penicillium spp.) initiated ting fermentation and the levels dropped rapidly during the first two days of fermentation although another mould species, Geotrichum candidum, frequently appeared towards the end of fermentation. Gram-negative rods (Flavobacterium, Erwinia herbicola and Enterobacter cloacae) increased in number over the first two days of the fermentation, then decreased, and lactic acid bacteria dominated the final stage of successful fermentation. The bacterium Leuconostoc frequently occurred during the middle of the fermentation and yeast numbers increased thoughout the fermentation. The addition of a starter inoculum, consisting of 10 per cent (v/v) of a previous fermentation reduced the time to reach the final desirable pH of 3.5 from 72 hours to less than 48 hours at 30°C.

No information on the nutritional value of ting was reported by Moss et al. (1984). This therefore is a matter which needs to be investigated. However, ting may be similar, nutritionally, to other acid-fermented cereal gruels like kenkey, kisra and pozol, with higher protein and vitamin contents than the unfermented maize dough.

Ahai and pito

Ahai is a maize beer brewed in southern Ghana. It has a sweet, malty taste and is usually served as a welcome drink and at outdoor ceremonies, wake-keeping and funerals.

Whitby (1968) reported that the traditional preparation of ahai is much the same as for pito, an acid-alcohol beer brewed from sorghum or millet, except that ahai is not boiled again after fermentation. Pito features predominantly at social gatherings of people from the northern regions of the Ivory Coast, Ghana, Togo, Benin and Nigeria. The traditional method of pito fermentation, the micro-biological and biochemical changes and its nutritional importance in the diet have been well documented in Steinkraus et al. (1983). No studies are known to have been made on the micro-biological, biochemical and nutritional changes that take place during ahai production.

Products from legumes and other seeds

Ogiri - watermelon seed fermentation

The seeds of watermelon (Citrulus vulgaris) are a good source of protein, minerals and vitamins and in West Africa they are used directly for the preparation of stews, soups and palavar sauce. In Nigeria, watermelon seeds are fermented by traditional methods to yield a product, ogiri, which is a highly priced food condiment. Its quality is variable and it has a short shelf life.

Dried melon seeds are dehusked either by soaking in water or placing them in sacks and breaking them up with a piece of stick and winnowing off the husks. The husked kernels are then wrapped in leaves and cooked for about three hours. The soft kernels, still wrapped in the leaves, are placed in earthenware pots, covered with jute bags and allowed to ferment for up to five days. Before it is used as a food condiment, the ogiri, still wrapped in the leaves, is smoked for two hours and then ground to a powder (Odunfa, 1981).

Ogiri is the product of bacterial fermentation and the organisms involved are Bacillus, Escherichia and Proteus species. Odunfa (1981) reported that Bacillus sp. particularly during the early stages of the fermentation and Proteus and Escherichia species constituted the predominant flora in the later stages. The pH during the fermentation increased from an initial 7.2 to 9.2 as a result of formation of ammonia by deaminating enzymes of the Bacillus and Proteus species. Odunfa (1982) studied the biochemical changes during ogiri fermentation and reported high levels of amylolytic and proteolytic enzymes. Lipase activity was minimal despite the fact that oil is a major component of melon seed, accounting for up to 53 per cent of the dry weight. Soluble products increased during the fermentation, resulting in high digestibility of the fermented product. Alanine, Lysine and glutamic acid were the predominant amino acids, with arginine and proline occurring in small quantities.

Although the microbiology, biochemical changes and nutritional value of this product are well investigated, further studies are required to improve the traditional method of production.

Ugba - African oil bean seed fermentation

Oil bean seeds are produced by the African oil bean tree (Pentaclethra macrophylla), a leguminous tree usually planted along the roadsides in big towns and cities. When the fruit matures it turns black and explodes to release glossy brown, edible seeds, usually eight in number. The seeds, rich in protein and essential fatty acids, are fermented to a product called "ugba" which is popular amongst the Ibos of Nigeria. It is reported that the production of ugba by traditional fermentation methods dates back to prehistoric times, but there was no published account of the method until recently, when Obeta (1983) outlined the process and indicated the predominant micro-organism involved as Bacillus spp.

The preparation of ugba follows a similar pattern to that of ogiri fermentation except that for ugba fermentation the soft beans are wrapped in banana leaves and fermentation takes 72 hours. As with ogiri, further studies are required to improve the traditional production method. The microbiology, biochemical and nutritional changes in ugba production also need investigation.

Lupin seeds

Lupins (Lupinus mutabilis), which are native to the Andean Indians, contain over 3 per cent alkaloids which render them bitter and cause some toxicity problems in man. Peruvians debitter lupins by boiling the seeds, placing them in a sack and leaving them in running water for three days. Keeler and Gross (1979) reported that soaking lupins in running water reduced the alkaloids to 0.003 per cent but also caused a large loss of dry matter and protein (25-60 per cent).

This debittering process for lupin seeds is similar to the Maoris' process for corn fermentation which was extensively reviewed by Yen (1959) and also to the "chuno" method found in Peru and in the high Andes of Bolivia, in which strong and bitter flavours in potatoes are removed by soaking.

So far no report has been published on the debittering of lupins by a fermentation process, but the soaking process may involve some fermentation.

Products from tubers, fruits and vegetables

Farinha puba

Farinha puba is a coarse, cream-coloured flour made from cassava and found in the Amazonian regions of Brazil, Peru and Ecuador. In Brazil the flour is known as "farinha de mandioca" and Woolfe and Woolfe (1984) presented an outline of the preparation of this product. They noted that the technology was exported to West Africa in the 19th century and presumably was adapted locally to give the gari process. Gari, a

popular West African staple food, is prepared by fermenting cassava and details of improved methods of production are given in Steinkraus et al. (1983).

Farinha puba is prepared by soaking the cassava tubers in a stream or tank of water for several days during which time they soften and ferment, resulting in the breakdown of the toxic glucoside and the leaching of the liberated cyanide. The softened tubers are peeled and crumbled through a sieve to remove fibre and further cyanide. The meal is then toasted in a pan to give the final coarse product. Another product, "farinha seca", produced in the Amazon region, is prepared by peeling and grating the cassava and pressing out the juice. The moist meal is then toasted. There is no report of the involvement of fermentation in the production of farinha seca.

The processes involved in the production of farinha puba and gari appear to be very similar. Unlike gari, however, very little information has been published on the methods of production, and on the microbiology, nutritional values and toxicological problems of farinha puba. Seneviratne (1985) reported that cassava fermention, as practised in Africa, Asia and Latin America, is an unreliable detoxification method and further reduces the already very low protein content. Other studies have shown that cassava fermention for gari production did not totally eliminate the cyanide content but reduced it by at least 65 per cent (Madungwa and Oben, 1981; el Tinay, Bureng and Yas, 1984; Avernor, 1985). The use of pure microbial cultures might bring about complete hydrolysis of the poisonous glycoside.

Kokonte

Kokonte is another important cassava-based staple, eaten in Savannah Africa by millions of people. Like many other fermented foods it is known by various names - "kokonte" in Ghana, "lafun" in Nigeria, "chikwangada" in East Africa - and a similar product is also prepared in Zaire and Central Africa.

The preparation of kokonte is probably less laborious than that of most fermented food products. Cassava is peeled, washed and cut into pieces about 5-10 cm by 2-3 cm. The smaller the size, the less days it takes to sun-dry thoroughly. The white-cream cassava chips are then sun-dried, during which time microbial attack, particularly fungal, becomes apparent. The sun-drying (fermentation) may take from 7 to 14 days or longer, depending on the weather. During the wet season, the cassava pieces are dried near to the cooking fire in the kitchen, and the heat, smoke and soot render them dry and dark brown or black. When dried, the chips contain about 10-18 per cent moisture and they are milled into powder and sold in the market. This is then cooked by adding water and heating on a fire, with constant stirring, to give the desired texture and consistency.

The organisms involved in kokonte fermentation have not yet been fully described. The author isolated several mould species from kokonte, with Aspergillus and Penicillium as the predominant organisms. These moulds always appear on kokonte regardless of the time of the year that the fermentation was carried out.

The kokonte process is one which could be scaled up using hot air or drying units. However, this may eliminate the fermentation stage which is undoubtedly essential since it brings about the detoxification of the cassava.

Masato

Masato, or cassava beer, is an alcoholic beverage produced in the Amazon from cassava. It has an alcohol content of 6-12 per cent by volume and is offered to guests as a sign of hospitality (Woolfe and Woolfe, 1984).

Masato is prepared by first washing, peeling and cooking the cassava. A portion of the cooked cassava is chewed and spat out into a large bowl. The rest of the cooked cassava is mixed with the chewed part to give a homogeneous dough which is left for 24 hours. The contents of the bowl are then boiled with water, transferred to pots already impregnated with wild yeasts from previous fermentations, and allowed to ferment for several days to give a white liquid. This is masato.

The chewing of the cooked casava as a source of enzymes to initiate masato fermentation, is similar to the chewing of maize in the preparation by the Andean Indians of an effervescent alcoholic beverage, "chica". In the traditional way of preparing chica, the older women chewed red corn flour, whilst in some regions the chewing of corn was traditionally done by young girls who had never chewed coca.

So far, no scientific account of the masato fermentation process has been published. Further studies on improving the traditional methods of production and on the microbiology of masato are necessary to save this ancient art of the Andean Indians from extinction.

Tepache

Tepache is a refreshing beverage prepared and consumed throughout Mexico. Ulloa (1980) noted that, in the past, tepache was prepared from maize, but that nowadays various fruits such as pineapple, apple and orange are used.

The pulp and juice of the fruit, commonly pineapple, are allowed to ferment for one or two days in water with added brown sugar. The mixture is contained in a lidless wooden barrel called a "tepachera" which is covered with cheesecloth. After a day or two, the tepache is a sweet and refreshing beverage, but if fermentation is allowed to proceed longer, it turns into an alcoholic beverage and later into vinegar.

Herrara and Ulloa (1978) studied the micro-organisms associated with the product and listed Bacillus subtilis, B. graveolus and the yeasts, Torulopsis insconspicna, Saccharomyces cerevisuae and Candida queretana as the main organisms.

Although no biochemial study on tepache has been published, it was reported that the product may be poorer in some vitamins than the beverage derived from the tree sap, pulque (Ulloa, 1980).

Colonche

Colonche is a sweet, fizzy beverage produced in Mexico by fermenting the juice of tunas (fruits of the prickly pear cacti - mainly Opuntia species.

The procedure for preparing colonche at present is essentially the same as has been followed for centuries (Ulloa, 1980). The cactus fruits are peeled and crushed to obtain the juice which is boiled for two to three hours. After cooling, the juice is allowed to ferment for a few days. Sometimes old colonche or tibicos may be added as a starter. Tibicos are gelatinous masses constituted of yeasts and bacteria, grown in water with brown sugar and they are also used to prepare tepache. Ulloa and Herrara (1978) reported Torulopsis taboadae as a new yeast species and this is apparently the first micro-organism isolated from colonche itself.

Like tepache, further studies are needed on colonche, particularly on the biochemical and nutritional changes occurring during the fermentation. It appears that more work on the microbiology of colonche is also needed.

Gundruk or Nepalese pickle

Gundruk is a fermented, dried vegetable produced in Nepal. It is served as a side dish with the main meal and is also used as an appetizer in the bland, starchy diet. The annual production of gundruk in Nepal is estimated at 2,000 tons and production is still done at the household level. In the months of October and November, during the harvest of the first broad mustard, radish and cauliflower leaves, large quantities of leaves accumulate - much more than can be consumed fresh. This then is when gundruk is prepared. The method of preparation and its role in the diet of Nepalese people was reported recently by Dietz (1984); Karki, Okada and Baba (1983) have written about the microflora of gundruk.

The radish, cauliflower or mustard leaves are allowed to wilt for one or two days and then shredded with a knife or sickle. The shredded leaves are tightly packed in an earthenware pot and warm water (at about 30°C) is added to cover all the leaves. The pot is then kept in a warm place. After five to seven days, a mild acidic taste indicates the end of fermentation and the gundruk is removed and sun-dried. This process is similar to sauerkraut production except that no salt is added to the shredded leaves before the start of gundruk fermentation. The ambient temperature at the time of the fermentation is about 18°C.

Pediococcus and Lactobacillus species are the predominant micro-organisms during gundruk fermentation. The fermentation is initiated by L. cellobiosus and L. pantarum, and other homolactics make a vigorous growth from the third day onwards. Pediococcus pentosaceus increases in number on the fifth day and thereafter declines (Karki et al. (1983)). During fermentation the pH drops slowly to a final value of 4.0 and the amount of acid (as lactic) increases to about 1 per cent on the sixth day. According to Dietz (1984), it appears that gundruk acts particularly as an important source of minerals. At the time when gundruk is most commonly consumed (March - June), farmers eat mainly starchy tubers and maize which tend to be low in minerals.

During the preparation of traditional fermented foods, loss of important nutrients may occur due to processes like heat treatment, soaking, grinding or sun-drying and gundruk is an example of this. It has been found that a disadvantage with the traditional process of gundruk fermentation is the loss of 90 per cent of the carotenoids probably during sun-drying. Improved methods of drying might reduce vitamin-loss.

Sudanese kawal

Kawal is a Sudanese, protein-rich food prepared by fermenting the leaves of a wild African legume, Cassia obtusifolia, and is usually cooked in stews and soups in a similar way to dawadawa.

The leaves of the leguminous plant are pounded into paste, placed in an earthenware jar and covered with sorghum leaves. The pot is buried in a cool place and the contents are mixed by hand every three days. After 14 days, the fermented paste is made into small balls and sun-dried.

The microbiological and biochemical changes that occur during kawal fermentation have not yet been reported. However, it was indicated recently that kawal contains the sulphur amino acids which are usually obtained from either fish or meat (Dirrar, Harper and Collins, as cited in Hecht, 1985).

Conclusions

Studies on methods to improve these lesser-known fermented products should be based on (1) isolation and/or selection of desirable micro-organisms to control the fermentation process, (2) the relationship between microflora and organoleptic properties, (3) optimizing the fermentation conditions, (4) consumer reaction to laboratory-made or pilot plant scale products and (5) the use of other plant materials. Plant materials, particularly the less familiar cereals like triticale (a hybrid of wheat Triticum and rye Secale), amaranth (genus, Amaranthus) and starchy root crops like oca (oxalis tuberosa) and achira (Canna edulis) which have been successfully grown in some countries in Africa and South and South East Asia, could be examined as alternative substrates for food fermentations. It should be noted, however, that "improvements" in the traditional methods could change the flavour, texture, colour, aroma or fragrance of the product and so its acceptability. However, the benefits may also be obtained.

Research and development studies on the fermented products could lead to products with improved quality, longer storage life, increased digestibility, exclusion or reduction in toxic substances, maximum utilization of raw materials, minimum production costs and improved nutritional values. Since the protein and vitamin contents of most fermented plant products are higher than those of the unfermented material, a more carefully controlled fermentation process may give a product with an even better spectrum of these essential nutrients. (Excerpted from Tropical Science, Vol. 26, 1986)

Chemical applications

New insecticides

The consumer sector of the insecticide market is big business. Americans spend $1 billion/year on insect killers for home and garden - including $550 million on roach control alone - and an additional $3 billion for professional pest control services. Yet, despite those tremendous outlays, there have been few lasting successes; insects generally become resistant to the latest insecticide and, as a result, return in full force. However, a new generation of insecticides is being prepared which are more specific than such earlier insecticides as DDT and chlordane, which, while killing insects, sometimes harmed birds and other animals. Indeed, the new insecticides - often based on compounds found in the insects themselves - are generally specific to a single insect species. The new products also take a new approach: Although earlier insecticides killed almost all targeted bugs immediately, the insects that survived reproduced and reinfested. Conversely, today's insecticides take longer to kill targeted bugs - sometimes days and even weeks - but attempt to kill all of those bugs.

Some of those items are now on grocery shelves. S.C. Johnson's Raid Flea Killer Plus, made up of two insecticides, is a good example. The company says it controls fleas for six months with a single application. The first ingredient is a mixture of natural pyrethrins, insect-specific nerve toxins isolated from chrysanthemums. Pyrethrins, which are not toxic to creatures other than insects, kill more than 90 per cent of adult fleas in a house within a couple of days, the company says.

The second ingredient, called flea juvenile hormone, works on the flea larvae in infested carpets, rugs, blankets and other places where pets sleep.

Juvenile hormone is produced by flea larvae in minute amounts to trigger the several stages of development that larvae pass through on their way to reaching maturity as adult fleas. Although the hormone is not toxic to the larvae, it alters the timing of a crucial developmental step when present in higher than normal amounts. The result is that the larvae do not become adults. In fact, juvenile hormones - and analogues of the hormones - are seen by major insecticide producers as the bug killers of the future for two reasons: The compounds are generally insect specific, and insects should be hard pressed to develop resistance to them, as they produce the compounds themselves.

Development of juvenile hormones has a drawback, though. All insects produce the hormones, so in theory researchers should be able to isolate the compounds and, after determining their structures, synthesize them in large amounts. However, a typical insect makes less than a billionth of a gram of its juvenile hormone. Thus, isolating enough hormone for structure determination is, at best, arduous.

Another new insecticide uses a slightly different approach. American Cyanamid's Combat, which kills roaches, uses a synthetic compound called hydramethylnon that slows an insect's metabolism to the point where it cannot generate enough energy to survive. According to Theodore Shapas, Cyanamid's manager of insect research, the key to Combat is not only its active ingredient: the way in which that ingredient is presented to the roach - in the darkness of an enclosed tray - also is essential.

The US Department of Agriculture is also developing new insecticides. One compound that the agency is testing is an inhibitor of chitin, the polysaccharide that makes up the outer skeleton of an insect. The compound prevents insects from forming new outer skeletons after they moult. Without a skeleton's protective coating, insects dry out and die. USDA is also testing a substance that prevents the outer skeleton of certain caterpillars from completely falling off when they moult. Thus, the mouth of the caterpillar is soon covered and the insect starves. (Extracted from Chemical Week, 22 July 1987)

Energy and environmental applications

Naphthalene - degrading genotype studied

The molecular microbial ecology of a naphthalene-degrading genotype in activated sludge is examined by J.W. Blackburn, R.K. Jain and G.S. Sayler of the University of Tennesses (Knoxville, TN). The concentration of cells in an activated sludge system having a gene known to take part in degradation of naphthalene was experimentally related to the biotransformation and mineralization of naphthalene. The gene probe analysis for the naphthalene catabolic genotype was more sensitive in this system as against other naphthalene degrader microbial analysis methods for catabolic cells. Other live cells present were 1,000-10,000-fold more numerous than the genotype. Naphthalene biotransformation and mineralization rates fell when the mean value of genotype replicates fell under 10 million genotypically positive cells per millilitre. The ability to enumerate a critical genotype and relate it to enzymatic activity in a mixed culture suggests a better capability for system understanding at the ecological level and possible process control at the genotype level. (Extracted from Environmental Science, September 1987)

Biodegradable plastics

Biodegradable plastics can be produced by combining petroleum-based polymers with cellulose or starch, according to R. Narayan and colleagues at Purdue University. The approach could help disposal problems and use some of the United States surplus corn. Natural polymers and polystyrene are not generally compatible, but they can be made compatible by adding a starch-polystyrene graft co-polymer that acts as an interfacial agent. Anionic polymerization techniques give good control of molecular weight and other properties of the graft co-polymer. Starch-polystyrene blends containing 20-30 per cent starch by weight behave much like conventional PS, but are much more susceptible to decomposition by soil micro-organisms. (Abstracted with permission from Chemical and Engineering News, 17 August 1987. Copyright (1987) American Chemical Society)

Microbe control in fouled fuel systems

A fuel preservative which can be used to control microbial infection in fouled fuel systems as well as to prevent bacterial and fungal growth in fuel tanks, storage tanks, and moving streams of fuel has been launched in Europe by Rohm and Haas (UK) of Croydon. Kathon FP 1.5 microbiocide is recommended for use in liquid hydrocarbon fuels, including kerosene, heating oils, diesel fuels, other middle distillates, coal slurries, and petrochemical feedstocks.

Bacteria and fungi can cause a range of problems if allowed to contaminate fuel systems. For example, their growth can result in the formation of dense mats at the interface of fuel and water, leading to blocked fuel filters, etc., and fuel turbidity haziness problems. Additionally anaerobic bacteria in fuel may secrete corrosive acids, damaging unlined tanks.

The product is claimed to provide rapid, long-lasting protection - field trials have shown prevention of recontamination from one month to a year, depending on the system. In addition, microbial counts are measurably reduced within five hours, and control of microbial growth achieved within 24 to 28 hours of the introduction of the material, claims the company. (Source: Manufacturing Chemist, August 1987)

Recycling organic sludge

Saz Pontesuero (Italy) has unveiled a system to recycle industrial, municipal and agricultural organic sludge using worms. The Airfoical system depends on the presence of worms that feed on organic sludge instead of usual animal manure. The Airfoical, an open-air cylindrical tank, is a system depending on animal energy for disposing of organic sludge by converting it into usable wormcasts. The system's advantages are low cost installation, minimum labour, no energy requirement, there is no smell or noise, and its output is fully usable as fertilizer. Redworms are put into the tank that have become conditioned to feed on sludge. The worms consume the sludge, eliminate 60 per cent of it and convert 40 per cent into wormcasts. (Source: Technology Update, 27 July 1987)

Enzymes treat organic waste

Combizyme from Biocatalysts of Pontypridd has been developed for effective treatment of organic waste effluents. The product contains a mixture of viable bacterial spores, hydrolytic enzymes and nutrient salts, the exact composition of which can be tailored to meet specific requirements. For example, effluent with a high fat content can be particularly difficult to degrade but by increasing the lipase content of the Combizyme, such waste can be treated readily, says the company.

In addition to creating an effluent composition that is more easily assimilated by sludge bacteria, Combizyme is claimed to correct any imbalance in nutrient supply, as well as aiding sludge settling and

providing a top-up of viable bacteria, ensuring the maintenance of a healthy, active sludge.

Combizyme is supplied in specified quantities and can be stored under dry, cool conditions for at least six months. (Source: Manufacturing Chemist, July 1987)

Biotechnology coal processing seen on the way

Researchers are growing bacteria and fungi to find new ways of turning coal into a better energy source. The genetically engineered bugs are being harnessed to transform coal into useful forms of liquid or gas and to remove polution-causing sulphur from the coal.

The implications are potentially immense for a world with dwindling oil reserves, an insatiable appetite for liquid fuels and centuries of coal supplies still available. Work is proceeding along several fronts at the Electric Power Research Institute (EPRI), the non-profit research and development arm of the US electric utility industry.

Researchers, for example, have found a fungus that will liquefy certain kinds of coal. Since new sources of gaseous fuel are also a high priority, one utility is scouring the earth in search of organisms that will biologically convert coal into methane. Other scientists are testing genetically engineered bacteria that remove sulphur and ash-forming metal impurities from coal before it is burned.

All this work is in its infancy. However, EPRI believes enough in the potential of biotechnology to support it in several ways.

Experiments in the early eighties turned up the surprising fact that a common wood rot fungus can transform lignite into a liquid. Building on this discovery, EPRI researchers last year isolated a key enzyme produced by the fungus that dramatically speeds up reaction times. Researchers are now looking at using the enzyme to liquefy coal underground, then pumping the converted fuel to the surface like oil.

In similar work, Houston Lighting and Power Company is exploring the use of methane-producing bacteria to gasify lignite. The utility is considering using caverns carved out of salt domes as reaction chambers for producing the biogas, which would then be used to run combustion turbines. Scientists are searching the bottom sediments of the Dead Sea and Utah's Great Salt Lake to find salt-tolerant bacteria that will eat lignite and excrete methane.

Not everyone wants to turn coal into a gas or liquid. With air quality of international concern, many researchers are trying to find ways to remove sulphur from coal before it is burned. In fact, sulphur removal may turn out to be the first commercial application of coal bioprocessing.

Although conventional coal-cleaning methods remove some of the pyritic sulphur particles that exist in coal as distinct veins or nodules, they do not remove the organic sulphur that is bound chemically into the coal molecules. More than half of the sulphur in some coals is in organic forms. (Source: Chemical Marketing Reporter, 14 September 1987)

Microbes may protect groundwater

As part of a US Department of Agriculture co-operative study between government and university research laboratories, scientists have found communities of micro-organisms at depths of 860 feet, much deeper than the levels at which it had been thought they could survive. The significance of the finding is that such microbes may be used to form biological barriers that would mitigate groundwater contamination by preventing the movement of subsurface contaminants. Study samples were collected from the Department of Energy's (DOE) Savannah River site at Aiken, S.C. Researchers may conduct similar studies at other spots, says Battelle Memorial Institute, which runs DOE's Pacific Northwest Laboratory. (Source: Chemical Week, 12 August 1987)

Fungus provides economical "filter" for industrial effluents

An unwashed coffee cup left standing in her laboratory provided that final answer to Professor Margalith Galun's lengthy research. A professor at Israel's Tel Aviv University, she had been seeking the right fungus to "filter" heavy metal from industrial waste water, and on seeing the film of fungus growing on the coffee residue, decided to experiment with it - and eventually found the fungus that is the key to a new process.

The process removes heavy metal contaminants (including mercury, uranium, lead, zinc, cadmium, nickel, silver, copper and chromium) from industrial effluents, and allows the continuous re-use of the water involved. Contaminated water, instead of polluting rivers and streams, can thus be cleaned up and recycled. Among the industries in which the new method may be used are mining, chemicals, metal processing, and electroplating.

Many micro-organisms are able to absorb metals from aqueous solutions. But the fungus used in Galun's method is much more efficient than the others because it has a higher absorptive capacity. It is also more economical: this particular species can be cultured on waste products from the food and beverage industry.

The absorption process is fast - it does not require long contact between the fungal mass and the effluent. The mass can be stored between production and use, and its absorptive capacity does not deteriorate in cool storage. The metal elements can be easily removed from the fungal mass and the fungus re-used. This procedure can be repeated several times.

Galun's method has been shown to work well in the laboratory. Ramot, the University Authority for Applied Research and Industrial Development Ltd., will market the industrial upscale of the process.

For further information, contact Mr. Zvi Shoshan at Ramot, 32 University Street, Ramat Aviv, telephone: 03-420113, or 03-428? . (Source: European Science News, May 1987)

Artificial marshes, fens and bogs

The humble cattail, bullrush, waterhyacinth and phragmites are being put to use. In artificial fens and bogs and specially created offshore wetlands, they do the work of massive and costly wastewater lagoons and supporting equipment. There is a possibility that benign natural processes involving such plants can be used to clean up toxic industrial leachates containing heavy metals.

Artificial marshes can treat waste water in roughtly one-third the area required for traditional lagoons. Research shows that a community of 20,000 would need about 24 hectares for such treatment, as opposed to about 40 hectares for conventional methods.

The high cost of services - fire, water and other utilities - in sprawling suburban areas is causing

problems. As inflation eats into budgets, cost-effective shortcuts for essential services like those cited above have become increasingly necessary. As natural bioengineering, these systems are based on the amazing power of marshes to digest nutrients in the extensive biological surroundings of the root system of each plant.

There are basically three kinds of systems. The first uses emergent species rooted in trenches and narrow ponds flooded with effluent. Primary sewage is not used, and the trenches seldom operate in winter. Harvesting is often recommended to prolong the life of the system.

In the second kind of system, using the larger marsh like the systems now being tested at Port Perry by the Ontario Ministry of the Environment, sites are retrofitted permanent lagoons kept flooded and covered with cattails and Typha.

Pretreatment is achieved with a facultative aeration cell. In experiments conducted elsewhere, the process has been successfully used for tertiary treatment - occasionally in a marine, estuarine wetland, as in a recent installation at Chesapeake Bay, MD.

The third type of system is the root-zone method developed by Professor Kickuth at Kassel University. It depends on the flow of waste water along the annular space - termed the rhizosphere - between the surrounding soil and rhizome of reeds, normally phragmites. Bacteria similar to those found in biological filters and activated sludge biochemically oxidize the impurities, the reeds providing an adequate supply of dissolved oxygen through their leaves and stems. Suspended solids in the sewage are aerobically composted with "straw" produced from dead leaves and stems at the surface of a reed bed. Reed beds are about 100 m long by 35 m wide. They serve a population of 2,600 people and are capable of handling 240 cubic metres of water a day.

According to Dr. Joan Herskovitz of the Ontario Ministry of the Environment, systems like these will soon begin to appear across North America. At present, most of the work is consultative, and development is still in the technology phase.

There is reason to believe that these natural systems are capable of extracting killer phenols and other toxic pollutants such as heavy metals from wastewater in industrial areas.

The Port Perry facility consists of two systems operating in parallel, one of 1.9 and the other of 3.9 hectares, handling a population of 4,000. When technology is ready (in about a year), the 1.9 hectare system is expected to be adequate.

Arthur Boon, from Anglian Water allied with the Water Research Centre in Stevenage, UK, recently toured North America to assess the application and cost effectiveness of the Root Zone Method (RZM), of which Anglian Water is currently monitoring about 12 versions. The major benefit is cost - less than one-half of the installation cost and about one-fifth the operating cost of conventional treatment. In addition, there is a major reduction in river loading.

The largest commercial effort underway is perhaps that at Chesapeake Bay. Projects like the Mayo Peninsula development in Anne Arundel County, MD, will be of vital importance to future urban health. This decentralized approach, costing $46 million, will save approximately $12 million, yet enhance the environment through the creation of attractive wetlands. It was designed by Lombardo and Associates of Boston as a mix of wetland, bog and estuarine wetland, and can very cheaply and esthetically deal with a community's wastewater treatment without adding the strong growth-producing attributes of traditional capital-intensive plants. In other words, it does not generate urban sprawl.

A vital aim of the project is to improve the area's ecosystem and help restore the quality of Chesapeake Bay. Characteristic of things to come, it takes existing septic systems several steps further. Wastewater is filtered through sand beds and allowed to flow by gravity into bullrush/cattail wetlands. There, nitrogen is removed together with various pathogens and a group of substances that increase biological oxygen demand. Next, ultraviolet radiation removes residual pathogens before the crucial step, removal of the phosphorus. Phosphorus can choke marshes to death, so it is removed in a man-made peat wetland. Peat, with its unique absorbent properties, rapidly takes away this chemical, and the water can be discharged into a protective offshore wetland after a final dose of ultraviolet radiation. This offshore wetland is typical in that it teems with productive life, submerged aquatic vegetation, shellfish and other marine organisms. Nearby, recreational activities can continue undisturbed. (Source: Canadian Research Biotechnology Canada, April 1987)

Extraction industry applications

Gold ore recovery

Giant Bay Resources' (Canada) bioleach process for gold ore recovered well over 90 per cent of the available gold in its first trial at a 10 tons per day demonstration plant at Giant Yellowknife Mines' Salmita mill in the Northwest Territories. The plant processed 500 million tons of ore over two months. Giant Bay uses Thiobacillus ferro-oxidans bacteria to break down sulphides on refractory ore before cyanide leaching. Gold recovery with the cyanide process alone averaged only 60-65 per cent. The economics of the bioleaching process appear to be very favourable and Giant Bay is discussing commercialization of the process with several firms. (Extracted from Chemical Engineering, 20 July 1987)

Industrial microbiology

Loudspeakers from bacteria

Sony has developed a way to make loudspeakers from bacteria. Acetobacter and Agrobacterium micro-organisms can be used to produce moulded material with the dynamic strength needed for speaker cones or diaphragms. The bacteria are fed on nitrogen, carbon and inorganic salts. They then produce a layer of cellulose gel which can be pressed and dried into a material for flat loudspeaker diaphragms. (Extracted from New Scientist, 25 June 1987)

A different kind of oil field

Under a programme of the US Department of Energy's Solar Energy Research Institute (Golden, Colo.), gasoline and diesel fuels could be produced from micro-algae by 1989. SERI recently signed a contract with Microbial Products Inc. (Fairfield, California) to design, fabricate and operate a micro-algae outdoor test facility at Roswell, N.M. The project is co-funded by the New Mexico Research and Development Institute (Albuquerque). SERI plans to sign one or two more contracts to convert algae oil into fuels. It is considering processes that employ trans-esterification or catalytic cracking.

SERI has collected about 3,000 algae strains and found 39 that produce up to 70 per cent of their dry weight as lipid oils. The biomass growth rate

obtained in the laboratory is about 50 g/m^2/d. SERI hopes to get similar results in the test facility, which will consist of a 1.25-acre pond for scale-up research and eight smaller ponds. This could mean an oil production of 150-400 bbl/year/acre, depending on the length of the growing season. However, preliminary estimates show that gasoline derived from algae will cost about $1.60/gallon, which will not make it economically feasible until about 2010. (Source: Chemical Engineering, 20 July 1987)

Waste yeast yields useful chemicals and forage

Surplus brewers yeast, Saccharomyces cerevisiae, is being mined for "various high-value chemicals", using separative techniques developed by Neil L. Morgan at the London Centre for Biotechnology. Crossflow membrane ultrafiltration and ion-exchange chromatography are recovering 10 mg of glutathione from one gram of yeast, plus variable amounts of thiamin and invertase. Simple cell disruption yields 0.22 g of glycan from the cell-wall fraction.

Invertase is used in the candy industry, Morgan notes; glutathione is a flavour-enhancer, and glycan "which tastes like fat without the calories", in food-thickening gels for processed meats.

Disposing of waste yeast, a by-product of brewing, "is a real problem for industry", says Morgan. Large enterprises can economically sell off the surplus in bulk for food and feed, but small and medium plants pay to have tons of it removed.

The London centre is a consortium of government, academia and food companies to exploit new biotechnology ideas in industry.

In Yugoslavia, leftover brewery yeast is being upgraded to a "highly valuable, biologically active additive for fodder", reports V. Maric of the food technology and biotechnology faculty at the University of Zagreb. To increase its viable cell-count and resistance to drying, suspended yeast is separated from green beer, thinned with tap-water, agitated, and enriched with wort, then dried and pelletized.

Fed to pigs over 45 days, a 0.4 per cent enrichment of starter feed increased average daily meat yield by 11.4 per cent, while lowering feed consumption per kilogram of yield by 26 per cent. (Source: McGraw-Hill's Biotechnology Newswatch, 20 July 1987)

Industrial equipment

Need for commercial production equipment

Commercial production equipment must be developed if biotechnology is ever to become a profitable industry. Only a few products can support the very high price that must now be charged for biotechnology products, according to R.C. Dean Jr. of Verax. A product-like tissue plasminogen activator will cost six times as much as conventional urokinase, and this could hinder demand. R.B. Nerem of the Georgia Institute of Technology claims that a revolution is needed in engineering equivalent to the revolution that has occurred in biology and genetics. Engineers need to develop aseptic processing techniques, new materials, automation, sensors, pumps, aerators, mixers, centrifuges, filters and chromatographic equipment. A major cost of biotechnology product production is separation. Adding compounds to encourage cell growth may just make purification even more difficult. (Extracted from Chemical Week, 10 June 1987)

E. PATENTS AND INTELLECTUAL PROPERTY ISSUES

Rule for patenting biological materials

Anyone trying to patent a biological substance, whether it is a plant, fungus, or bacterium, will probably have to submit a sample of the biological material with the patent application, according to a new proposal from the US Patent & Trademark Office. Although continuing a long-standing practice, the rule would set up formal conditions spelling out such things as which biological materials need be submitted, how much material is needed, and what kind of materials need be submitted. Because of recent decisions that are likely to increase the number of biological patent applications, PTO is updating its rules. The proposal would require submission of materials capable of self-replication, including bacteria, fungi, yeast, algae, cell lines, plant cells, and seeds. If the material is part of a living cell, such as a virus or vector, the host cell would be deposited. PTO says that material analogous to chemical compounds, such as proteins and enzymes, are not subject to the regulation. (Reprinted with permission from Chemical and Engineering News, 14 September 1987. Copyright (1987) American Chemical Society)

UK court overthrows patent on gene splicing

A judge in the High Court in London ruled that a key patent on a protein made by genetic engineering is invalid. The patent would have given the company at the centre of the case, Genentech of California, rights over all versions of the protein made with recombinant-DNA technology.

The other company in the case, the Wellcome Foundation of Britain, claimed that Genentech's patent did not fulfil the criteria of inventiveness and novelty. Wellcome claimed that it had the right to manufacture and to sell its own version of the protein made by genetic engineering.

It was the first time that a British judge has made a ruling on a patent involving the new technology of gene splicing. Patent lawyers around the world looked upon the dispute as a test case for future rows over who invented what in the technology of recombinant-DNA, in which scientists identify, isolate, modify and grow tiny pieces of genetic material.

The dispute between Genentech and Wellcome is not over, however. Immediately after the judge announced his decision, Genentech issued a statement from its headquarters in San Francisco saying that it intends to appeal.

Genentech's patent is for the production of tissue plasminogen activator, t-PA, a protein that occurs naturally. Laboratory and clinical trials have shown that the protein is twice as effective as existing remedies for dissolving clots in blood vessels. The pharmaceutical industry expects the sale of such a drug to exceed $1 billion by the early 1990s.

The court case in London was important for Genentech because other companies may now take Wellcome's lead and start to make t-PA by genetic engineering.

A further blow to Genentech is that it failed to satisfy the US's Food and Drug Administration that t-PA, which the company wants to sell under the tradename Activase, is safe enough to give to heart patients. A committee of the FDA said last June that the company must provide more clinical evidence that the drug is safe before the company sells t-PA in the US.

The court case in London centred on a British patent awarded to Genentech on 26 February 1986. At issue was whether the patent covered a technique that was truly novel, and that someone had not thought of it before. Also, Genentech had to show that its patent was for a process that marked an "inventive step", in other words that the process was not obvious to someone skilled in the relevant technology.

The decision includes a discussion of each of the 20 claims covered by Genentech's patent, ranging from processes for making t-PA to pharmaceutical compositions containing it. One claim covers "human t-PA as produced by recombinant DNA technology", and another covers "all processes for producing t-PA by recombinant DNA technology".

The decision accepts that Genentech was the first to discover the full sequence for producing t-PA, and as such "there might have been scope for a limited process claim"; but that discovery "does not justify the broad claims made". The claim covering any DNA technology for t-PA "is too wide and is bad. There is no basis for it", the decision states.

The judge, Mr. Justice Whitford, says, "What Genentech did was achieved by what, in my judgement, was rather more than the exercise of proficiency - it involved laborious and costly effort, and to deny any monopoly protection to those who are prepared to put as much time, skill and money into research as Genentech did is only too likely to discourage workers in this field from making advances which may be of the greatest public benefit." But in what might be viewed as a contradictory statement, he continues, "To grant them a monopoly which would stop others attempting to discover alternative, possibly wholly unknown and possibly better routes to that end, would be to stifle research which, in the public interest, it ought to be open to other investigators to pursue and over which other investigators, in their turn, if they make a valuable contribution, might be able to secure proper protection."

It is likely to be at least a year before the British Court of Appeals can hear what has now become a case of legal technicalities, and another year if the legal battle goes on to the House of Lords. Meanwhile, Wellcome is continuing to produce t-PA for use in its clinical trials; under US law, this is not considered a patent infringement. The legal battle has done nothing to stop the race for the lucrative t-PA marketplace.

Genentech, however, looks set to become embroiled in another patents row over its tissue plasminogen activator. The company is currently seeking an injunction against Japan's Toyobo Biotech to prevent it from manufacturing and selling t-PA. The claim is based on Genentech's patent claims to t-PA in Japan which it applied for in April. Since it applied for Japanese patents, 28 firms have already filed objections, alleging that the company's claims are too broad and vague.

So far, Genentech has received approval for t-PA in France, New Zealand, the Philippines and Austria, although it only has permission to market the drug in the latter two countries. (Extracted from New Scientist, 16 July 1987, Nature, Vol. 328, 16 July 1987 and European Chemical News, 31 August 1987)

US Patent and Trademark Office rules animals may be patented

The US Patent and Trademark Office has ruled that genetically engineered higher life forms, including mammals, may be patented. The decision may increase the commercial and agricultural applications of new genetic engineering processes and new life forms. A Congressional subcommittee plans to hold hearings on ethics and regulations covering genetic engineering. Future developments in the field of biotechnology could include insertion of viral or bacterial genes into plants to enable them to make their own insecticides or fertilizer. After the new "transgenic" plants are field-tested, they will begin to be used instead of conventional crop varieties. Cells that produce sperm and eggs will be manipulated to allow breeders to select the characteristics of animals. Scientists will routinely transplant genes from one species to another. Previously, concerns about genetic engineering focused on the environmental release of novel forms of bacteria designed to improve the resistance of plants to bad weather, disease and pests. However, the ruling by the PTO raises new legal, constitutional and policy questions about the genetic manipulation of higher life forms.

The newly announced policy that it will grant patents for new forms of animal life has already stirred controversy. Hearings are being held on the topic by the House Subcommittee on Courts, Civil Liberties and the Administration of Justice. The Senate has already passed legislation directing the Patent Office not to issue any animal patents at least until the Fiscal Year 1988, so Congress can establish some policy. Farmers are concerned that a few large corporations could totally dominate production of major livestock breeds.

A coalition of farm organizations, animal welfare groups and environmental organizations will lobby for legislation to prevent patenting of animals. Actually, the Supreme Court ruled in 1980 that General Electric could patent a bacterium modified to eat oil, declaring that patents could be issued for "anything under the sun made by man". The policy was extended in 1985 to include higher plants. The Patent and Trademark Office, however, tried to reject a patent application for inducing polyploidy and sterility in oysters, saying that oysters are governed by laws of nature and the procedure was therefore not a patentable manufacturer of man. The Board of Patent Appeals overruled that decision, however. Thus PTO issued its policy that any non-naturally occurring non-human multicellular living organisms can be patented. PTO now has at least 15 applications pending for patents on new animal forms. OTA is conducting its own study of the ramifications of animal patents.

In the meantime, drastic changes in European patent law will be urged by the World Intellectual Property Organization (WIPO) at a conference in Geneva in early July. WIPO's Industrial Property director, Ludwig Baeumer, gave a preview of these recommendations to a symposium on the protection of biotechnological inventions, jointly sponsored here last week by WIPO and Cornell University.

The proposed reforms in European patent law drawn up by a WIPO commission organized in 1984, include these key changes:

Plants, animals and micro-organisms would be patentable. This reverses the European Patent Convention's Article 53(b), which prohibits patenting plant and animal varieties. It would put Europe on a par with the USA and Japan.

In applying for a patent, deposits may replace, rather than merely supplement, a written description. This provision drew fire from many symposium participants, including depository managers. Said one: "For a single organism, a deposit is excellent. However, most claims are broader; they need description."

Patent protection for products that are living matter would not be limited to the product itself, but may include the results of replication, differentiation or derivation. For example, a purchaser of patented seed may grow it for crops, but not for further seed production.

A person who carries out an activity concerning a new plant or animal variety, which represents significant progress in a patent-protected area, shall have a right to obtain a license, under the patent, to carry out an improvement. This license-mandating provision is calculated to help ensure the unimpeded progress of European technology.

Turning the WIPO recommendations into law will require endorsement by individual European nations, and subsequent incorporation into the European Patent Convention. Such a modified statute would have a strong influence on international patent law. (Extracted from New York Times News, 8 June 1987, Chemical and Engineering News, pp. 4 and 5, 22 June 1987 and McGraw-Hill's Biotechnology Newswatch, 15 June 1987)

Antibody-linking technology patented

Technology to link molecules such as antibodies to other molecules to make diagnostic and therapeutic agents for cancer has gained a patent (US 4,680,338) for Immunomedics, Newark, NJ. The linker bears a fast-reacting anhydride, acid chloride, or activated ester group (such as of N-hydroxysuccinimide) to bind to amino groups of drugs or radioisotope chelators. The linker also has a slow-reacting isocyanato or isothiocyanato group to bind to amino groups of lysine residues of antibodies. The different reactivities of the two group types allow the two reactions to occur cleanly in sequence. For example, the company has reacted 4-isothiocyanatobenzoic anhydride with deferoxamine through the anhydride and then reacted the product with an antibody against carcinoembryonic antigen, which occurs in colorectal cancer. The deferoxamine moiety was used to chelate gallium-67. Immunomedics patent counsel says, however, that the technique is more general, capable of linking fluorescent tags to enzymes, enzymes or drugs to antibodies, or modifying groups to hormones.

Cytogen has been granted a patent on its technology for linking drugs to antibody molecules. The patent covers technology for binding isotopes or drugs to antibodies in such a way that the antibody is still able to target and bind to antigens such as those expressed by tumour cells. The patent also includes Cytogen linker mechanisms that can release drugs so that adjacent cells are also destroyed. (Source: Chemical and Engineering News, 27 July 1987, p. 24 and Chemical Marketing Reporter, 15 June 1987)

Genentech in human blood Factor VIII:C patent infringement

Genentech's purified form of human Factor VIII:C has infringed Scripps Clinic and Research Foundation's patent (US 32,011), licensed exclusively to Rorer Group. The patent covers the molecule itself and several methods for purifying it from pooled human blood plasma. Scripps licensed the patent to Rorer Group, Inc., which sued Genentech for infringement. Rorer has also sued Chiron and Baxter Travenol, both working on the recombinant factor.

The dispute is seen as the first trial case of "an isolator versus a cloner". Several of the major products being developed by biotechnology companies using recombinant DNA technology may also be isolated from blood or tissue. Although things found in nature cannot be patented, current US patent law provides protection for companies that find a way to produce a substance in a form that is "more pure" than that which occurs naturally. Factor VIII:C is the active clotting portion of the Factor VIII complex found in blood, and purifying it is therefore patentable.

The purity of Factor VIII is a central issue, because the handful of current producers get their plasma from paid donation centres. Until 1985, donors were not screened for the AIDS (acquired immune deficiency syndrome) virus, even though a significant proportion of them had used intravenous drugs. As a result, according to a National Haemophilia Foundation study, two-thirds of the roughly 20,000 haemophiliacs in the United States had been infected.

Although donor-screening and heat-sterilization are now routine for Factor VIII manufacturers, producing it by recombinant DNA techniques would totally remove the risk of viral infection. However, since the US District Court did not issue an injunction, Genentech will continue to work on a recombinant form of Factor VIII:C, at least until a decision is reached on the validity of the Scripps patent when it goes to trial in 1988. Genentech is one of three biotechnology firms that have devised a method to produce the complex protein through recombinant technology, or cloning.

Rorer's Armour Pharmaceutical subsidiary awaits US Food and Drug Administration approval to produce human Factor VIII:C from blood plasma using a monoclonal antibody process. The highly purified form of Factor VIII will not expose newly diagnosed haemophiliacs to the AIDS virus and may actually revitalize the compromised immune system of 66 per cent of haemophiliacs who already have been exposed to the deadly virus. Neither the Scripps method or any of the three cloning methods have received FDA approval. (Extracted from Chemical and Engineering News, p. 13, 3 August 1987 and Wall Street Journal, 23 July 1987)

Genentech licensee gets t-PA approval

Boehringer Ingelheim International GmbH, has received approval to market tissue plasminogen activator in Austria for treatment of heart attack patients. The product, a human protein that dissolves blood clots that cause heart attacks, has been approved in the Philippines, New Zealand and France and is awaiting approval in 20 other countries around the world. (Extracted from Chemical Marketing Reporter, 17 August 1987)

F. BIO-INFORMATICS

New journals

Enzyme Inhibition

The Journal of Enzyme Inhibition is an international and interdisciplinary vehicle publishing new knowledge and findings on enzyme inhibitors and inhibitory processes. It publishes research papers, short communications and reviews on current developments across the disciplines of enzymology cell biology, microbiology, physiology and pharmacology, drug design and biophysics. Among the various fields of enquiry, special attention is given to structural and molecular studies, kinetics and inactivation mechanisms, structure-activity relationships (including QSAR and graphic techniques) within a chemical series or group, drug development studies, and control mechanisms in metabolic processes.

The Editor-in-Chief is H.J. Smith, The Welsh School of Pharmacy, Cardiff, Wales. The journal will be published by Harwood Academic Publishers, London, UK and New York, US. The corporate subscription price per volume (four issues per volume) is $270;

university/academic library price $168; and individual subscription $84.

Protein Sequences and Data Analysis

Protein Sequences and Data Analysis is devoted to the publication of newly determined sequence data and to the organization, retrieval and analysis of this information using data banks. The journal will consist of four parts:

1. "Sequencing Results", reporting the experimental determination of new protein sequence data. Partial sequences, often of great importance in sequence comparisons or in nucleic acid work are included, as are protein sequences determined indirectly by DNA sequence analysis when experimental evidence for the existence of the protein is provided. Through the co-operation of participating data banks, newly determined sequences are automatically transmitted for data bank entry upon acceptance for publication, thus eliminating much delay in their availability for further research.

2. "Sequence Data Analysis", providing a forum for work involving the using of sequence data: sequence comparisons, evolutionary or functional relationships among proteins and structural analysis.

3. "Data Bases: Progress and News", devoted to the medium itself, covering aspects such as data base management, new data bases for special collections, software tools for sequence analysis, programme development, software portability and special hardware.

4. "Protein Sequence Data Bank Outprints", presenting printed output of recent entries to the National Biomedical Research Foundation data bank in Washington, D.C., and to co-operating protein sequence data banks at the Max Planck Institute in Martinsried (FRG) and at the Tokyo Science University (Japan). Subscribers to the journal will thus have, in one source, immediate access to virtually any known protein sequence reported in the current literature.

This journal will be published by Springer International, P.O.B. 503, 1970 AM Ijmuiden, The Netherlands. The cost of the journal for the US, Canada, and Mexico is $296 per volume consisting of six issues per year. Professor A. Tsugita, Science University of Tokyo, is Chairman of the international advisory board for this journal.

GLIA

Interest in research on neuroglia cells has increased greatly in the last decade, due in part to the fact that these ubiquitous cells have been shown to play an important role in normal and abnormal brain function. Since the study of neuroglia is crucial to an understanding of the functions of the nervous system, there is a need for a single, comprehensive publication that examines exclusively this rapidly expanding branch of biomedical investigation.

GLIA is an international journal devoted primarily to the study of the form and function of neuroglia cells in health and disease. Providing a forum for a rich diversity of research disciplines, including anatomy, physiology, pharmacology, pathology, biochemistry and clinical neurology, GLIA will cover a broad range of experimental topics related to research on GLIA.

The journal's bimonthly appearance will assure the prompt publication of full-length original research articles, reviews and short communications. The journal will use a large format, insuring that figures and photomicrographs will be reproduced with the greatest possible fidelity. Preference is given to articles that have broad cross-disciplinary interest and impact.

The Editors-in-Chief are Bruce R. Ransom, Department of Neurology, Yale University School of Medicine, New Haven, Connecticut, and Helmut Kettenmann, Institute of Neurobiology, University of Heidelberg, FRG, and the editorial board consists of an international roster of scientists. The journal is published by Alan R. Liss, Inc., 41 East 11th Street, New York. The institutional subscription price is $150 and individual price is $65.

Biocatalysis

Biocatalysis is an international journal that covers the industrial exploitation, both actual and potential, of biological catalysis and the mechanistic principles derived from these catalysts for the interconversion of chemical species. The journal will focus particularly on the kinetics and thermodynamics of biocatalytic process, biocatalytic stability, the use of alternative biocatalytic environments, biocatalytic modification (by genetic or protein engineering), biomimetic and bio-organic systems, alternative and novel activities of biocatalysis in relation to process design and subsequent downstream processing. The journal will publish both full-length research papers and reviews, and occasional shorter communications.

The Managing Editor is David Best, Biotechnology Centre, Cranfield Institute of Technology, Cranfield, Bedford, UK. The editorial board is international in scope. The journal is published by Harwood Academic Publishers, London, UK, and New York. The corporate subscription price is $248 per volume (4 issues per volume). The university/academic library price per volume is $152 and individual subscription price per volume is $76.

Oncogene Research

Oncogene Research is a monthly journal dedicated to reports of significant research in the genetics and molecular and cellular biology of oncogenes, their products and factors involved in the regulation of growth of normal and cancer cells. Oncogene Research is intended to provide a vehicle for rapid publication of reports in this growing area of biology. The journal will publish research papers, minireviews and short communications. Decisions on submitted papers will be made as rapidly as possible, usually within four weeks from the date of receipt. Publication of accepted manuscripts will be within three months.

Some of the various topics that will be considered for publication are:

- Molecular structure of oncogene proteins
- Function of oncogene proteins
- Cellular transformation
- Expression of oncogenes during development
- Growth factors and their receptors
- Oncogenes - gene rearrangements and other mutations
- Recessive oncogenes and tumour suppressor genes
- Tumour viruses as mutagens
- Viruses associated with human tumours and cancers
- Evolution of oncogenes
- Regulation of cell proliferation.

The Editors-in-Chief are Claudio Basilico, Department of Pathology, New York University School of Medicine, New York, and Hidesaburo Hanafusa, The Rockefeller University, New York. The editoral board consists of internationally known scientists. The

journal is published by Harwood Academic Publishers, London, UK, and New York. The corporate subscription price is $160 per volume (4 issues per volume). The academic price is $130 per volume and the individual subscription price is $35 per volume.

Brain Injury

Brain Injury will be launched in July 1987 and the first volume will contain two issues. From 1988 it will be a quarterly publication.

This major new international journal is designed to be the primary vehicle of communication for professionals whose main interest is in the area of brain injury. The thrust of the journal is to present vigorously refereed papers which have scientific validity yet are readable by any professional. It will be a multidisciplinary publication including subject reviews and editorials, with contributions from scientists, neurosurgeons, neurologists, psychiatrists, psychologists, and all the rehabilitation professionals.

The Editor-in-Chief of Brain Injury is Henry H. Stonnington, Virginia Commonwealth University, US. The European Editor is William W. McKinlay, Western General Hospital, Edinburgh, UK, and the Japanese Editor is Takashi Tsubokawa, Nihon University, Japan. The editorial board is composed of an international group of scientists. The publisher of the journal is Taylor and Francis Ltd., London, UK, and New York and Philadelphia. The subscription price for academic libraries is $55 for Volume 1, 1987 and $28 for a personal subscription.

Clinical Materials

This new international journal is dedicated to the preclinical and clinical applications of existing and novel materials. It is intended for those in clinical practice, research and industry who are concerned with patient care. Thus the new Clinical Materials satisfies a demand for rapid publication and cross-fertilization of ideas in the development and clinical application of materials in surgical, medical and dental practice. Hence it provides a common reference tool for all practicing clinicians, bioengineers, biochemists and material scientists. The original scientific papers, surgical case studies, authoritative reviews and commentaries presented in the journal are intended to ensure that the true clinical potential of modern materials is realized. Readers will also be kept up to date through book and data base reviews, calendars of meetings and information on new patents.

The chief editor is Dr. Christina Doyle, Department of Materials, Queen Mary College, University of London, UK. The journal has an international advisory editorial board with members from West European countries as well as the US, Israel, Canada and Japan.

The journal is published quarterly by Edward Arnold Ltd., 41 Bedford Square, London, UK. The cost of the journal for US and Canada is $75 per volume (institutional) and $50 per volume (individual) inclusive of air freight service to New York. Each volume contains four issues.

Microbiology and Immunology

A new section of the Federation of European Microbiological Societies' (FEMS) Microbiology which will deal specifically with microbiology and immunology is being prepared in response to the growing concern regarding acquired immune deficiency syndrome, and a realization of the magnitude of problems of infection. New rapid methods are urgently needed in virology, bacteriology and parasitology to facilitate treatment and control of epidemics and outbreaks. Veterinary microbiology and immunology are also important, as some of the most serious problems of human infection are acquired directly or indirectly from the the animal world. The application of molecular biology techniques to the study of infection will affect diagnosis, and offers new possibilities of treatment by improving our ability to make vaccines or other biological products. These and other topics of interest to microbiologists and immunologists will be covered by this new section which will publish original papers dealing with all aspects of immunology in infectious disease. Preference will be given to works describing the mechanisms of immunity and how these can be exploited in the diagnosis and treatment of disease.

The Editor-in-Chief of this journal is Heather M. Dick, University of Dundee, UK. The first issue was published in August 1987. The journal is published by Elsevier Science Publishers, Amsterdam, the Netherlands and New York. The institutional rate per volume (9 issues) is $177.75 and the personal rate is $55.50.

Proteins: Structure, Function and Genetics

The aim of the new journal, Proteins: Structure, Function and Genetics, is to keep readers abreast of significant advances and offers investigators a vehicle for reporting their important new work. The journal concentrates on advances in all areas of protein research (structure, function, genetics, computation, and design). Specific areas covered include:

- Structure-function relationships of proteins and inhibitors
- Structure determination, including discussions of new techniques
- Design of new proteins and small molecules that can interact with them
- Studies of the interactions between proteins and nucleic acids
- Modifications of proteins by altering the genes that encode them
- Modifications of proteins by chemical means
- Results and methods of computational analysis for protein structures and function.

The journal welcomes full-length articles reporting new experimental and theoretical results. In addition, each issue includes review articles. The Editor-in-Chief is Cyrus Levinthal (Department of Biological Sciences, Columbia University, New York). The composition of the editorial board is international, including scientists from the US, The Netherlands, France, UK, Japan, Canada, Sweden, Federal Republic of Germany, and Switzerland. The journal is published monthly by Alan R. Liss, Inc., 41 East 11th Street, New York, New York 10003, US. The cost of the journal per year is $225 (institutional rate) and $90 (personal rate).

Computer-Aided Molecular Design

The Journal of Computer-Aided Molecular Design has been established to provide a forum for disseminating information on both the theory and the application of computer-based methods in the analysis and design of molecules. The aim of the publishers (ESCOM Science Publishers, P.O. Box 214, 2300 AE Leiden, The Netherlands) is that the journal should become a premier source for reporting computer simulations in chemistry, physics and biology.

The scope of the journal encompasses papers which report new and original research and applications in the following areas:

- Theoretical chemistry
- Computational chemistry
- Computer and molecular graphics
- Molecular modelling
- Protein engineering
- Drug design
- Expert systems
- General structure-property relationships
- Molecular dynamics
- Chemical database development and usage.

The journal will also include a feature section, entitled Perspectives, where experts will be invited to comment on developments in various aspects of the fields covered by the scope of the journal. The use of colour is encouraged, particularly for the reproduction of computer graphics displays. A minimum charge is levied on authors from commercial organizations but may be reduced for those in academic institutions. The subscription price for 1987, Volume 1 (four issues) is $141.50 plus $10.50 for postage and handling.

The journal is typeset and initially will be published quarterly, with a view to becoming a monthly publication when this becomes justified. There are no page charges to publish in this journal and authors will receive 50 free reprints (black and white only) per contribution. All colour reprints carry a charge.

Contributions on computer-aided molecular modelling studies in polymer materials and surface sciences as well as other molecular-based disciplines are particularly welcome to complement contributions from the pharmaceutical sciences. It is intended that the journal will communicate original research and applications in the use of computers in the analysis and design of molecular structure. Authors reporting the results of applications are encouraged to include predictions of structures and properties which can be computationally verified and experimentally tested. Submissions about new methods or theoretical formalisms should include discussion and the need for, and utility of, such approaches.

The Editors-in-Chief are:

For the Americas and Australasia - Professor G.R. Marshall (Department of Pharmacology, Washington University School of Medicine, St. Louis, Missouri).

For the UK - Dr. J.G. Vinter (Smith Kline & French Research Limited, The Frythe Welwyn, Herts., UK).

For Continental Europe, the Middle East, and Africa - Professor H.D. Holtje (Department of Pharmacy, Free University of Berlin, Berlin, Federal Republic of Germany).

The editorial board is international in scope, including scientists from Australia, Federal Republic of Germany, the UK, US, The Netherlands, Yugoslavia, France, Belgium and Switzerland.

Bioluminescence and Chemiluminescence

The aims and scope of the new Journal of Bioluminescence and Chemiluminescence is to provide comprehensive coverage of the fundamental aspects and applications of light-emitting reactions, both chemical (chemiluminescence) and biological (bioluminescence). The journal will publish original scientific papers, short communications and review articles on fundamental and applied aspects of bioluminescence and chemiluminescence. It will also have a News and Events section which will contain details of forthcoming meetings, information on new products and book reviews. A special feature of this journal will be a quarterly survey of the recent world literature on bioluminescence and chemiluminescence.

Chemiluminescent and bioluminescent methods are used as research tools in many disciplines (chemistry, clinical sciences, environmental monitoring, microbiology) and the scope of the journal will reflect this diversity as follows:

- Instrumentation
- Fundamental studies
- Applied chemiluminescence
- Applied bioluminescence
- Luminescent immunoassay
- Luminescence in microbiology
- Phagocytosis
- Low-level luminescence.

The journal is being published by John Wiley & Sons Ltd., West Sussex, UK, in four issues per year at a cost of $120 per year.

AIDS Patient Care

This new bimonthly magazine, edited and published by Mary Ann Liebert, hopes to meet the urgent needs of physicians, nurses, administrators and other health care professionals who are, and will be, concerned with diagnosis and treatment of persons with AIDS and ARC. The problems this disease presents to the health care community are complicated and mounting. It is a fatal disease that is extremely demanding of the health care system and its members - physically, emotionally, and financially.

AIDS Patient Care is also aware of the concerns of health care professionals in terms of their own physical and emotional well-being.

The editorial board is composed of leading authorities in both the public and private sector who are involved and concerned with AIDS. Their active participation assures that AIDS Patient Care will recognize all of the pertinent areas surrounding the delivery of care and the concerns of the professionals who administer this care.

A plethora of materials have been and are continuing to develop: resource sharing will be fostered so that unnecessary duplication of effort can be avoided and available funds used to the best advantage.

AIDS Patient Care expects to provide the medical community with its own forum and asks to be kept abreast of work, training, programmes, protocols and publications of its readers. Articles for publication based on personal experience and point of view are called for.

Subscriptions to Vol. 1, 1987 (3 issues) and Vol. 2, 1988 (6 issues) are $90 for the 9 issues ($140 - overseas/air) and are payable in advance in US currency. Inquiries should be sent to Mary Ann Liebert, Inc., Publishers, 1651 Third Avenue, New York, NY 10128, USA.

Trends Classified

Elsevier Publications has a new fortnightly recruitment journal which is dedicated solely to life sciences and is mailed free of charge to the subscribers of the eight "Trends" journals. More details may be obtained from Trends Classified, Elsevier Publications Cambridge, 68 Hills Road, Cambridge CB2 1LA, UK. Telephone: 0223 311114, telex: 81623, FAX 0223 321410 Dialcom/Telecom GOLD Box 84: MNU 146.

BioFactors

BioFactors is a new bimonthly international journal from January 1988 aimed at identifying and increasing understanding of the precise biochemical

effects and roles of the large number of trace substances that are required by living organisms. These include vitamins and trace elements, as well as growth factors and regulatory substances made by cells themselves. The elucidation, in a particular organism or cell line, of the roles of substances active in trace quantities, is frequently applicable directly to many other forms of life. In keeping with this unified view of biochemistry, BioFactors will accept articles dealing with the identification of new substances and the elucidation of their functions at the basic biochemical level, as well as those revealing novel functions of trace substances already known. In launching and supporting this journal, the International Union of Biochemistry recognizes the importance of this area of research to such worldwide concerns as the improvement, through better nutrition, of the health and quality of life of the human population.

Subscription rates: Volume 1 (1988) 6 issues: libraries, etc. US$165/£90, reduced US$80/£45. The reduced subscription rate is available for individuals who declare in writing that the journal copies are for their own use only and will not be donated to a library, and who either have local access to the journal subscribed at the full rate, or who can show themselves to be members of an IUB-affiliated society. Details from: IRL Press Ltd., P.O. Box 1, Eynsham, Oxford OX8 1JJ, UK, or IRL Press Inc., P.O. Box Q, McLean, VA 22101-0850, USA.

Monitoring the biotechnology labour market

Demand for highly qualified biotechnologists in the UK has grown steadily over the past three years, but industry is filling vacancies at the expense of research posts in higher education. According to a report by the Institute of Manpower Studies for the Science and Engineering Research Council's Biotechnology Directorate, the number of staff now employed in UK Biotechnology, at graduate level or above, has risen by two thirds to 3,500 since 1983.

Career opportunities are dominated by industry, with few openings in research centres and higher education, IMS says. Higher education institutions are unable to attract biotechnologists because many posts are for short-term contracts with relatively low salaries and poor career prospects.

Manpower shortages are likely to be exacerbated by limitations of funding, high training costs, low student interest and limited supervision time which could restrain the growth of new skills via PhD programmes. Unless training and development of new and existing highly qualified staff increases, skill shortages could become more widespread, IMS warns.

The "brain drain", particularly among senior staff, has declined since 1983 due to a reduced overseas demand, especially in the USA, and improved opportunities in the UK, the report shows. The outflow now is dominated by post-doctorates. Details from SERC, Polaris House, North Star Avenue, Swindon SN2 1ET (Source: Chemistry & Industry, 20 July 1987)

Details of Biotechnology in Japan

A report of a visit by a group of UK biotechnologists to Japan in April 1986 has been published by the Science and Engineering Research Council's Biotechnology Directorate. Site visits were made to a range of research laboratories, in the fields of protein engineering and plant molecular biology. These were mainly academic in nature, although some industrial laboratories were included. There is considerable interest in UK-Japan exchanges and a brief guide is given on some of the schemes available for such exchanges. Inquiries should be addressed to: Science and Engineering Research Council, Polaris House, North Star Avenue, Swindon, Wiltshire SN2 1ET or on 0793 26222 ext. 2310. (Source: Biotechnology Bulletin, Vol. 6, No. 7, August 1987)

US Federal Biotechnology Programmes Directory

The first two volumes of OMEC's Biotechnology Information Series, Federal Biotechnology Programs Directory (151 pages, $95.00) and Federal Biotechnology Information Resources Directory (162 pages, $95.00) are available. The first covers online databases, culture collections, information and referral centres, and other sources of information. The second describes over 450 biotechnology-related programmes and activities within 37 agencies and departments of the federal government. Details from: OMEC International Inc, 727 Fifteenth Street, NW, Washington, DC 20005, USA or on (202) 639 8900.

Frost & Sullivan report on cancer therapy products market in US

The single most important factor determining the long-term potential of a cancer therapy product, according to Frost & Sullivan's new report Cancer Therapy Products Market in the US (A1702), is specificity - how well it can destroy or inhibit cancer cells without damaging normal cells.

At present, chemotherapeutic agents dominate the US market (74.5 per cent), with radiation therapy representing the second largest market segment (21.4 per cent). Looking to the 1990s, however, the report finds greater market potential for immunotherapy products, which are much more specific in targeting cancer cells. They are also relatively free of direct side effects.

As a whole, Frost & Sullivan say, the US cancer therapy market has been growing at an average annual rate of about 20 per cent through the 1980s. It was a $313 million market in 1981, $609.8 million by 1985 and $705.6 million by 1986. The report forecasts growth to $813.2 million in 1987 and to nearly $1.4 billion by 1990.

Although growth is expected both in the chemotherapy market (13 per cent yearly growth to $851 million in 1990) and radiotherapy (with equipment sales expected to grow at 5 per cent a year to $187 million in 1990), immunotherapy products are expected to take the market share from the chemotherapy segment. Two alpha interferon drugs accounted for the $15 million immunotherapy market in 1986. By 1988, as more products come on the market, the report forecasts a $70 million market. By 1990, a $300 million market is thought likely - and this could grow further to $1 billion by 1995.

Products due to enter the market include gamma interferon as well as more alpha interferon drugs, interleukin products (notably interleukin-2), tumour necrosis factors, monoclonal antibodies and colony stimulating factors. Details from: Customer Service, Frost & Sullivan Ltd., Sullivan House, 4 Grosvenor Gardens, London SW1W 0DH or on 01-730 3438. (Source: Biotechnology Bulletin, Vol. 6, No. 7, August 1987)

Biotechnology and Genetic Engineering Reviews, Vol. 5

The fifth hardback volume in this series, edited by Gordon E. Russell, Emeritus Professor of Agricultural Biology, University of Newcastle-upon-Tyne, UK, contains 11 authoritative review articles covering a number of important areas of industrial, agricultural and medical applications of biotechnology and genetic manipulation. The volume comprises approximately 420 pages with a comprehensive index and

illustrations. The titles of the articles and their authors are as follows:

Potato protoplasts and tissue culture in crop improvement (Angela Karp, Michael G.K. Jones, Gert Ooms & Simon W.J. Bright (UK));

Cell and tissue culture technology for the genetic manipulation of temperate fruit trees (David J. James (UK));

The introduction and expression of foreign genes in plants (D.M. Shah, N.E. Tumer, D.A. Fischhoff, R.B. Horsch, S.G. Rogers, R.T. Fraley & E.G. Jaworski (USA));

Bacterial ice nucleation: Molecular biology & applications (Gareth J. Warner (USA));

Bacterial culture collections: Their importance to biotechnology and microbiology (Khursheed A. Malik & Dieter Claus (Fed. Rep. Germany));

Genetics and potential biotechnological applications of thermophilic and extremely thermophilic micro-organisms (P.L. Bergquist, D.R. Love, J.E. Croft, M.B. Streiff, R.M. Daniel & W.H. Morgan (New Zealand));

Effects of temperature on lipid unsaturation (Saul L. Neidleman (USA));

Yeast B-glucosidases (M. Leclerc, A. Arnaud, R. Ratomahenina & P. Galzy (France));

Semisynthetic enzymes: design of flavin-dependent oxidoreductases (Donald Hilvert & E.T. Kaiser (USA));

Biocatalysis with immobilized cells (Cavit Akin (USA));

Safety testing of novel food products generated by biotechnology & genetic engineering (Diana Anderson & W.F.J. Cuthbertson (UK));

ISBN 0 946707 10 3; ISSN 0264-8725; price held at £80.00 (US$120.00) until 1 January 1988

Published by Intercept Ltd., P.O. Box 402, Wimborne, Dorset BH22 9TZ, England.

Microbial Information Network Europe (MINE)

Sponsored by the EEC Biotechnology Action Programme, MINE is an integrated catalogue project, incorporating a European network of microbial culture collection databanks. The basic objective is to improve awareness of the strains available and to facilitate ordering. All participating national nodes and individual collections will be able to access MINE on line, free of charge. Access for potential customers will be free through national nodes.

Initially, four European partners are to be national nodes: the United Kingdom (CAB International Mycological Institute), the Netherlands (Centraalbureau voor Schimmelcultures), Federal Republic of Germany (Deutsche Sammlung von Mikroorganismen) and Belgium (Programmation de la Politique, which co-ordinates the Belgian network of laboratories).

Data input agreements have been reached with the following UK collections: European Collection of Animal Cell Cultures; National Collection of Type Cultures; National Collection of Industrial Bacteria; National Collection of Marine Bacteria; National Collection of Pathogenic Fungi; National Collection of Wood Rotting Fungi; Culture Collection of Algae and Protozoa; National Collection of Yeast Cultures; and National Collection of Food Bacteria. Details from: MINE project administrator, CAB International Mycological Institute, Ferry Lane, Kew, Surrey TW9 3AF or on 01-940 4086. (Source: Biotechnology Bulletin, Vol. 6, No. 8, September 1987)

Modelling software for new workstation

Biograf, the three-dimensional molecular modelling software developed by BioDesign Inc., Pasadena, has been adapted to run on Sun Microsystems' new Sun 4 workstations. BioDesign says Biograf/Sun is the first integrated computer-assisted molecular-design package to run with the Unix operating system. To provide three-dimensional modelling capabilities on the Sun 4, the software supports Evans & Sutherland's PS300 family of 3-D graphics terminals, which until now, according to BioDesign, have been available only on more expensive computers. (Source: Chemical & Engineering News, 27 July 1987, p. 24)

Protein programmes

The Gene-Master DNA workstation, from BioRad, is an advanced system of hardware and Staden based software for sequence entry and analysis on the IBM AT computer. These capabilities have been further enhanced with the addition of protein analysis programmes and the protein identification resource database. The programmes include: Chou-Fassman secondary structure, hydrophobicity plots, reverse translation, molecular weight, dot matrix and alignment. The PIR database can be accessed in less than ten seconds by key word and protein sequences may be compared directly with the database.

Fermentation process management software

Developed by BCS for the supervision and control of a wide range of fermenters and processes, BIO-i is a multi-user software package designed specifically for researchers in bioprocessing. Designed for use with the DEC range of equipment, or for use with IBM or IBM-compatible PCs, the package employs well-proven systems software, programming languages and real-time process plant databases. Details from: Biotechnology Computer Systems Ltd., Cleveland House, Church Path, Acton Green, Chiswick W4 5HR or on 01-995 3625. (Source: Biotechnology Bulletin, Vol. 6, No. 6, July 1987)

Genetic engineering software

New software for computer-aided genetic engineering is available. 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. The system uses and integrates genetics and provides information with DNA protein sequences to generate colour graphic displays of complex structures. No other computer software system offers this combination. Details: Battelle Memorial Institute, 505 King Avenue, Columbus, OH 43201-2693. (13246) (Source: International New Product Newsletter, August 1987, p. 6)

Japanese Ministry plans data base

Japan's Ministry of International Trade and Industry is to start preparing a comprehensive biotechnology data base. Within the next three to five years MITI hopes to have complete protein and gene data banks to provide information for research and patent/copyrights related to proteins or genes. (Source: European Chemical News, 21 September 1987)

G. MEETINGS

1987

21-25 November 1987	Workshop on Genetic Engineering Techniques - an introduction to recombinant DNA, Kuwait. Details: Kuwait Institute for Scientific Research, P.O. Box 24885, 13109 Safat, Kuwait.
8-10 December 1987	Smith Kline and French Research Symposium: HyperCipidaemia and Atherosclerosis, Cambridge, UK. Details: Networks (NI), 19 Chaucer Rd., Cambridge CB2 2EB, UK.
14-16 December 1987	Molecular Recognition (Nucleic Acids and Molecular Biology Group 20th Anniversary Meeting), Birmingham, UK. Details: Dr. R. Patient, Dept. of Biophysics, King's College (KQC), 26-29 Drury Lane, London WC2B 5RL, UK.
16-18 December 1987	625th Meeting of the Biochemical Society, London, UK. Details: The Meetings Officer, The Biochemical Society, 7 Warwick Court, London WC1R 5DP, UK.

1988

4-6 January 1988	Application to Seeds and Soil. Organized by British Crop Protection Council. Details: Ms. Rosemary Bishop, Frank Bishop Conference Planners, 20 Bridport Road, Thornton Heath, Surrey CR4 7QG, UK.
5-6 January 1988	Inter-University Software Committee Workshop on Molecular Biology Software, Cambridge, UK. Details: Dr. M.J. Bishop, University of Cambridge, Computer Laboratory, Corn Exchange Street, Cambridge CB2 2QC, UK.
17-23 January 1988	Biological and Molecular Aspects of Atrial Peptides, Streamboat Springs, Colorado, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
21-23 January 1988	COGENE-Symposium/FEBS Advanced Course: Genetic Experimentation and Evolutionary Change, Basel, Switzerland. Details: COGENE-Symposium, P.O. Box 141, CH-4007, Basel, Switzerland.
24-30 January 1988	Oxy-radicals in Molecular Biology and Pathology, Park City, Utah, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
24-30 January 1988	Growth Factors and their Receptors: Genetic Control and Rational Applications, Keystone, Colorado, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
24-30 January 1988	Growth Inhibitory and Cytotoxic Polypeptides, Keystone, Colorado, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
24-31 January 1988	Mechanisms and Consequences of DNA Damage Processing, Taos, New Mexico, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
26-28 January 1988	Horizons in Molecular Biology, Keio Plaza Hotel, Tokyo, Japan. Details: Nature Conference Secretariat, c/o International Conference Organizers, Inc., Crescent Plaza 1F, 4-6, Minami Aoyama 2-chome, Minato-ku, Tokyo 107, Japan.
26-28 January 1988	AgBIOTECH '88 International Conference and Exposition, Sheraton Washington, Washington, D.C., USA. Details: Ms. Judy Green, Seminar Director, Conference Management Corporation, 200 Connecticut Ave., Norwalk, Connecticut 06856-4990, USA.
27-29 January 1988	First Canadian AIDS Research Conference, Toronto, Canada. Details: Conference Office, New Biotech, Suite 4, 1172 Pembina Highway, Winnipeg, Manitoba R3T 2A4, Canada.
30 January - 6 February 1988	Technological Advances in Vaccine Development, Park City, Utah, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
31 January - 4 February 1988	Synthetic Peptides: Approaches to Biological Problems, Park City, Utah, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
31 January - 7 February 1988	B-Cell Development, Taos, New Mexico, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California Los Angeles, CA 90024, USA.
6-12 February 1988	Gene Transfer and Gene Therapy, Tamarron, Colorado, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.

6-12 February 1988	Molecular Biology of the Eye: Genes, Vision and Ocular Disease, Santa Fe, New Mexico, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
8-12 February 1988	The Miami Bio/Technology Winter Symposium, Hyatt Regency, Miami, Florida, USA. Details: The Miami Bio/Technology Winter Symposium, P.O. Box 016129, Miami, FL 33101, USA.
16-20 February 1988	Liposomes in the Therapy of Infectious Diseases and Cancer, Lake Tahoe, California, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
19-21 February 1988	Second International Conference on Lymphocyte Activation and Immune Regulation, Newport Beach, USA. Details: Conference Secretariat, Division of Basic and Clinical Immunology, Room C-264A Medical Sciences 1, University of California, Irvine, CA 92717, USA.
21-26 February 1988	Cellular Proteaser and Control Mechanisms, Lake Tahoe, California, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
27 February - 3 March 1988	First World Congress on Clinical Nutrition, New Delhi, India. Details: Dr. R.B. Singh, Executive Director of ICN, Medical Hospital and Research Centre, 398 Civil Lines, Moradabad-10, India.
28 February - 6 March 1988	Cell Biology of Viral Entry, Replication and Pathogenisis, Taos, New Mexico, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
6-12 March 1988	Bone Marrow Transplantation: Current Controversies, Tamarron, Colorado, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
21-25 March 1988	NATO Research Workshop on Plasma Oxidoreductase in Control of Animal and Plant Growth, Cordoba, Spain. Details: Dr. F.L. Crane, Director, Department of Biological Sciences, Purdue University, West Lafayette, Indiana, 47907, USA.
26 March - 1 April 1988	Metal Ion Transport and Storage: Molecular Biology and Chemistry, Frisco, Colorado, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
26 March - 2 April 1988	The Molecular Basis of Plant Development, Steamboat Springs, Colorado, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
3-10 April 1988	Cellular and Molecular Biology of Muscle Development, Steamboat Springs, Colorado, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
4-10 April 1988	Molecular Biology of RNA, Keystone, Colorado, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
4-10 April 1988	DNA-Protein Interactions in Transcriptions, Keystone, Colorado, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
10-17 April 1988	Stress-Induced Proteins, Keystone, Colorado, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
10-17 April 1988	Molecular Biology of Stress, Keystone, Colorado, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
12-14 April 1988	75th Anniversary Symposium of the British Ecological Society, London, UK. Details: Administrative Office, British Ecological Society, Burlington House, Piccadilly, London W1V 0LQ, UK.
12-14 April 1988	CANBIOCON '88 Biotechnology Conference and Exhibition, Montreal, Canada. Details: Biotech Canada Inc., 100 Alexis Nihon, Suite 875, Montreal, Qc. H4M 2P4, Canada.
12-15 April 1988	626th Meeting of the Biochemical Society, Sheffield, UK. Details: The Meetings Officer, The Biochemical Society, 7 Warwick Court, London WC1R 5DP, UK.
17-23 April 1988	Molecular and Cellular Mechanisms of Human Hypersensitivity and Autoimmunity, Keystone, Colorado, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.

17-23 April 1988	Cell Activation and Signal Initiation: Receptor and Phospholipase Control of Inositol Phosphate, PAF and Ecosinoid Production, Keystone, Colorado, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
23-30 April 1988	Human Tumor Antigens and Specific Tumor Therapy, Keystone, Colorado, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
23-30 April 1988	Mechanisms of Action and Therapeutic Applications of Biologicals in Cancer and Immune Deficiency Disorders, Keystone, Colorado, USA. Details: UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024, USA.
24-29 April 1988	Seventh Workshop on Vitamin D. Rancho Mirage, California, USA. Details: Conference Secretary, Vitamin D Workshop Inc., Department of Biochemistry, University of California, Riverside, CA 92521, USA.
27 April 1988	Ion Channels as Drug Targets, London, UK. Details: Conference Secretariat, Society of Chemical Industry, 14/15 Belgrave Square, London SW1X 8PS, UK.
19-23 May 1988	Advances in the Biology and Chemistry of N-Nitroso and Related Compounds, Omaha, Nebraska, USA. Details: Ms. Terri Eastman, Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha, NE 68105, USA.
22-26 May 1988	International Conference on Diet, Lipids and Cancer, Yulara, Ayers Rock, Australia. Details: Dr. John R. Sabine, Waite Agricultural Research Institute, Glen Osmond, S.A. 5064, Australia.
15-18 June 1988	Second International Conference on Molecular Biology and Pathology of Matrix, Philadelphia, Pennsylvania, USA. Details: Dr. Darwin J. Prockop, Jefferson Institute of Molecular Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA 19107, USA.
19-22 June 1988	International Symposium: Basic and Chemical Approaches to Virus Chemotherapy, Helsinki, Finland. Details: Antivirals 1988, Secretariat, The Finnish Medical Society Duodecim, Kalevankatu 11A, SF-00100 Helsinki, Finland.
3-8 July 1988	Workshop on Basic Pharmacokinetics, Manchester, UK. Details: Prof. M. Rowland, Department of Pharmacy, University of Manchester, Manchester M13 9PL, UK.
4-8 July 1988	18th Linderstrøm-Lang Conference: Aspartic Proteinases; Biochemical, Physiological and Clinical Aspects of Pepsin, Chymosin, Renin and Related Proteinases, Elsinore, Denmark. Details: Prof. Bent Foltmann, Institute of Biochemical Genetics, University of Copenhagen, Oster Farimagsgade 2A, 4., 1353 Kopenhagen K., Denmark.
10-15 July 1988	14th International Congress of Biochemistry, Prague, Czechoslovakia. Details: Secretariat of the 14th International Congress of Biochemistry, Flemingovo 2, 166 50 Prague 6, Czechoslovakia.
17-22 July 1988	Eighth International Biotechnology Symposium, Paris, France. Details: VIII Symposium de Biotechnologie, SOCFI, 14 rue Mandar, 75002 Paris, France.
18-20 July 1988	Calcium Channels: Structure and Function. London, UK. Details: Conference Dept., The New York Academy of Sciences, 2 East 63rd St., New York, NY 10021, USA.
20-22 July 1988	627th Meeting of the Biochemical Society, Nottingham, UK. Details: The Meetings Officer, The Biochemical Society, 7 Warwick Court, London WC1R 5DP, UK.
20-26 July 1988	Fifth European Bioengineering Conference, Aberystwyth, Wales, UK. Details: Prof. R.B. Beechey, Department of Biochemistry, University College of Wales, Aberystwyth, Dyfed SY23 3DD, UK.
20-27 August 1988	16th International Congress of Genetics. Toronto, Canada. Details: Mr. L. Forget, Office of Conference Services, National Research Council, Ottawa, Ontario K1A 0R6, Canada.
29 August - 2 September 1988	First Biennial Water Quality Symposium: Microbial Aspects, Banff, Alberta, Canada. Details: Dr. B.J. Dutka, Co-Chairperson, Water Quality Symposia Committee, National Water Research Institute, CCIW, P.O. Box 5050, Burlington, Ontario L7R 4A6, Canada.

12-13 September 1988 — Second International Symposium on Lipid Metabolism in the Normoxic and Ischemic Heart, Maastricht, The Netherlands. Details: Dr. G. J. van der Vusse, Department. of Physiology, University of Limburg, P.O. Box 616, 6200 MD Maastricht, The Netherlands.

19-24 September 1988 — Second International Exposition and Symposium on Biotechnology and Life Sciences, Shanghai, P.R. China. Details: The Secretariat, Biotech Expo 88, c/o China International Convention Service Ltd., Suite 602, Harbour Crystal Centre, Tsimshatsui East, Kowloon, Hong Kong.

4-7 October 1988 — BIOTEK INDIA '88. International Exhibition and Conference on Biotechnology, Ashok Hotel, New Delhi, India. Detail : Ms. Anu Kapoor, General Manager, The Pioneering International Exhibition and Conference on Biotechnology, 14-F, Basant Lok, Vasant Vihar, New Delhi 110057, India.

H. REPRINTED ARTICLES

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Lesser-known plants of potential use in agriculture and forestry by Noel D. Vietmeyer

Food crops

It might be supposed that a world short of food would use all its available food crops. But that is not so. Throughout history, mankind has used some 3,000 plant species for food, but over the centuries, the tendency has been to concentrate on fewer and fewer. Today, most of the world's food comes from a mere 20 or so species. Therefore, large numbers of the world's edible plants may have the potential to be developed to make a much greater contribution to the global diet.

Many lesser-known food crops that remain outside the fold of science have not been rejected due to any inherent inferiority. They have been overlooked merely because they are native to the tropics, a region generally neglected because the world's research resources are concentrated in the temperate zones. In Central America, for instance, the pejibaye palm (Guilielma gasipaes) bears chestnut-like fruit containing carbohydrates, protein, oil, minerals, and vitamins in nearly perfect proportions for the human diet. It has been called "probably the most nutritionally balanced of all foods", but still remains unknown to many parts of the tropical world that are chronically malnourished.

Another unusual palm, Jessenia polycarpa, occurs in the rainforests of the Amazon. It bears large bunches of fruit containing an oil similar to olive oil in appearance, composition, and culinary quality. It is sold as an edible oil in Colombia, but is virtually unknown to the rest of the world. It, too, could become a major tropical crop if it were given agronomic attention. A century ago, the African oil palm was about as obscure as this, its American counterpart, is today; now it is a major world resource, even though its oil is far inferior to jessenia oil.

Although many food crops are neglected because they grow in the tropics, even more are neglected because they are scorned as fit only for the poor. Peanuts and potatoes, among other common crops were once also shunned for this reason. In the United States, the peanut was considered to be "merely slave food" until little more than a century ago, and in the 1600s the English refused to eat potatoes because they considered them to be "Irish food". Cultural bias against peasant crops is absurd; the plants that poor people grow are usually robust, productive, self-reliant, and useful - the very species needed to feed the hungriest parts of the world.

One notable crop still suffering unwarranted prejudice is grain amaranth (Amaranthus cruentus, A. caudatus, and A. hypochondriacus). Five hundred years ago, amaranth was an important food to Central and South American indians; it was esteemed by the Aztecs and Incas. When heated, the tiny seeds burst and take on a flavour reminiscent of popcorn. However, because Aztecs created idols out of popped amaranth and ate them in pagan ceremonies involving human sacrifice, the conquering Spaniards banned amaranth's cultivation and forced the crop into obscurity. Although this helped destroy the Aztec religion and culture, a few farmers in isolated mountain villages of Mexico and South America continued to carry on the ancient tradition of growing amaranth. In the 1970s, an Australian researcher, W.J. Downton, obtained a few amaranth seeds and learned that they have unusually high levels of both total protein and of the nutritionally essential amino acid, lysine. This amino acid is usually deficient in plant protein - including the protein in all common varieties of major cereal crops. Today, amaranth is beginning its comeback, but it is still virtually unknown to most cereal researchers.

Overlooked legumes

Of all the food plants man consumes, only grasses are more important than legumes. However, while enormous resources have been expended on grasses such as rice, wheat, maize and sugarcane, among the legumes only soybeans, peanuts and common beans have received much attention. Yet in developing countries, especially, the cultivation of legumes is the best and quickest way to augment the production of food proteins.

Many legume species have on their roots peppercorn-sized swellings in which bacteria convert nitrogen gas from the air into soluble compounds that the plant absorbs and utilizes. Thus, leguminous plants usually require little or no nitrogenous fertilizer, they can survive on poorer soils that are nitrogen-deficient, and their residues leave the soil enriched with nitrogen.

People generally do not think of legumes as root crops, even though at least 25 leguminous roots are eaten in various parts of the world. One of them, the groundnut (Apios americana), was once an important Indian food over the entire eastern half of North America. The Pilgrims survived their first winters by eating the golfball-sized tubers of this tiny relative of the soybean. Its swollen roots contain several times the protein of potatoes, and in preliminary trials at Louisiana State University, some plants have yielded more than a kilogram of tubers each year.

This finding suggests that the edible legume tubers are an important resource and should be further explored. Other promising examples are the yam beans (Pachyrhizus species) of Central South America whose large swollen roots have been feeding people throughout history. Palatable, nutritious and productive, they also deserve scientific attention. One species, Pachyrhizus erosus, now appears in

supermarkets across the United States under its Mexican name, jicama.

Beyond unusual legume root crops, there is a little-known plant eaten by the poor that is actually one of the major foods of the world. The bambara groundnut (Voandzeia subterranea) is grown by villagers throughout most of Africa south of the Sahara. Like peanuts, it forms seeds underground. The seeds, although containing less oil and protein than peanuts, are a well-balanced food with a calorific value equal to that of a high-quality grain. They also taste good, and Africans often prefer them to peanuts. The bambara groundnut can thrive in arid soils where peanuts fail, resists pests and diseases, and, if managed well, can give high yields. Yet it has received very little research attention.

Clearly, importance to people does not necessarily translate into importance to science - a fact borne out traditionally by the plight of the winged bean (Psophocarpus tetragonolobus). An ancient peasant crop of South-East Asia, this vigorous pole bean produces four-sided pods with wings projecting from each corner. It is an exotically-shaped succulent green vegetable that can be eaten raw, steamed, boiled, or stir-fried. Its flowers, tendrils, pods, leaves, seeds and tubers are all edible. The seeds are comparable to soybeans in composition and the tuberous roots have exceptional amounts of protein. Nevertheless, like the bambara groundnut, the winged bean is not usually included in mainstream agronomic research programmes.

This is discouraging because, despite its current obscurity, such a crop could rise rapidly into prominence. Only 50 years ago, the soybean was known mainly in Japan, China and other Asian nations. It was so unappreciated in the United States that it was not listed in our national agricultural statistics. Now it is our major oilseed and third largest crop.

Today, Japan's second most important bean, the adzuki bean (Vigna angularis), receives about as little recognition here as soybeans did in the 1920s. These small, reddish-coloured, oblong beans have been popular in the Japanese diet for at least 1,500 years. A paste made from adzuki beans and sugar is an ingredient in pastries, confections, ice cream toppings and even soft drinks widely sold in Japanese vending machines. Given attention, the adzuki bean, like the soybean, might gain enormous popularity.

Many crops (including the soybean) are important commercially only because of the efforts of "crop champions", people who dedicate their talents, energies and emotions to advancing them. With underdeveloped crops, huge advances can be made by such individuals. Even some wild legumes have potential. For example, three decades ago, the narrowleaf lupin (Lupinus angustifolius) was a wild legume with an almost worthless seed. Its seeds resemble smooth white peas and taste like the split peas used in soups. Currently, they are used in rations for poultry, pigs, sheep and cattle. However, it seems likely they will also become a significant food for humans. If so, the narrowleaf lupin will be the first major field crop domesticated for food in modern times.

This remarkable result is due to Western Australian scientist John S. Gladstones. Starting in the mid-1950s, Gladstones sorted through millions of lupin plants looking for low-alkaloid varieties with seeds that were not bitter. During a 20-year search, he eventually found "sweet" types with white flowers and white seeds (useful as genetic markers because the bitter types are blue-flowered and dark-seeded), nonshattering seed heads (to hold the seed so that it does not fall wastefully to the ground), and early maturity (so that they set seed before being shriveled by Western Australia's sporadic summer droughts). By combining all these characteristics, he produced the first sweet narrowleaf lupin varieties suitable for large-scale production. Now Western Australian farmers are tending it in fields covering several hundred thousand hectares; in 1984, their production totalled 500,000 metric tons. This man-made crop is a possible forerunner of a collection of food crops belonging to the genus Lupinus that will one day be commercially produced in many parts of the world.

Crops for arid lands

Drylands present the world with one of its most seemingly intractable problems. The agony of drought-stricken Africa, for instance, appears never-ending. Ten years ago, babies little more than skin and bones stared with lifeless brown eyes through our television screens; last year, the horrifying vision was repeated; and 10 years from now, it is likely to be with us again.

With 70 million mouths to feed in roadless, mostly waterless regions stretching farther than from New York to Alaska, it is clear that Africans will have to develop better ways to feed themselves - in good years as well as bad. Helping them find ways to achieve this goal is one of our most urgent challenges.

Part of the solution undoubtedly lies in cultivating plants that are adapted to aridity. Thus, as a start, we should gather and evaluate all the crops of the world's desert regions. The crops of the Bushmen of the Kalahari, the Aborigines of Australia, the Indians of southwestern North America, and other native peoples of such dry zones should all be given intensive trials in several parts of the world. This would create a resource base of the world's most drought-tolerant useful plants.

Among leading candidates are various species of cactus (Opuntia and other species). If any single plant type can stop the relentless expansion of deserts, it is these bristly, water-filled natives of the New World's drylands. Cacti often produce fruits, green vegetables, forage, gum for adhesives and for thickening foods, and strong fibres. Moreover, the living plants provide fences, windbreaks, food and cover for wildlife, and they suppress erosion and stabilize sand dunes. Yet cacti are largely ignored. The literature on their economic potential is sparse, old, fragmentary and hard to find. And some cactus crops are not minor. Mexico alone produces more tunas (fruits of the prickly pear) than twice the world's tonnage of apricots, papayas, strawberries or avocados.

In the United States, there are neglected desert species that should be in that world collection - the tepary bean (Phaseolus acutifolius), for instance. This legume has long been grown for food by the Indians of the southwestern United States and northwestern Mexico. It has the advantage of thriving in arid and hot regions, as well as in the poorest soil. Like the plants in Arizona's famous Painted Desert, it is an "ephemeral" that matures so quickly that one desert downpour is normally enough to get it to set its flowers and mature its seeds.

The desert dwellers of the dry Kalahari region of southern Africa have their candidates, too. One, the marama bean (Tylosema esculentum or Bauhinia esculenta), has edible seeds that taste good and have more protein than peanuts and more than twice the oil found in soybeans. Moreover, below ground, this legume produces a sweet-tasting tuberous root the size of a sugar beet. Like the seeds, it is eagerly sought by tribesmen in the Kalahari Desert. Despite this, marama bean cultivation has not been systematically attempted.

To help the world's deserts, we should also be gathering salt-tolerant plants (halophytes) because salt is increasingly devastating irrigated dryland agriculture all over the globe. Moreover, many desert regions have beneath them large aquifers of saline water that could be used to cultivate halophytes.

Among the most promising halophytes are saltbushes (members of the genus Atriplex). These shrubs make useful forage, resist low temperatures, withstand heavy soils, and tolerate high salinity. In Israel, some experimental plots of Australian and North American saltbushes are now being grown with seawater pumped directly out of the Mediterranean.

Shrubs

Saltbushes are just one example of hundreds of useful shrubs that suffer the same obscurity. Shrubs are a botanical resource without a constituency. Too tall for agriculture, too short for forestry, they fall between the disciplines and their potential as a resource is overlooked.

Shrubs are no less worthy than herbaceous plants or trees. Indeed, they are a tenacious form of life often with special characteristics for survival in arid regions. Shrubs also can provide many valuable resources: food for people; feed for animals; ingredients for drugs and medicines; fibres for paper pulp; materials for housing, fencing, tools and handicrafts; and rubber, resins, gums, oils, and rope for industry. Moreover, shrubs are one of the most promising answers to the third world's massive shortages of firewood.

Among the shrubs that are promising for food are the chayas (Cnidoscolus aconitifolius and C. chayamansa). These fast-growing Central American bushes provide nutritious greenery, require little maintenance, and keep yielding for years. From Mexico to Costa Rica, they appear as attractive hedges from which the poor pick their daily food. Chaya plants tested in Puerto Rico have out-produced all herbaceous leafy vegetables.

Paradoxically, one of the most endangered of all plants is a shrub that could make an important contribution to the world's arid zones. Ye-eb (Cordeauxia edulis) is native to the semi-desert Horn of Africa. It survives where rainfall is as sparse as 150 to 200 millimeters a year. Yet, it produces tasty nuts with a potential that has been likened to that of macadamia and pistachio. During the recent African drought, ye-eb seeds were one of the few foods available in northern Somalia; nomads and their livestock devastated the few remaining native stands. This plant is now threatened with extinction and is in urgent need of protection and concerted cultivation before it is lost.

Ye-eb provides both food and forage, and it is characteristic of many shrubs that they can provide several products. This multipurpose character is a most important quality for the third world villager. Having the flexibility to harvest several products spreads the risk of failure and enhances the economic viability of his small land area. Unhappily, modern crops are almost all single-purpose species, one of the reasons why they are sometimes not adopted readily in developing countries.

One example of multipurpose shrubby legumes, of which there are hundreds, is dhaincha (Sesbania bispinosa). Its seeds contain a water-soluble gum that produces a smooth, light-coloured, coherent and elastic film that is potentially useful for sizing textiles and paper, as well as for stabilizing the mud used in oil drilling. The plant can be grown as a rotation crop to fertilize and improve soil. It also provides windbreaks, hedges, erosion control, and shade for crops. It is reported to make good cattle fodder and appears easy to grow on a large scale with little care or investment. Moreover, dhaincha shows remarkable ability to survive on saline and wet soils. Amazingly, agronomists outside the Indian subcontinent have largely ignored it.

Conclusion

Only a tiny fraction of the thousands of underexploited members of the plant kingdom have been described here. Other researchers would have different, equally deserving lists of candidates, perhaps emphasizing underexploited plants for energy, pharmaceuticals, food colourings, perfumes, industrial raw materials and other valuable products.

We should begin to explore nature's storehouse and sample its offerings - particularly because we may be losing species and genotypes through the rapid loss of native habitats in the tropics and deserts.

Given the power of biotechnology, it is now possible to rummage through that storehouse. Biotechnology can enhance nature's generic resources by highlighting and teasing out the unusually promising genetic traits. Thus, economic botany and biotechnology should be proceeding in tandem. In this powerful combination are the potential solutions to many of the world's most pressing problems.

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