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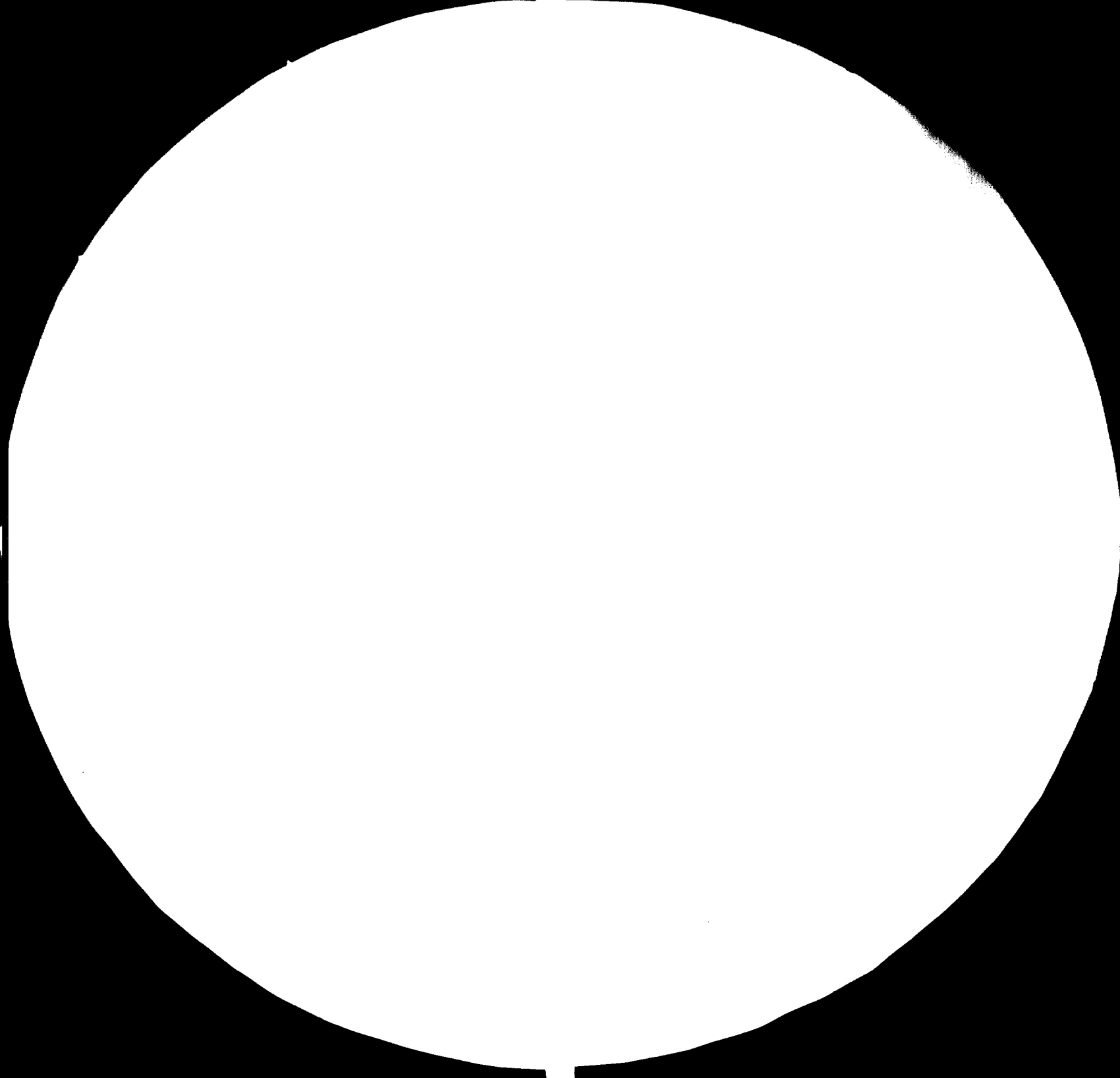

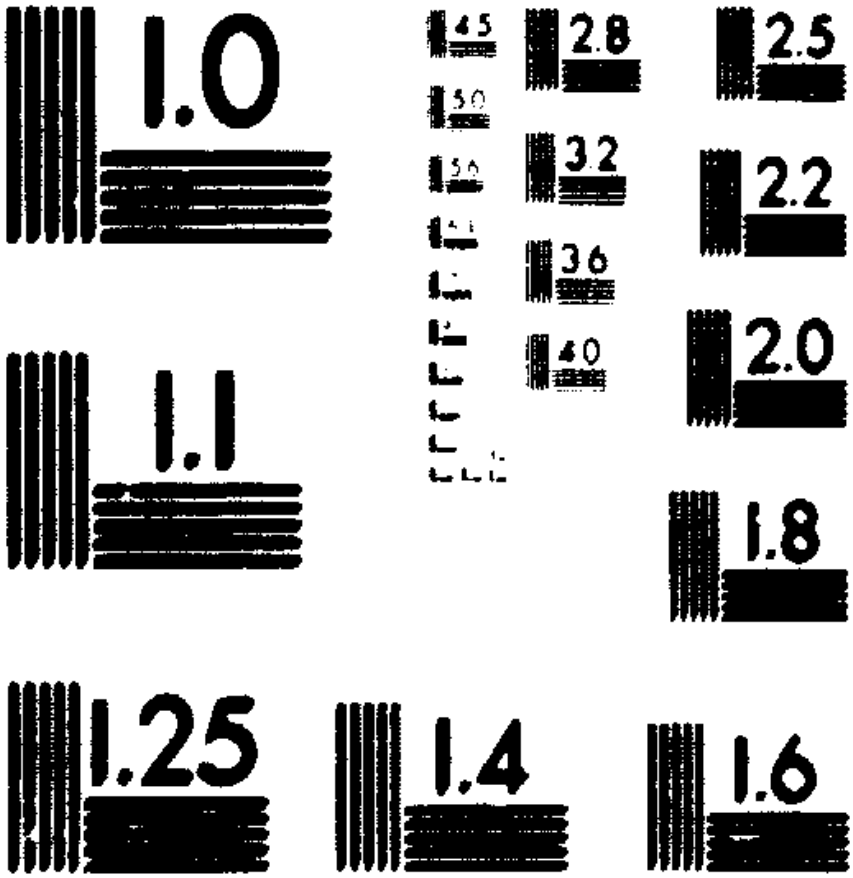

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

Genetic Engineering and Biotechnology Monitor

Issue No. 8

Dear Reader,

Since you received the last issue of the Monitor, we are nearer our goal of setting up the International Centre for Genetic Engineering and Biotechnology. The plenipotentiary meeting held at the beginning of April set the seal on the Centre's locations - one in Trieste, Italy and the other in New Delhi, India. Affiliated centres would be established at a later stage.

Another very gratifying bit of news is that the Italian Government has again demonstrated their generosity by offering to provide $400,000 to a UNIDO trust fund to enable the financing of a number of preparatory research, training and development activities. This is in addition to their considerable financial assistance in the establishment of the Centre.

In the Industrial Development Board of UNIDO in May 1984, a number of delegations welcomed the establishment of the Centre, commended UNIDO's initiative, and called on all countries to join the Centre.

In the American Association for the Advancement of Science (AAAS) meeting in May 1984, UNIDO organized a special symposium on strengthening genetic engineering and biotechnology capabilities in developing countries. This has hopefully contributed to greater awareness among scientists of the challenge of addressing genetic engineering and biotechnology to the problems of development.

UNIDO will be holding its Fourth General Conference from 2 to 18 August here in Vienna, and no doubt we shall have ample opportunity to hear the views of many delegations from countries who did not participate in the initial meetings on the ICGEB, all of which will be interesting for us here in the Secretariat.

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A. POLICY, NEWS AND OTHER EVENTS

UNIDO News

Plenipotentiary meeting decides on final location of the International Centre for Genetic Engineering and Biotechnology

The International Centre for Genetic Engineering and Biotechnology will be sited in New Delhi and Trieste. Coming at the end of a plenipotentiary meeting of 25 countries of the North and South, on 4 April, the decision on this crucial issue represented the culmination of three years' efforts to bring the benefits of this new science to developing countries. The meeting focused on the proposal of a preparatory committee to locate the Centre in both India and Italy. Although consensus was sought on this, the meeting finally took a vote of 13 in favour, three against and two abstentions after a 24-hour extension of deliberations.

As adopted, the proposal also calls for affiliated centres in individual countries to participate in the main Centre's training, research and development activities. They, in turn, may establish integrated networks in specialized areas, which would further the work of the main Centre.

As envisaged by statutes adopted last September at a ministerial-level gathering in Madrid, the Centre will promote international co-operation in developing and applying peaceful uses of genetic engineering and biotechnology, especially for developing countries. It will assist them in strengthening their scientific and technological capabilities in the field, helping with activities at regional and national levels. In this regard, the Centre is expected to act as a focal point for the network of affiliated research centres. It will also serve as a forum for exchange of information among scientists of member states.

Aside from R + D; training of scientific and technological personnel from the third world - both at the Centre and elsewhere - will be one of its main functions. Advisory services will be provided to members to develop national technological capabilities. Among the other functions are a programme of bioinformatics, as well as collection and dissemination of information.

Voting for the proposal were Afghanistan, Algeria, Argentina, Bulgaria, Chile, Cuba, Greece, India, Italy, Mexico, Peru, Trinidad and Tobago, and Yugoslavia; against were Egypt, Pakistan and Sudan; and abstaining were Iraq and Nigeria. China, Indonesia, Mauritania, Thailand, Tunisia, Venezuela and Zaire did not participate in the vote. Membership attending the meeting was composed of 25 of the 30 countries that have so far signed the Centre's statutes.

Countries signing a protocol on the seat of the Centre in New Delhi and Trieste were Argentina, Bulgaria, Chile, Cuba, Greece, India, Italy, Peru, Venezuela and Yugoslavia.

Social issues

Human genetic experiment

The first experiment in genetic engineering on humans may be proposed later this year. A group of medical researchers at the University of California in San Diego and the Salk Institute believe that a rare genetic disease among children, Lesch-Nyham syndrome, can be cured if a cloned human gene is inserted into the bone marrow of victims.

The scheme will soon be presented to the Recombinant DNA Advisory Committee (RAC) in the US.

In 1982, the Californian medical researchers isolated the human gene responsible for producing an enzyme, hypoxanthine phosphoribosyltransferase (HPRT). Children suffering from Lesch-Nyham syndrome cannot produce this enzyme. The devasting symptoms of the syndrome include mental retardation, cerebral palsy and uncontrollable, self-mutilating finger-biting.

Scientists at the Salk Institute have cloned and successfully inserted the sound human gene into mouse bone marrow, where it produced the enzyme. This success suggests that the process may work for Lesch-Nyham patients, once a strain of retrovirus (the carrier of the healthy gene) that will reproduce unassisted in the patient has been perfected.

Human trials could begin in a year or two - after approval from the RAC and local safety committees. (Extracted from New Scientist, 19 January 1984)

Regulatory issues

New regulations for gene-therapy

American researchers contemplating experiments in human gene-therapy will probably face much stricter controls. At its next meeting, the Recombinant-DNA Advisory Committee (RAC), the body that oversees much of the government-sponsored research in genetic engineering, will debate a plan to tighten up its regulations in this controversial area of research. At present, proposals for research require the approval of a local institutional safety committee only. The new guidelines will require all researchers who receive funds from the National Institutes of Health to seek approval for their DNA experiments from both the RAC and the National Institutes of Health. The new regulations would cover such experiments as replacing diseased human tissue with genetically engineered cells capable of producing healthy tissue. They would include altering the DNA of human embryos outside the womb, but not other experiments on embryos. The more immediate reason for the RAC's move is to endorse the now-defunct President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioural Research. The commission recommended in its report Splicing Life that the RAC "broaden its scrutiny" to include "issues raised by the intended uses of the genetic engineering technique". (Extracted from New Scientist, 12 January 1984)

Canadian Committee to provide guidelines on biotechnology

The creation of a National Advisory Committee on biotechnology has been announced by Canada's Minister of State for Science and Technology and for Economic Development Donald J. Johnston.

The minister has appointed 25 members drawn from the private sector, universities and government to serve on the committee. They will advise the minister directly on the development of biotechnology in areas such as energy, food, drugs, chemicals, plastics, mining and agriculture.

The federal government has allocated $22 million to implement the national biotechnology strategy so that Canada benefits from new developments in this area. This strategy supports research networks, involving industry, universities and government, which concentrate on using biotechnology to enhance industrial development and the use of Canada's resource base. (Extracted from Canada Weekly)

General and miscellaneous information

Round-table discussion on Biotechnology and the Third World

A round-table discussion organized by the International Center for Law in Development and the Council on International and Public Affairs, two nonprofit, public policy research organizations based in New York and working informally together on biotechnology and its implications for developing countries was held in New York last September. Both organizations are concerned with increasing access of the Third World to biotechnology on equitable terms and tracking the social and economic consequences of the introduction of this technology into developing countries, especially for the poor.

The objectives of the round-table were to provide an opportunity for those present to:

Pool their experience and to learn about the interests, research efforts and projects of others related to both applied research and research on the socio-economic impact in the Third World of developments in biotechnology;

Discuss which of the issues related to developments in biotechnology were not being adequately dealt with by the various organizations and institutions concerned with the topic; and to

Explore possibilities for future co-operation among those present.

Participants included scientists directly involved in research; members of international organizations, including the United Nations system, with active programmes related to the impacts of biotechnology; corporate executives, including both large corporations with R & D programmes involving biotechnology, and smaller companies whose activities are primarily related to biotechnology; and university-based investigators probing the impact of biotechnology on various socio-economic/scientific spheres.

As a result of this diversity in participants and the complexity of the subject, the discussions tended to be far-ranging, but a central theme running throughout was the concern with the privatization of the scientific research being carried out, especially in developed countries, and the impact this would have on the ability of the developing nations (which already have a myriad of other problems in implementing successful R & D efforts in these areas) to benefit from such research either through their own R & D programmes or through the results of developed country efforts.

The issue of privatization was of crucial importance to all participants in the discussion. Privatization affects all aspects of the emerging technology, but there was divided opinion on whether or not this would significantly restrict Third World access to the technology and the opportunity to benefit from it. Those most concerned with possible negative effects of patent laws and other forms of privatization viewed this as likely to lead to patterns of Northern domination and control similar to what has been experienced in other areas of advanced technology. That is, the development of processes and products would occur first in the industrialized countries largely reflecting the priorities of these countries and then be transferred to Third World countries through marketing of products or licensing of manufacturing primarily on terms determined by the North.

One of the more important results of such developed country dominance is that the problems faced by developing countries which are potentially addressed by biotechnology are not necessarily taken into account in R & D programmes conducted in developed countries.

A related concern is that, unlike the Green Revolution where most of the basic and applied research was in the public sector, for-profit organizations are involved in biotechnology at the basic research stages, and are less inclined to be investigating areas which will not result in a product suitable for profitable marketing.

Another argument was that the commercial development of processes is crucial to realizing the potential of this technology through much more rapid and widespread dissemination than is likely to occur when the public sector is involved and that the processes or the products based on them are available to all interested parties. This earlier availability, some participants suggested, would be likely to lead to more extensive replication by Third World scientists.

Most of the smaller companies involved primarily with biotechnology (as is the case with several of the larger corporations) maintain that they actively promote discussions through seminars, lectures, meetings, etc., between their scientists and scientists at universities and other research institutions, as well as other companies on issues related to basic research. They thus maintain that while the direction of their research efforts may very well be directed towards areas not of immediate concern to Third World scientists, the fact that they work for private companies does not infringe on the access of other scientists to their discoveries. It was suggested that the internal culture of many of these small companies was much more akin to the university rather than the corporate world.

Another concern, which bridges both the privatization issue and the Third World capability issue, relates to access to germplasm and the maintenance of existing genetic resources. The developed countries that are carrying out research involving biotechnology are largely dependent on developing countries for variety in germplasm. This dependence has not, however, significantly benefited developing nations as they do not effectively control these resources.

This results in companies in industrialized countries being able to market products, based on germplasm originating in the Third World, without any payment to the source of the germplasm.

A related question is how to maintain existing genetic resources. This question is of immediate concern as the diversity of existing genetic material is shrinking, and it is impossible to recreate this material once it is lost. There seemed to be unanimity at the

round-table about the vital importance of preserving as much as possible of the diversity of the world's genetic material but no consensus about which institutions - private companies, government agencies, or research institutes - should play what roles.

Of crucial importance in developing policies to promote R & D activities in the Third World is the status of existing programmes and potential capabilities of these nations. In response to a suggestion that entrepreneurs based in developing countries should be encouraged and relied upon to assure rapid progress from discovery to use, several participants observed that the status of entrepreneurial activity in most developing nations was not the same as in OECD countries and that private sector entrepreneurs would not be likely to perform this function in the same way. Others based their observation on experience with recent innovations in agricultural technology, including high-yielding varieties of foodgrains. Scientific capacities in Latin America, at least, have not been developed by local private enterprise, but by the public sector and multinational corporations. In Mexico, for example, 95 per cent of funds for research come from the government.

One point which it seemed all present agreed on was the necessity, if development of biotechnology were to take place in and for the Third World, for training of scientists to take place either through programmes conducted in developed countries or expanded education and research facilities in developing countries. Varying points of view were expressed about the role which governments of developing countries should play in building up local capacity in biotechnology. Several participants pointed out the need for greater co-operation between the developed and developing countries in training Third World scientists and in providing other kinds of support for developing local capabilities in technology and related scientific fields. Others urged more co-operation among developing countries themselves. Still others urged that the task of strengthening capabilities in biotechnology, especially the commerical application of research, be left in the hands of the private sector.

These two broad issue areas were viewed during the conference as playing a central role on the impact of biotechnology on the Third World. This impact is viewed as likely to have both positive and negative aspects. A crucial question seems to be whether the negative impacts of the technology, including displacement of existing sources of income and employment by products not originating in the Third World, will precede, coincide with, or follow the benefits which will accrue to these same areas, including greater productivity of existing resources, better control of disease, and other potentialities of biotechnology. (Extracted from report of round-table discussion on biotechnology and the third world, New York, 15 September 1983)

World Genetic Congress - New Delhi, India

The 10-day World Genetic Congress opened with a call from the Prime Minister, Mrs. Gandhi, to scientists working in genetic engineering to ensure that the balanced genetic heritage of all species which had evolved over millions of years is to be preserved.

The recent advances in research in genetic engineering were most fascinating and at the same time frightening, Mrs. Gandhi told the assembled geneticists from all parts of the world.

Mrs. Gandhi cautioned them about possible unforeseen effects of genetic engineering and possible misuse of the potential of genetic manipulation of life at the hands of those whose motivations might be different. "We have come to a stage when the sanctity of life as we understand it may be questioned".

She noted that genetic engineering could be used to create better human beings but wondered as to who would decide what was "better". She felt that if new traits could be introduced in human beings it would be desirable to control tendencies towards violence and narrowness of mind. Science should work for the harmony of people.

Mrs. Gandhi also called for conservation of genetic material and regretted that the earlier advances in natural science had led to exploitation and denudation of nature. In India, too, everyone was conscious of the genetic erosion in the Himalayan regions, she said, and mentioned the efforts taken for conservation through the national bureaus for preservation of genetic resources and biosphere reserves.

Co-operation: Mrs. Gandhi emphasised the need for international co-operation in the field of biotechnology. She referred in this context to the setting up of a national biotechnology board in India.

Dr. M. S. Swaminathan, chairman of the national organising committee urged world governments to declare genetic material a common heritage and suggested the setting up of a global network of genetic resources centres to enable free exchange of germplasm. Such a global grid should be linked to national and regional hybridisation centres to help developing countries towards plant and animal conservation efforts, he said.

Even though availability of genetic variability would not provide any insurance against genetic vulnerability for many developing countries, they should be assisted in animal and plant breeding programmes, said Dr. Swaminathan, who is Director of the International Rice Research Institute, Manila.

Dr. Swaminathan cited the national hybridisation gardens in sugar cane operated by the Indian Council of Agriculture Research (ICAR) at Coimbatore and Cannanore in south India as a good example of organising "purposeful" cross-breeding centres.

Referring to suggestions about patenting of specific genes, he cautioned that it could lead to the emergence of monopolies in genetic material for specific traits. However, this could be avoided if a sample of existing variability was also maintained at a government controlled genetic resources centre, Dr. Swaminathan said.

On the need for mobilising financial resources for genetic work, Dr. Swaminathan agreed with the suggestion of the Netherlands Government for establishing a world gene fund. Such a fund would help accelerate collections in endangered habitats, train more geneticists from developing countries and organise international hybridisation gardens. (Source: The Hindu, 24 December 1983)

Training opportunities

As a result of a summit conference of heads of State and Government held in June 1982 at Versailles, France, an International Network of Biotechnology was created in order to meet the shortage of multidisciplinary biotechnologists in most countries. To meet the needs of developing nations, France, the United Kingdom, Canada, Italy and Japan agreed to voluntarily participate in an international training network to assist and sponsor students from those countries. This network will be based on centres already in existence. There is scope for considerable variety in training courses and each centre will determine the most effective way in which it can meet national and international requirements. The most important aspect will be the provision of one-year courses with three to six months basic training in the essential technologies important to the practice and development of biotechnology. This would be followed by participation in a research programme appropriate to the student, his or her country of origin and the institution in which training was received. As the network becomes established, additional courses will give more emphasis to research techniques and projects. Short specialist courses will also be developed to meet specific requirements. Training is open to post-doctoral students, engineers and technicians wishing to continue their studies.

For further information please write to: Secretariat International du Projet, Réseau International de Biotechnologie, 5, rue Descartes, 75005 Paris, France.

B. COUNTRY NEWS

Canada

Financial grants to aid Canadian research

A $6-million capital investment grant from Canada's National Research Council (NRC) will develop the Prairie Regional Laboratory at Saskatoon to an all-Canada Plant Biotechnology Laboratory. The funds will add a 2,800-meter^2 extension to the laboratory.

Among the newly enlarged centre's research concentrations, will be nitrogen fixation, cell culture, fermentations and new strains of plants.

Meanwhile, Quebec is about to invest $27 million in biotechnology. The province's minister of science and technology, Gilbert Paquette, has announced that the government-owned Société Générale de Financement will put $7 million into bio-industrial research, and expects to begin generating revenues after the first year of operations. Another $25 million will establish a corporation to undertake research and development in biotechnology and medical areas. This fund will guarantee the salaries of more than 100 scientists who will be employed in the project. Most of them come from the Ayerts, McKenna & Harrison Laboratories, Inc., in Montreal, which shut down its research department this year. (Extracted from McGraw-Hill's Biotechnology Newswatch, 19 December 1983)

France

Biotechnology transfer centre established in Marseilles

The Provence-Alpes-Cote d'Azur of France has its own biotechnology transfer centre. It is the first time that a true institutional interface has been established in France. Marseilles is becoming a kind of pilot unit, a link in the national network that the Ministry of Industry and Research is trying to develop. The main elements of this network are bioengineering in Compiegne, microbiological engineering in Toulouse, plant health and biology in Marseilles, dairy biotechnologies in Brittany, pharmaceutical industries in the Centre, and bioreagents and vaccines in Rhône-Alpes.

Administratively, the Centre is attached to the Regional Chamber of Commerce and Industry, and is headed by Daniel Pardo, head of research at the CNRS on assignment to the Centre. The initial tasks of the Centre are to evaluate the region's potential and the immediate needs of industry, provide a technological watch, launch an information newsletter, and develop a training programme for personnel in the public and private sectors. The goal is to bring the "fundamentalists" out of their laboratories and ease their blending into the industrial fabric, and encourage the entrepreneurial spirit. There are some precedents right in Marseilles: Immunotech and Germe.

The next stage will be implementation. Few companies are able by themselves to carry out all the development phases of new techniques and products. Prototype development will be the job of the public sector. A novel feature: the mandate of the transfer centre will be to monitor contracts and see that they are completed within deadlines compatible with market demands. As of now, one area has priority: the industry of essential oils and aromatics centered around Grasse (2,500 jobs, one-third of the Department's exports, and 15 per cent of world sales in this sector). The usefulness for this industry of *in vitro* methods of cultivating plant cells can easily be imagined.

Other countries around the Mediterranean are becoming active. The Heraklion Institute of Biotechnology in Crete has a growing reputation, and Algeria has also recently made the decision to engage in biotechnology. (Extracted from L'usine nouvelle, 8 September 1983)

France strengthens biotechnology research and co-operation

Biotechnologies must be given priority both in France and in Europe, according to what the Minister of Industry and Research, Mr. Laurent Fabius said in a statement on 5 September on the campus of the Pasteur Institute, at the inauguration of a "week of biotechnologies" and the groundbreaking ceremony for a building that will be entirely devoted to those technologies.

The object of this international biotechnological network was to prepare for the future and make sure that it can be controlled.

The scope of this task, the difficulties it involves, the prospects it opens up, all obviously call for international co-operation, a source of progress and mutual confidence for countries in the North as well as in the South. The network - the president of which is Mr. Pierre Douzou and the vice-president Professor Coleman, of the British Department of Industry - would not only manage the exchange of information between member countries (France, Great Britain, Canada, Japan and the European Communities), but would also contribute to the training of future biotechnologists and would manage joint projects.

In agreement with the wishes expressed at the Versailles summit in 1982, the network will also contribute to improve the transfer of know-how from the North to the South. It would mark the beginning of a new step toward a new world economic order of shared progress.

The international network remained to be created, but the political determination to achieve it had been clearly expressed at the highest levels, and it could be one of the elements that could make it possible to shape future society, based on 'the technologies of the future:' biotechnologies, new materials, electronics, data-processing and robotics.

The government has decided to take the following measures to help the expansion of biotechnologies in France:

1. Incentive state credits for biotechnological research will be given priority in the Ninth Plan budget. Credits will be allocated by priority to joint projects of public and industrial research organizations that would lead to an improvement of the technological level of French enterprises.

2. The authorities will consider increasing the means devoted to basic research in research organization laboratories, and will also encourage the transfer of the knowledge and know-how thus acquired to the industry.

3. One of the top priorities of the industrial modernization fund will be to consider the bio-industrial sector. It will thus expand and increase the efforts made by the Committee for the Development of Strategic Industries.

4. Data and strain banks will be created; they will rely on the expertise of the Pasteur Institute, the Museum of Natural History and the Paris-V University.

5. An expert-training programme (researchers and engineers) will be prepared during the next few months jointly by the Ministry of Industry and Research and the Ministry of National Education. The Ministry of Industry and Research will redirect its research subsidies.

6. Finally, the regions will be asked to define objectives and programmes compatible with their scientific, technical and industrial potential. (Extracted from AFP Sciences, 8 September 1983)

Poll illustrates focus of French research

On the first anniversary of the start of a programme that is mobilizing all bio-technological resources, the Ministry of Research and Industry took a census of French companies that are concerned with biotechnology and are doing research in every direction in this field. The following table taken from AFP Sciences of 13 October 1983 shows the existence of overlapping interests among these companies. It is the field of fermentation and cell cultures for the production of food and agricultural products that comes first in attracting the manufacturers' interest, just ahead of medical drug production.

French research institutions form closer links

The National Center for Scientific Research and the INRA National Institute for Agricultural Research have signed a co-operation agreement that provides for more closely linked research efforts. Three and a half million jobs, the feeding of the nation and rural area management depend on the activity of the agricultural and food sector. The association between these two organizations, aimed at better satisfying the future needs of that socio-economic area, will bring into agronomic research the scientific knowledge acquired by the CNRS in fields of biology, chemistry, engineering sciences and social sciences. On the other hand, the INRA's thematic scope will help finalize some of these departments' projects. The two institutions have long co-operated with one another, sharing several laboratories (pheromones at Saint-Remy-les-Chevreuse, nitrogen fixation at Toulouse) and programmes (such as the "Moulon Farm" GIS [expansion unknown] for cereal improvement); however, these two organizations wish to extend the scope of their activities in microbiology, molecular plant biology, plant physiology, organic soil chemistry, agrochemistry, process engineering for food and agriculture, forestry, studies of rural France (history, economy, etc. ...). (Extracted from Chimie Magazine, October 1983)

Industrial Participants in Biotechnological Activities

Subject	Drugs (including antibiotics, immunology derivatives, hormones)	Reagents (including monoclone antibodies & enzyme reagents)	Food & Agricultural products (including seeds, foods & animal feeds biopesticides)	Raw Materials Chemistry, Energy-producing compounds	Biodegradation & Anti-pollutants
Genetic Engineering, Microbiology	G3 Transgene Genetica Roussel-Uclaf Sanofi	Intergene	Transgene Roussel-Uclaf Sanofi BSN		
Cell Fusion	Rhone-Poulenc	Immunotech Hybridolab	Clause SNEA		
Enzymes, Enzyme engineering	Rhone-Poulenc		Roquette		
Fermentation Cell cultures	Roussel-Uclaf Rhone-Poulenc Sanofi Merieux Inst. Synthelabo	Merieux Inst.	Lafarge-Copee Bel. Bongrain Sodima Rhone-Poulenc Protex Pernod-Ricard Air Liquide	EMC Rhone-Poulenc	
Instrumentation, development of extraction & purification processes	Rhone-Poulenc Biolafitte	Biosys	Biolafitte Nordon Setric Technip (IFP) Speichim BSN		Degremont (Lyons Waters) General Water Company
Strain collections Data banks	Pasteur Institute		Museum		

Federal Republic of Germany

German State University - Business initiative in Berlin

The Berlin Senate has officially given the "green light" to the planned Institute of Cell Biology. The Berlin Senator for Science and Research has transmitted to the House of Delegates a bill for decision, according to which the Province of Berlin jointly with the Schering AG is supposed to participate in such an institute. Beginning in 1984, a new structure will be erected on the land of the Max Planck Institute for Molecular Genetics in Berlin-Dahlem. Here, mainly basic research in the area of cell biology and the investigation of the application of genetic engineering methods will be carried on. (Source: Europa Chemie, 7 October 1983).

Government tops up industry biotechnology fund

The Federal Ministry for Research and Technology (BMFT) of the Federal Republic of Germany has agreed to contribute DM 4m. to the chemical industry's DM 10m. biological chemistry fund which was set up in 1982. The cash will be used to support university research in biochemistry, toxicology, physiological chemistry, microbiology and related areas. Herbert Grünewald, chairman of Bayer and president of the German chemical industry association, VCI, praised the government's contribution. In accepting state funding for a few large projects in biotechnology, industry assumes the responsibility to see that the money is used properly, Grünewald said. He added that the research ministry is considering increasing its grants to industry for R & D personnel costs. (Source: European Chemical News, 24 October 1983)

Sweden

Thirty-five million Kroner annually for Swedish biotechnology research

The Administration for Technical Development (STU) budgets about 35 million Kronor annually for biotechnical research. Together with Pharmacia, STU is investing, for example, 18 million Kronor for research in cell biology and gene technology over a 6-year period at the Wallenberg laboratory in Uppsala. In many places there is ambition for increased co-operation between universities and industry - the above is one example, and the KabiGen interferon project in co-operation with Umea University is another.

Briefly, biotechnical research at the universities looks like this: Uppsala: Advanced separation technique and research with applications within human medicine, agriculture and veterinary medicine; Stockholm: At the universities and at Karolinska Institute (KI) immunological and immunotechnical research, as well as studies around large-scale extraction of biological substances, is being conducted, at KI there is also gene-technological research and at the Institute of Technology there is apparatus technology, fermentation technology, enzyme technology and microbiological synthesis; Lund: at KemiCentrum the emphasis is on technical applications of biochemistry and microbiology; Goteborg: anaerobic bacteria and marine microbiology; Umea: at the Unit for Applied Cell and Molecular Biology the human gene for the plasminogene activator (a blood protein) has been cloned, for example. Other research centres are the National Bacteriological Laboratory (biotechnical production of vaccines and detection of infections) and the National Agricultural University (biological nitrogen fixation, biological disease control and forest genetics).

The companies in the forefront are KabiGen, KabiVitrum, the Diagnostics division of Pharmacia, further Cardo, which - together with Sockerbolaget - owns KabiGen, new AC Biotechnics (together with Alfa-Laval) and the plant breeding company Hilleshog. Perstorp has also begun to look at biotechnology through, among other things, certain investments in a few U.S. gene companies. Carbohydrates and prostaglandins have high priority. (Extracted from Svenska Dagbladet, 18 October 1983)

New company formed

A new biochemical company, Biocarb Inc., has been formed in Lund. Starting in autumn 1983, it will carry out development work in the field of biologically active carbohydrates on behalf of itself and of customers. The company is a so-called intermediary firm, which links research to the needs of industry and society. (Source: Svenska Dagbladet, 19 October 1983)

Switzerland

Work scheduled for Ciba-Geigy AG's new laboratory

Production of tissue plasminogen activator (TPA) by biotechnology will be the major project at Ciba-Geigy AG's new $20 million laboratory just opened in Basel, Switzerland. Ciba plans to invest considerable resources to scale up TPA output, either by cloning in microbes or by culturing human cells.

The TPA synthesis method Ciba has chosen - bacterial cloning or mammalian-cell culture - will depend on how important glycosylation of the native molecule turns out to be. Enough material is expected to have been synthesized by late 1984 to start clinical trials. TPA, which has already been cloned by Genentech, Inc., of South San Francisco, is expected to save the lives of heart-attack victims by reopening clogged coronary arteries.

Other therapeutic products to be cloned in Ciba's new laboratory, which has pilot-plant capacity of several thousand litres, includes the protease inhibitor eglin, which the firm's scientists think may be useful in treating emphysema and septic shock. Eglin, secreted in nature by leeches after attaching to their host, limits tissue destruction by the enzymes that break down "neutral" proteins, such as elastase in the lung, during microbial infection. In the same way, it is thought this inhibitor can control the attack on body tissue by cathepsin G, an enzyme that bacteria release when they are lysed by macrophages during severe septic infections.

Yields of eglin cloned in Escherichia coli average 10 milligrammes per litre of fermenter broth, and are not considered to pose a problem. The problem could well be establishing the biological activity of the product in humans.

Another of the company's research products on the way to commercialization is a tissue- culture method for producing the sedative scopolamine from the plant Hyoscyamus aegypticus. Researchers are using air-lift fermentation to grow the suspended plant cells. Yields of the drug must be enhanced by a factor of one thousand, most likely by using protoplast mutation and somaclonal variation. Genetic engineering could be used as a last resort. (Extracted from McGraw-Hill's Biotechnology Newswatch, 21 January 1984)

United Kingdom

£1.4 million for genetic engineering research

A £1.4 million government-sponsored basic research programme in genetic engineering was announced last autumn. Four big groups - Glaxo, Shell, Unilever, and May and Baker - have joined it and three more companies are now being sought. The five-year programme will be run by the Institute for Biotechnological Studies, a resource centre set up on minimal initial funding by University College, London, Kent University, and the Central London Polytechnic. The Department of Trade and Industry is providing half the money, matching the contributions from industry. The scientific programme has been designed to investigate generic problems in the extended use of biocatalysts. The programme will focus on the creation of a UK centre of expertise in the extended use of micro-organisms as catalysts, especially in immobilized form. The interdisciplinary research team will be drawn from all three academic centres, with a nucleus of 24 academic staff, 50 post-graduates, and 18 technicians. (Source: The Guardian, 6 September 1983)

New programme of collaborative research into enzymes

Private UK firms will fund a new programme of collaborative research in universities to investigate fundamental properties of enzymes. ICI, Glaxo, Shell, Tate & Lyle, Unilever, Wellcome and Beechams will sit on the steering committee for the programme that will draw on expertise from Imperial College, Birkbeck College, the Medical Research Council and other institutions. One aim of the programme will be to improve enzyme activity using genetic engineering. Enzymes are widely used in the detergent industry, for tanning leathers, in meat tenderizers and as feedstuff additives. (Source: New Scientist, 1 December 1983)

Government support to British biotechnology

Long beset by high taxes, powerful labour unions, and an antibusiness image, Britain has launched a massive campaign to bolster its technology base and attract new overseas

investment. The drive is aimed partly at traditional manufacturing industries (especially in the economically depressed North and West), but most of the plums are being reserved for new technology ventures by both foreign and domestic companies.

Biotechnology is slated for special treatment in the government's scheme. By 1990, the world market for biotechnology products could hit $30 billion, from an estimated $17 billion in 1980.

British researchers have always held a commanding position in biotechnology, but the field is only now assuming a commercial look in England. The first international biotechnology conference - last May's Biotech '83 - was held not in the US or Japan but in London. The Department of Industry (DoI) announced last year that it would award about $28 million (1982 dollars) to new biotechnology ventures by the end of 1985, and more later. For foreign or domestic biotechnology companies, DoI has tabbed several processes, products, and techniques that may qualify for support (in certain cases grants of a third or more of capital costs). For a company uncertain about its capabilities in biotechnology, the government will even pay for a consultant to help executives make up their minds. Funding of up to 50 per cent is offered for strategic studies and risk assessment, up to 75 per cent for feasibility studies on specific products and processes, and 100 per cent for problem-solving studies (primarily for small and medium companies with specific technical or manufacturing problems).

Until recently, however, commercial biotechnology ventures have been pursued less energetically. A lapse of business acumen occurred in the mid-1970s when Cesar Milstein - then a researcher with the government's Medical Research Council (MRC) - developed a hybridoma technology for making monoclonal antibodies. Few in England then saw monoclonals' huge diagnostic and therapeutic potential, and the technique was seized by researchers elsewhere. The British government responded in 1980 by creating Celltech, a biotechnology company now located in Slough, Berkshire, on London's western outskirts. The company has since become a major force in recombinant DNA contract research and in the sale of diagnostic kits, enzymes, and cell hybridization processes. Last autumn Celltech opened what it claims is the world's largest monoclonal production facility, with a fermentation capacity of more than 300 litres. Not only was Celltech forged with about $27 million in public and private funds, but it was also given exclusive access to all of MRC's monoclonal R & D. One result was an uproar among other biotechnology companies, charging that Celltech was given an unfair advantage in the new process. Another result, according to MRC's James Gowans, was a new corporate interest in biotechnology - especially in products and processes already under study in government laboratories.

At about the same time, ICI (Britain's largest chemical company) was readying a new process for making single cell protein, at Billingham. Several companies had attempted a similar process - using natural bacteria to make high-protein feed additives from methanol - but were hindered by contamination problems. ICI devised an entirely new configuration, at a cost so far of about $150 million. The company is now the world's only commercial producer of single-cell protein (although at least one US company has announced plans to enter the business). ICI-Billingham can turn out up to 60,000 tons of "Pruteen" per year in its 1500-cubic metre fermenter. Primary markets are in Western Europe, where Pruteen is being boosted as a replacement for soya and other conventional protein sources for animal feeds.

Celltech and ICI are among the UK's most visible biotechnology leaders, but several others are becoming internationally prominent:

PA Technology is one of the nation's leading contract biotechnology R & D laboratories. Projects focus on process design and scale-up, enzymes, biosensors and bioelectronics, diagnostics, and plant genetics.

The Leicester Biocentre is a new joint venture between Leicester University (long recognized for its molecular genetics skills), the government, and private industry. The partnership will focus on basic genetic research and contract R & D, and provide graduate programmes in gene manipulation.

Cruachan Chemical (Livingston, Scotland), a broadly based biotechnology firm, has recently introduced a line of reagents for the solid-phase synthesis of gene fragments. The products will soon be expanded into a complete system for automated gene synthesis.

Inveresk Research (Musselburgh, Scotland) is a primarily contract medical and biological R & D company. Fields of study include mammalian cell culture and the use of monoclonals as tumour cell markers and in diagnostic kits. One example: a kit to identify the potentially fatal cytomegalovirus in pregnant women. (Extracted from High Technology, December 1983)

Interferon may be on sale in Britain before end of year

The British subsidiary of an American pharmaceutical company, Kirby-Warrick of East Anglia, is hoping by the end of the year to sell genetically engineered interferon to hospitals specialising in the treatment of cancer. It has asked the Committee on Safety of Medicines for a licence to sell interferon for the treatment of two specific diseases, probably cancer of the kidney and cancer of the bone-marrow cells (myeloma). The parent company, Schering-Plough, made a similar request at the end of last year to the US's Food and Drug Administration and will soon ask for permission for interferon to be sold in the US as a prophylactic against the common cold. Interferon could be on sale in Britain before this because obtaining approval in the US is slow.

The cost of treatment with interferon is likely to be similar to the cost of the most expensive conventional drugs - more than £5,000 for a complete course. (Extracted from New Scientist, 23 February 1984)

United States of America

14 MIT projects share microbiology grant

Fourteen research projects in microbiology at the Massachusetts Institute of Technology will share grants from a fund set up by W. R. Grace & Co. of New York. Established in July 1982, the fund provides MIT with $6 million to $8.6 million for microbiology research over five years. The grants are awarded annually for projects selected by a joint committee representing the university faculty and the chemical company's management.

This year's 14 projects are:

Biospecific adsorption with immunoadsorbents for isolation of biological compounds.

Microbial production of serine.

Overproduction of threonine, and enzymatic synthesis of specific dipeptides.

Enhancement of selective immunity to infectious agents.

Isolation of yeast nuclear cytochrome genes.

Liquid-liquid extraction of biopolymers.

Cloning Caenorhabditis elegans genes by purification of DNA from free duplication.

Enzymatic separation of racemic mixtures of hydroxy compounds.

Structural basis of protein stability.

Thermal stability of proteins.

Construction and production of active enzyme fragments, and polyproteins with multiple activities.

Corynebacterium glutamium

Plasmid biology.

New concepts in bioreactor operations.
(Extracted from McGraw-Hill's Biotechnology Newswatch, 2 January 1984)

New trade group

Eleven US biotechnology firms and one technical publisher have formed the Association of Biotechnology Companies - a new gene-splicing trade group. The organization is the

second of this type in the biotechnology field; it rivals the 30-member Industrial Biotechnology Association, which was formed three years ago by seven companies.

Promoters of the new group say that the field has become big enough to support two such groups, and that IBA tends to represent the interests of large companies, including several traditional chemical and pharmaceutical concerns that have entered the field only as a secondary activity. In contrast, the new ABC is being billed as sort of a "common man's group" of small and emerging biotechnology enterprises. The larger IBA charges $10,000/year, while ABC's annual dues ($75) are far more modest.

One of the regulatory issues that ABC will be looking at is an interferon decision by the US Food and Drug Administration. FDA says interferon manufacturers must obtain written statements explaining how laboratory customers will use the material in clinical tests, and stating the amounts involved. Shipping companies also must verify that the laboratories are actually conducting proper research. Manufacturers, says FDA, should investigate all improper-use allegations. (Extracted from Chemical Engineering, 6 February 1984)

Yugoslavia

Serbian industry to invest in new R & D effort

Yugoslavia is moving this month to develop its fledgling biotechnology R & D effort both nationally and internationally. An initial plan to expand the pharmaceutical industry of Serbia, the country's most populous republic, by setting up a research and development facility for recombinant-DNA technology is about to be extended to other industries as well, notably food-processing and chemicals. Even the Zastava automobile factory at Kragujevac near Belgrade, which makes cars under license to the Italian Fiat works, is expected to invest in the biotechnology programme.

Molecular biologist Vladimir Glisin of the University of Belgrade is directing the expansion. A decision of Serbia's parliament adopted last July made "genetic engineering and biotechnology" one of the republic's two main industrial priorities for 1984, the second being electronics. Initial emphasis was all on pharmaceuticals, but as the year began, the other industries moved for a share of the R & D potential. The size and shape of the final programme should be spelled out by the end of this month.

Professor Glisin served on the site selection commission of UNIDO, the United Nations Industrial Development Organization, in its search for a country to host an International Centre for Genetic Engineering and Biotechnology. Glisin notes, there is little or no indigenous drug production; 90 per cent of the country's pharmaceuticals must be imported. (Extracted from McGraw-Hill's Biotechnology Newswatch, 16 January 1984)

C. RESEARCH

Research on human genes

Gastric hybridoma cells

Researchers of the Beijing Municipal Cancer Prevention Institute have successfully cultured the first gastric hybridoma cells in China, an important development in the key national scientific task of gastric-cancer prevention research. Produced through tumour hybridization, this cell secretes immunoglobulin. The most outstanding characteristics of the cell are that it can be cultured externally to the human body and that the immunoglobulins it produces are specific and can distinguish cancer cells and carry "killer agents" such as cytotoxins, which inhibit the growth of cancer cells. Scientists are pursuing their research in order ultimately to apply the drug to early diagnosis and treatment of gastric cancer. According to experts, this research was rigorous in design, advanced in method and equal to world standards. (Source: Renmin Ribao, 2 October 1983)

Human alpha 2 interferon DNA inserted into B. subtilis

The human alpha 2 interferon DNA segment can be inserted into the Bacillus subtilis bacterium, which then secretes human alpha 2 interferon, according to C. Weissman of Biogen. Currently, the interferon is produced by genetically engineered E. coli, but only 1-2 grammes of interferon can be extracted from 1 litre of suspended bacteria. Since B. subtilis secretes the interferon, the yield can theoretically be increased by a factor of 10. Actual

yield was not this high, perhaps because B. subtilis enzymes break down the interferon. Meanwhile, scientists at Genentech are attempting to produce IFN-gamma in yeast. Gamma interferon is the most likely interferon to be used as an anticancer drug, and Biogen is now testing it in human cancer patients in the Netherlands. (Source: Science News, 1 October 1983)

Gene controlling external secretion discovered

A gene that controls external secretion of substances such as insulin and growth hormone has been discovered by the Japanese Institute of Physical and Chemical Research. The discovery could allow mass production of substances from coliform bacilli, since useful proteins could be secreted. The gene, discovered in bacillus 170, can be inserted into coliform bacillus using plasmid vector PMB9, and has been used to produce penicillinase externally. Coliform bacilli usually produce useful substances internally, so that production of a particular substance never exceeds the amount the bacteria themselves need. Separation of useful products is also very difficult. The new gene allows external production of up to 80 per cent of the product. (Source: Japan Chemical, 10 June 1983)

More insight into retinoblastoma

The loss of an entire chromosome has been implicated in retinoblastoma, a cancer transmitted by inheritance of specific genes, according to research carried out at the University of Utah. The finding suggests that some compounds suspected of causing cancer may do so in ways other than inducing genetic mutation. Some human retinoblastoma tumour cells contain two copies of chromosome 13, although peripheral blood cells contain one chromosome 13 with a mutant gene and one with a normal gene. This may indicate that the chromosome with the normal allele was lost during retinal tissue development, allowing the remaining chromosome to be duplicated, thus permitting the mutant retinoblastoma gene to be expressed. Most oncogenes already characterized are dominant at the cellular level, but the retinoblastoma gene appears to be recessive. A scientist at the Massachusetts Eye and Ear Infirmary stated that children of former retinoblastoma patients should have funduscopic examinations every few months until two years old, and less frequently until five. Early detection results in an 85 per cent cure, often without loss of the eye. Genetic screening would spare children additional testing if they did not inherit the mutant gene. Potentially carcinogenic agents may act by causing chromosome alteration as well as gene mutation. (Source: Medical World, 26 September 1983)

Smallpox vaccine's new job

Using recombinant DNA technology, researchers have created three new vaccines by coupling genes from hepatitis B, herpes simplex and influenza viruses to the innocuous vaccinia virus. Vaccinia (cowpox) has been used for nearly 200 years to vaccinate against its chemical cousin, smallpox, and is responsible for the eradication of that disease. The spliced-on genes direct the vaccinia to produce proteins characteristic of the parent virus, and the protein alerts the immune system. When that protein is encountered in an infection, the immune system will go after it and presumably get the virus as well. The organism reacts as if it is infected not only by vaccinia, but by, for example, herpes. So the animal mounts an immunological response in defense against herpes. Vaccinia have been used with genes from each of the three viruses to provoke antibody production in rabbits at a level that, in humans, would protect from disease. And usually lethal doses of herpes failed to kill mice vaccinated with the herpes simplex-vaccinia virus. The researchers selected an accommodating host - unlike many other virus vaccines, the hardy vaccinia does not need refrigeration and tolerates freeze-drying. It can be administered with a pinprick. Most important for the recombinant DNA technique, the virus has a long DNA molecule capable of incorporating new genes. (Extracted from Science News, Vol. 124, November 1983)

Epstein-Barr virus

Epstein-Barr virus, a herpes virus that causes mononucleosis and is believed to cause Burkitt's lymphoma, has now been linked to a rare form of brain cancer. Scientists from Harvard, Yale, the Centers for Disease Control and the University of Pennsylvania report in the September 29 NEJM finding the virus in central nervous system lymphomas in five patients. They did not find the virus in surrounding brain tissue, indicating, they say, "induction of the lymphoma by Epstein-Barr virus". (Extracted from Science News, Vol. 124, November 1983)

Role of oncogenes

Research on oncogenes is part of the ongoing fight against cancer. Research indicates that a combination of two different types of oncogenes is necessary to trigger the tumour phenomenon. Normal cells transformed by an injection of one type only will form tumours which grow only to a limited size, and then stop. This is contrary to the cell growth triggered by combined oncogenes which form tumours that grow until they kill the host. The possible conclusion is that cancer is a two-stage process. (Source: The Economist, 26 August 1983)

Japanese and US teams clone blood-pressure protein

Two laboratories claim to have cloned human renin, an elusive peptide implicated as a high-blood-pressure trigger. A Kyoto University Medical School research team headed by Prof. Shigetada Nakanishi reported they had cloned the renin gene. California Biotechnology, Inc. (CBI) has reported a similar feat and are attempting to clone the gene for another enzyme [presumably angiotensinogen].

The aims of the two teams are to produce enough renin and angiotensinogen for sequencing, determine their three-dimensional structures, and then design specific inhibitors to them. Earlier this year Nakanishi and co-workers deduced the amino-acid sequence of rat angiotensinogen from its cDNA blue-print. Now they report that human renin's genetic sequence codes for a 406-amino-acid glycoprotein. The first 20 amino acids are a signal peptide; the next 46 are a preprotein segment, followed by the renin A and B chains of 293 and 47 amino acids, respectively. The DNA sequence is about 70 per cent homologous with mouse submaxillary renin, which until now was the major source of readily obtainable research renin.

In the joint research project, Prof. Kazuo Murakami, department of applied biology and science at Tsukuba University, used a mouse-renin cDNA probe to find the human cDNA segment copied from the mRNA of kidney vascular tissue of hypertensive patients - tissue which was actively secreting renin. Murakami's co-workers took the enzymatically-copied cDNA to Nakanishi's lab, where they succeeded in cloning it in Escherichia coli. They are also trying to isolate the gene directly from human chromosomes.

Renin research in Japan is taking three directions. Assistant Professor Kunio Yamane in Murakami's department is working on scaling-up bacterial production of renin, as well as developing a direct enzyme-linked immuno-assay for the molecule.

Prof. Ikuo Moriguchi of the department of pharmacy, Kitazato University, is doing a three-dimensional computer analysis of renin's structure based on these first reports of its amino-acid sequence. From this, he hopes to design and screen renin-inhibitor drugs.

Murakami's group is also looking at hereditary high blood pressure by analysing the renin gene sequences of strains of laboratory rats with morbid hypertension. (Extracted from McGraw Hill's Biotechnology Newswatch, 7 November 1983)

Synthetic growth hormone

Doctors in San Francisco who have used growth hormone to increase the height of short but otherwise healthy children have issued a warning against the indiscriminate use of the drug. The doctors from the pediatrics department at the University of California in San Francisco (UCSF) say that the "extrapolation" of their results to justify widespread use of the growth hormone for short normal children would be "premature and unwarranted".

Their research and comments come amid a mounting controversy in the US over whether healthy children should be given a drug to achieve a "desirable" height - especially when the long-term effects of the drug are not known. It is possible that in large doses the growth hormone could cause gigantism and acromegaly - the abnormal enlargement of bones.

The controversy has arisen because it is now possible to make virtually unlimited quantities of synthetic human growth hormone using recombinant-DNA techniques. It is expected that in 1984 the Food and Drug Administration will approve use of the drug for the treatment of children with hypopituitarism, in which defects of the pituitary gland reduce the production of growth hormone and impair a child's growth.

The San Francisco study, which was published in the New England Journal of Medicine on 27 October, involved 14 healthy children, aged from four to 15 years, who had normal levels of growth hormone in their blood but were growing from 2 to 4 cm a year less than usual.

Doctors injected the children with natural human growth hormone three times a week for six months. Six of the children responded and almost doubled their previous growth rate. The rate fell again when they were taken off the drug for six months. Four of the children were introduced to the drug again and the same thing happened. They grew by 7 cm per year with treatment and by 4 cm without treatment.

One important finding was that the level of somatomedin - a growth mediator - in the system did not predict which children would respond to therapy. It had been widely thought that short children with normal or high somatomedin levels would respond better to therapy. But children with low levels also benefited, according to the UCSF's research. (Extracted from New Scientist, 10 November 1983)

Gene marker for Huntington's chorea

A Venezuelan woman with 14 children died of Huntington's chorea more than a century ago. Now her family tree of more than 3,000 members has provided the key to identification of a genetic marker for the chorea and determination of the chromosomal location of the gene.

This discovery is the first success of recombinant DNA methods to find a gene whose location had been unknown. The technique is expected to allow diagnosis of Huntington's chorea before any symptoms are evident.

More than 20,000 people in the United States alone suffer from the symptoms of Huntington's chorea, usually beginning after the age of 30. The hereditary disorder causes involuntary movements, intellectual impairment and psychological problems, especially depression. Every child of a parent with the disease has a 50 per cent chance of having inherited the disorder, but there has not been a way of determining whether or not an individual has the disease before symptoms appear. About 100,000 people in the USA have a parent with the disease and don't know yet whether they have it, and thus whether they could pass it on.

The genetic marker for the disease is a sequence of DNA lying close to the gene. James F. Gusella of the Massachusetts General Hospital in Boston found that depending on the sequence, a DNA-cutting enzyme can give one of four different patterns of DNA pieces. In an individual family, one of the patterns is associated with the defective gene causing Huntington's chorea. Other members of the family showing the same pattern are very likely to have the disease.

The first hint of this linkage was in a large US family in Iowa. The linkage was confirmed with data from the Venezuelan family. An expedition of investigators from 18 institutions, led by Nancy Wexler of the Hereditary Disease Foundation in Beverly Hills, California, performed neurological examinations and collected skin and blood samples from 570 members of this family who still live in a tiny village built on stilts in a remote lagoon.

The Huntington's chorea gene was localized to human chromosome four by Gusella and Susan L. Naylor of Roswell Park Memorial Institute in Buffalo, N.Y. (Source: Science News, 12 November 1983)

Protein secretion aid

Use of a gene to help E. coli to secrete desired proteins will aid biotechnology, according to K. Horikoshi of the Japanese Institute of Physical and Chemical Research. Without the new gene, the outer membrane prevents up to 80 per cent of the desired protein from leaving the cell. With the gene, 90 per cent of the desired product is secreted into the culture medium. The new gene has been used to aid production of penicillinase, which was secreted into the surrounding medium in pure form. The gene could also be used to aid production of proteins such as insulin, interferon or growth hormones. (Source: New Scientist, 29 September 1983)

Chromosomal changes observed in malignancy

Chromosomal changes have been observed for the first time in cultured cells that become spontaneously malignant by scientists at the Los Alamos National Laboratory. Such changes are closely associated with cell immortalization and other early stages of cancer. The fact that spontaneous development of cancer cells was preceded by the appearance of extra chromosomes and DNA material inside the cell suggests that cell culture models used to indicate possible carcinogens may not be as dependable as currently believed. Cultured cells can become cancerous without exposure to radiation or chemicals. (Source: Chemical and Engineering News, 11 July 1983)

Myelin gene identified

The rapid transmission of signals along the long, output arm of a nerve cell depends on the insulating coating myelin. The major structural protein of this material is abundant in the central nervous system and represents 30 per cent of the total protein. This myelin basic protein is very similar in rodents, pigs, sheep, cattle and humans. Scientists have now identified a rodent gene that produces it. They expect this finding to aid study of such human diseases as multiple sclerosis or Guillain-Barré Syndrome, in which myelin deteriorates.

The recent studies used brains of 18-day-old rats, at which age the greatest amount of myelin is synthesized. Messenger RNA, the molecules that carry information from the genes to the protein-making machinery of cells, was isolated and used as a template for making DNA molecules called cDNA. The scientists used the known amino acid sequence of rat myelin basic protein to chemically synthesize short pieces of DNA that would bind specifically to the cDNA representing that protein. When they analysed this cDNA they found it to match at 126 of 127 positions, the reported amino acid sequence for one of the two myelin basic proteins from the rat. Two different species of rat were used in the determinations, therefore this single variation is likely to reflect a genetic difference.

The shiverer mouse is a mutant animal in which myelin is not properly wrapped around nerve cell fibres. At two weeks old the mouse shows tremors which eventually lead to seizures and death. These mice have less than one per cent of the normal levels of myelin basic protein and it was found that shiverer mice make no messenger RNA that corresponds to the rat myelin basic protein messenger RNA, and analysis of the shiverer DNA indicates pieces of the gene are missing. (Extracted from Science News, Vol. 124, 26 November 1983)

Monoclonals could prevent autoimmune diseases

Monoclonal antibodies could be used to prevent or suppress autoimmune diseases, according to researchers at Stanford University. Antibodies reduced experimentally induced autoimmune diseases in mice with multiple sclerosis, myasthenia gravis and systemic lupus erythematosus. Most patients with autoimmune disorders are heterozygous for a particular Ia antigen. A monoclonal antibody directed against one of the Ia genes inhibited production of antibody to a corresponding synthetic peptide. The response did not require continual injection of the antibody, persisting for three to six months after the treatment was completed. The monoclonal antibodies may suppress autoimmunity by inducing T-cell production and by blocking Ia antigens on immune cell surfaces. (Source: Medical World, 14 November 1983)

Research progressing on anti-herpes agents

The most urgently needed antiviral agent today is one that will control genital herpes infections, caused by the herpes virus type II. According to the Centers for Disease Control (Atlanta), genital herpes is now epidemic. Furthermore, the disease is not just painful. Of babies born when their mothers are having herpes outbreaks, more than 75 per cent die.

Research to date has centred on controlling rather than completely killing the virus, and several drugs that accomplish this task have recently been developed. The targets of these drugs are several viral enzymes important in viral DNA replication. Acyclovir, the first antiviral drug to gain approval for use in treating genital herpes, resembles one of the building blocks that becomes part of DNA during viral replication. When the drug enters a cell infected by the herpes virus, an enzyme called thymidine kinase, produced only by viral DNA, modifies the acyclovir molecule by adding a phosphate group to it. Phosphorylated acyclovir is further modified by two human enzymes produced by the infected cell and then serves as a substrate for viral DNA polymerase. When the viral enzyme tries to add the compound to a growing DNA chain, the modified acyclovir somehow interferes with the process and stops viral replication.

Acyclovir, developed by Burroughs Wellcome (Research Triangle Park, N.C.) and marketed under the brand name Zovirax, has been shown to decrease the healing time of herpes lesions (sores), the duration of viral shedding from the lesions, and the duration of pain in the initial infectious state. Yet the drug does not prevent outbreaks from recurring after the virus has become latent in the patient's nerve cells, and acyclovir-resistant strains of herpes virus type II have already been reported.

Another anti-herpes drug, Ara-A, has been developed by scientists at Warner-Lambert (Morris Plains, N.J.), but has been found effective only for herpes type I infections of the eye. However, the drug offers the first effective treatment for herpes encephalitis, a rare and usually fatal brain infection caused by another herpes strain. Ara-A's major drawback is that it is degraded rapidly by a human enzyme, adenine deaminase.

An adenine deaminase-resistant analog of Ara-A, called carbocyclic Ara-A, has been designed by Robert Vince, a medicinal chemist at the University of Minnesota (Minneapolis). The new compound has been remarkably effective against herpes virus type II infections in limited clinical trials. Like acyclovir, carbocyclic Ara-A works by interfering with viral DNA replication, but it is activated, not degraded, by human enzymes. "The drug is thus activated much quicker than acyclovir and it is also resistant to adenine deaminase," says Vince.

Until five years ago, antiviral research was hampered by the need to grow viruses in animal cells. But with recent advances in tissue culture techniques, many of which have come from the biotechnology industry, this is no longer a major problem. Today the primary task facing virologists is to find weaknesses in a virus's life cycle with which a drug could interfere, just as antibiotics interfere with certain bacterial processes. But with viruses this is a much more difficult task, because most of the enzymes they use during their lifetime belong to their human host. Thus many of the drugs that could kill a virus would also prove toxic to humans. (Source: High Technology, December 1983)

New process to produce DNA

University Patents has developed an efficient process to produce DNA. Nucleoside phosphoramadite chemicals can be used manually or in automated instruments, establishing new standards for a procedure widely used in biochemical and genetic engineering labs. Synthetic DNA is routinely used to identify genes that carry the code for a protein used to synthesize new gene fragments, or genes used to redirect an organism's biochemical apparatus. Applied Biosystems also markets synthetic DNA and an automated instrument that produces fragments of genes in under one day at a fraction of the cost using older methods. (Source: Chemical Marketing Report, 21 November 1983)

Simpler genetic engineering using rRNA

Recombinant RNA will make interferon, insulin and other proteins at lower cost, higher quality and greater purity than recombinant DNA processes. The technique, developed by Columbia University, is based on the fact that RNA is the agent in a cell that assembles amino acids into proteins. It acts as "contractor" to the DNA "blueprint". The new process is based on a discovery several years ago of a virus that consists of a single RNA molecule surrounded by a protein coat. When the virus infects a bacterium, the bacterium begins making a special enzyme that manufactures duplicates of the virus RNA. The viral reproduction process can take place in a test tube containing the enzyme, the necessary raw materials and a single piece of the virus RNA, which then reproduces itself in large quantities. A version of RNA coded to produce interferon can be inserted into the virus RNA, which can then be reproduced to give a large quantity of viruses carrying interferon-coded RNA. These viruses can then invade host cells, triggering interferon production. The recombinant-DNA process does not stop the bacterium from producing other proteins, and in some applications must use cancer cells instead, with consequent safety problems. (Source: Wall Street Journal, 10 November 1983)

Biologically active HCG

Integrated Genetics has produced biologically active human chorionic gonadotropin (HCG), a fertility hormone, using rDNA technology. To produce the molecule in mammalian cells grown in culture involves assembling two separate gene products, to which are added carbohydrates. The resultant genetically engineered HCG has more uniform characteristics and higher purity than previously possible. Integrated Genetics believes its technology will make human fertility hormones available in larger quantities at a lower cost. (Source: Chemical and Engineering News, 21 November 1983)

Premature atherosclerosis

A genetic defect may lead to premature atherosclerosis, according to S. K. Karathanasis of Harvard Medical School. The gene directs production of apolipoprotein, which is the major protein component of high-density lipoprotein (HDL). An extra piece of DNA in the apo A-1 gene has been discovered in two sisters with premature atherosclerosis. The defective gene also prevents activity of another nearby normal gene for another lipoprotein. HDL has been linked with increased longevity and decreased incidence of heart disease. (Source: Science News, 26 November 1983)

Human tetanus antibody developed

Green Cross Corporation of Japan has developed monoclonal antibodies to tetanus toxin that will replace the company's current globulin-antiserum drug, Tetanobulin, but output of the all-human hybridomas is still too low for commercial scale-up.

Company researchers achieved a stable human-human hybridoma cross by fusing a tetanus-antibody-producing lymphocyte from an immune healthy donor with a proprietary rapidly growing lympth-cell line. These immortalizing "lymph gemmules" are by-products of the company's alpha-interferon research.

Green Cross is selecting the hybridoma strains which produce the strongest hemagglutination reaction with the toxin, but so far, the cells are only producing some 10 units of antibody per millilitre of culture. In other experiments, lymphocytes immortalized with Epstein-Barr virus (EBV) have increased antibody output 10-to-100-fold. Therefore, the next step is to splice a segment of this virus into the lympth-gemmule parent stock. However, if these antibodies are to be used in prevention and treatment of tetanus, all traces of EBV - which has been linked to human cancers - must be removed. (Extracted from McGraw-Hill's Biotechnology Newswatch, 19 December 1983)

First cloning of gene for haemophilia factor claimed

Genetics Institute, Inc. has taken a lead in the race for cloning a crucial clotting factor for the treatment of haemophilia.

So far, the partial gene sequence cloned by the firm has not actually expressed factor VIII protein, but a full clone is expected in a few weeks or months.

Baxter-Travenol Laboratories, Inc., Chicago, for which Genetics Institute is doing its factor VIII research under contract, estimates the present world-wide market for haemophilia-treating blood products to be worth $180 million, but forecasts even higher sales for a recombinant-DNA product that will be cheaper and more abundant, and therefore more available to patients who now go without.

It is estimated that the size of the human gene is 240,000 to 360,000 daltons, which makes cloning the entire DNA sequence a lengthy, complicated task. However, it is hoped that within the next two years expression and purification leading to a material safe for clinical testing will be achieved. Genetics Institute will use Escherichia coli, yeast and mammalian cells as host organisms.

To arrive at the cloning of the human factor VIII gene sequence, Genetics Institute obtained several partial amino-acid sequences of porcine factor VIII from the Mayo Clinic, Rochester, Minn. From these peptide fragments, Genetics Institute synthesized small stretches of DNA, some of which match the DNA sequence of the factor VIII gene. These synthetic DNA molecules were used to identify bacterial clones containing fragments of the pig DNA coding for factor VIII. The porcine DNA was used to "fish" for portions of the human gene. The research has also determined for the first time where in the body factor VIII is synthesized. This finding is being kept proprietary for the time being, for competitive reasons. (Extracted from McGraw-Hill's Biotechnology Newswatch, 19 December 1983)

Research into multiple sclerosis

Evidence that a component of nerve tissue is shared by natural killer cells supports the theory that multiple sclerosis is an autoimmune disease in which the body's defences attack healthy tissues, according to scientists at the University of Vienna, Austria. A monocolonal antibody that binds specifically to natural killer cells also binds to myelin and the cells

that manufacture myelin. The specific component of myelin involved is not identified. Some multiple sclerosis patients have malfunctioning natural killer cells, which could be a clue to the causes of the disease. (Source: New Scientist, 1 December 1983)

Clue to understand eye mechanism

The Nobel Laureate, Dr. Hargobind Khorana, who synthesized the first functional gene, said a protein present in the membrane of a common bacterium held prospects for direct electricity production from sunlight and for understanding the working of the human eye. Addressing a crowded meeting of the World Genetics Congress in New Delhi last December, he said work was under way in his laboratory to synthesize the gene responsible for this protein and to produce the protein through genetic engineering. The protein "Rodoxin" was isolated from the purple membrane of "halabacterium" commonly found in coastal areas. Genetic techniques would be used to produce this protein. Dr. Khorana said the purple membrane in the bacterium worked like a "proton pump", siphoning the positively-charged protons from inside the cell to the outside through the membrane whenever the bacterium was exposed to sunlight. Asked if this property could be exploited in direct conversion of sunlight into electricity, he said, "It is possible in principle". Two groups in the USSR and in the US were working on this. Dr. Khorana said the "proton pump" of the purple membrane was driven by Vitamin-A. The presence of this vitamin was indicative that the purple membrane had something in common with the retina of the eye which also had Vitamin-A. (Source: The Hindu, 24 December 1983)

Erythropoietin cloned

Scientists at Amgen report the first cloning and quantity expression of erythropoietin (EPO), the elusive human hormone, made mainly in the kidney, that controls red-blood-cell formation from purified, native EOP extracted from human urine, which yields the protein in minute quantities.

This development will make it possible to investigate the mechanism of erythropoietin action in the body. With more than three million patients suffering from chronic kidney disease - which causes bouts of severe anemia - it is estimated that the annual world market for gene-spliced EPO would be $100 million. Genetically engineering EPO proved a complicated problem because there is not a good source of messenger RNA from human cells that produces the protein. Therefore an unconventional approach had to be taken involving a combination of proprietary techniques developed at Amgen, ranging from protein microsequencing and gene synthesis to novel [nucleic-acid] hybridization techniques. These enabled researchers to distinguish the correct gene sequence for EPO from other sequences that differed by only a single base change.

The work entailed hundreds of oligonucleotide probes. Conventional hybridization techniques are limited to some 32 probes per incubation when scientists are searching for a specific stretch of DNA, but Amgen is now able to use more than 200 probes per cycle. Because the Amgen probes are extremely sensitive, the research team was able to target two very specific areas in the DNA of interest. The detected EPO gene represents less than one part per million in human DNA. However the identification of the cloning vehicle or host organism has not been disclosed, or the yield of EPO expressed; (the protein has a molecular weight of 40,000 daltons). The company has filed patent applications on the EPO product and many of the processes it developed for its manufacture. (Extracted from McGraw-Hill's Biotechnology Newswatch, 2 January 1984)

Lung cancer antibody being developed

Using an immortalizing cell line that grows in non-serum culture medium, Morinaga and Co. Ltd. of Japan is developing low-production-cost all-human, monoclonal antibodies which they describe as targeted against lung cancer.

Dr. Hironori Murikami, professor of food and chemical engineering at Kyushi University, initially developed the parental lymphocyte cell line that multiplies in serum-free culture medium. The high cost of serum is an economic barrier to commercialization of human cell culture. Now MBKL researchers are fusing this parent stock with cells collected from lymph nodes of lung cancer patients, and selecting those hydridomas that produce antibodies to pulmonary tumor-associated antigens.

But so far these antibodies have exhibited broad affinities toward various types of malignancy, reacting in vitro with prostate and breast-cancer cell lines and malignant melanomas as well as pulmonary neoplasms.

Lung cancer tumors are genetically different than normal tissue, according to M. Barbacid of NCI. A single sub-unit change among the 45,000 sub-units of the K-ras gene was identified. The gene has been implicated in cancer development. The fact that the lung tumor gene is different from the patient's normal tissue gene indicates that the abnormality was not inherited, but occurred during the patient's lifetime. (Extracted from McGraw-Hill's Biotechnology Newswatch, 2 January 1984 and Science News, 15 October 1983)

RNA molecule may catalyze cleavage of target molecules

A small RNA molecule can, under certain laboratory conditions, catalyze the cleavage of appropriate target molecules, according to scientists at Yale University and the University of Colorado. RNA can in at least one case rearrange itself without the aid of any protein enzyme. In at least part-protein, part-RNA enzyme it is the RNA component, not the protein, that performs a catalytic action. This enzyme, ribonuclease P, breaks the chemical bonds of nucleic acids. The protein may hold the reacting nucleic acid molecules in the proper position. The new-found enzymatic abilities of RNA strengthen the argument that RNA was the genetic material in primitive organisms and also provided the first enzyme-like activities. Small RNA molecules bound to modern proteins are involved in several biochemical reactions important to expression of genes. (Source: Science News, 31 December 1983)

"Sleeper" vector yields 25 per cent of cell protein

Using a "sleeper" vector, gene splicers at Japan's Kikkoman Corporation have tricked Escherichia coli into producing a quarter of its intracellular protein as a cloned gene product. At the company's Bio-Science Research Institute, a modified lambda phage was used to scale up production from test tube to a two-litre vessel. The hybrid vector is normally dormant at 30° C, but increases its copy number per cell a thousandfold at 42° C to 43° C. This high-stability vector, slpls, was originally developed by the Noda Institute for Science Research. The Kikkoman researchers stitched in a tandem pair of glycerokinase genes, each 2.7 kilobases long. They further linked control of the two genes to both a phage promoter and glycerokinase's own promoter, and put the entire package into a strain of E. coli lacking the gene for the enzyme. After three to four hours at the elevated temperature, glycerokinase activity was 6.8 units per ml. The tandem coupling of the genes and the dual promoters were helpful in increasing expression. (Extracted from McGraw-Hill's Biotechnology Newswatch, 16 January 1984)

r-DNA breakthrough

The productive life of recombinant-DNA organisms has been prolonged to 50-60 hours, compared with the normal 10-20 hours, by researchers at the University of California (Davis). Working with the Escherichia coli bacterium for producing amino acid, the scientists improved productivity by separating the process into two distinct steps: the growth stage, and then production or expression. The two steps are done in separate vessels. Besides genetic manipulation, chemicals are added in both stages and fermentation conditions are controlled to improve yield. The basic goal of the work is to improve the stability of genetically-engineered organisms and thereby improve productivity. Instability is one of the key problems and in order to minimize this, another potential solution is being investigated, i.e. chemical regulation to partition or separate the gene from other molecular species that might reject it. (Extracted from Chemical Engineering, 6 February 1984)

More research on AIDS

Research with rhesus monkeys at the research centre in California has offered new clues to the cause of AIDS, which point to the cause being an infectious agent possibly from retroviruses. The research also offers further evidence that AIDS can be transmitted through the blood. Scientists from the University of California at Davis reported they had successfully transmitted an AIDS-like disease from sick to healthy monkeys by using blood extracted from monkeys suffering from Simian AIDS (SAIDS).

In one experiment blood was injected directly into a healthy animal. In the second experiment, blood was mixed with a culture of monkey kidney-cells which were grown through many generations to increase the amount of the infectious agent. An extract of the kidney cells was then injected. In both cases the healthy monkeys contracted AIDS. Electron microscopy of the infected tissue-culture cells revealed only one virus of the class known as retrovirus (Simian Retrovirus D). However, it is possible that some other infectious agent which eluded the electron microscope was also present in the tissue-culture cells. Proof that the disease is caused by Simian Retrovirus D will come when the research team is able to clone the virus, inject it into healthy monkeys and induce the disease. By cloning the virus they would reduce the infectious agent to a single virus. (Extracted from New Scientist, 8 March 1984)

Breakthough in genetic engineering

Chinese scientists at the Shanghai Institute of Cell Biology of the Chinese Academy of Sciences achieved a major breakthrough in genetic engineering recently by separating 40 milligrammes of proinsulin protein from one litre of bacterial culture, four times more than the existing international standards.

The breakthrough was achieved by Assistance Research Fellow Guo Lihe and three other scientists. Scientists elsewhere in the world have been trying to separate proinsulin protein from bacterial culture for a long time. So far, they have only managed to get 10 milligrammes of the substance from one litre of bacterial culture. (Extracted from China Daily, 9 March 1984)

Research on animal genes

Nanjing University develops swine thymosin

Swine thymosin, a new drug that possesses great medical value, has been successfully developed by Nanjing University and the Taizhou Biochemical Pharmaceutical Co. Thymosin is a hormone extracted from animal thymic tissue and regulates the immunological system. Research in this field developed only within the last decade, with bovine thymosin first being applied clinically by the US in 1974.

Nanjing University's Department of Biology and the Taizhou Biochemical Pharmaceutical Co. began developing thymosin in 1977 and decided to focus their research on swine thymosin. After several years of effort, this distinctively Chinese preparation was experimentally produced. Compared with bovine thymosin produced in the United States, the drug is similarly competent and nontoxic and has no side effects. In the United States bovine thymosin is employed principally to treat primary cellular immunodeficiency and some tumours, while in China swine thymosin is used primarily for autoimmune disease. The results of 625 clinical test cases, however, indicate that swine thymosin can also be used to treat, with distinct curative effect, refractory diseases such as hepatitis gravis, rheumatoid arthritis, systemic lupus erythematosus and recurrent apthae.

Currently the group is continuing its investigation into the way in which thymic hormones promote T-cell development. The Jiangsu Provincial Public Health Department has formally approved production of swine thymosin by the Taizhou Biochemical Pharmaceutical Co. (Extracted from Wen Hui Bao, 12 August 1983)

Animal vaccines

A vaccine could be developed to protect animals against herpes, hepatitis B and influenza simultaneously, according to researchers at the New York State Department of Health and the US National Institutes of Health. The modified vaccinia virus, which is generally used to produce antibody against smallpox, was genetically engineered to induce antibody responses in rabbits and mice against herpes simplex I, hepatitis B and influenza. A recombinant vaccine for herpes simplex II has also been developed, but has not yet been tested. A team at the National Institute of Allergy and Infectious Diseases has inserted genetic material from hepatitis B virus into vaccinia virus, stimulating antibody production against hepatitis when injected into rabbits. It will be at least three years until testing of human herpes and hepatitis vaccines will begin. (Source: Science News, 5 November 1983)

Viruses to treat disease

Viruses that can kill bacteria could be used to treat diseases. Scientists at Houghton Poultry Research Station have treated severe diarrhoea in calves and piglets infected with strains of E. coli using bacteriophages. Uncontrolled research was conducted in the 1920s on the use of bacteriophages for treating infectious diseases in humans, but the development of antibiotics reduced this research. Cure of experimentally-induced enteric infections in farm animals could also be achieved using antibiotics, but phage therapy has several advantages. Phage-resistant mutants were less virulent than parent phage-sensitive bacteria. The phage-resistant bacteria produced no harmful effects when given to susceptible animals, probably because they lack parental K antigens which are known to be virulent factors. Samples of faeces from phage-treated calves did not harm susceptible animals even though the samples contained enough pathogenic E. coli to kill the animals. This is because the samples also contain sufficient phage to prevent E. coli proliferation. One problem with using the phages is their narrow range of activity, since they are usually active only on specific strains of E. coli. (Source: New Scientist, 10 November 1983)

Antibody genes

Antibody genes injected into mouse eggs become active only in the approporiate tissue of the adult mouse and not in other tissues, according to R. Brinster of the University of Pennsylvania and U. Storb of the University of Washington. The researchers injected genes needed to make one chain of an antibody into 192 fertilized mouse eggs. Only 11 of the mice survived, and only six contained the injected gene. The gene in those mice was active in spleen cells, but not in the liver. Isolated antibody genes contain specialized regions of DNA that seem to prevent them from being made in tissue other than lymphocytes. If an antibody gene is inserted into a skin cell, nothing happens, but if the gene is inserted into a lymphocyte, it is decoded and begins to produce protein. Other genes may also have tissue-specific signals. (Source: New Scientist, 1 December 1983)

Ways to immunize mosquitos under study

If you cannot kill the dreaded mosquitos, replace them with a genetically different strain of the same species which does not bite or transmit disease. This new approach to controlling mosquito-borne diseases like malaria and filaria is being studied by scientists at the London School of Hygiene and Tropical Medicine.

Such population replacement is practicable because of the great genetic variability that exists within a single species of mosquito in their tendency to bite man and in their susceptibility to infection, Dr. C. F. Curtis told the World Genetics Congress, held in New Delhi last December.

Evidence being accumulated showed that mosquitos within a species genetically differed in their tendency to enter homes and bite people. While some strains were susceptible to infection, certain others of the same species were not. Dr. Curtis and his colleagues selected a strain of mosquitos immune to malaria, housed them in a cage, and released vulnerable mosquitos of the same species into the cage. The theory behind the experiment was that genes responsible for the immunity would be introduced into the offspring of the mosquitos in the case - thus replacing them with a different, immune strain of the same species. (Source: The Hindu, 24 December 1983)

Altered insect cells produce interferon

A novel and perhaps simpler form of interferon cloned in a vector is now in pre-clinical animal trials. Entomologist Gale E. Smith of Texas A & M University linked the structural gene for beta interferon to the promoter sequence of an insect-virus gene, inserted the hybrid DNA message in a culture of insect cells and obtained expression of the protein. Using the insect cell as a host organism and the insect virus as vector, produces a glycosylated peptide similar to that synthesized in nature whose yield is copious, thanks to the power of the gene promoter, which is designed to secrete its original viral protein in quantities up to half of the infected cell's mass. Initial experiments yielded five million units of interferon per million cells, 100 times better than recovery by previous methods using eukaryotic, animal or yeast, cells.

Eukaryotic cells, unlike genetically engineered bacterial hosts, glycosylate the peptides they produce. Smith's beta interferon, synthesized in insect cells, is not only glycosylated but displays the same in-vitro activity in human cells as natural, glycosylated interferon.

They obtained the beta interferon gene from geneticist John Collins of the German Federal Republic's Institute for Biotechnology Research in Braunschweig-Stöckheim, and fused this structural DNA sequence to the promoter of a gene for polyhedrin, a protein abundantly synthesized by an insect virus. This virus, Autographa californica, in nature preys on various insects that attack a variety of useful agricultural plants. A. californica is well-known and widely used by farmers as a bioinsecticide for control of field crops. The protein that this double-stranded-DNA virus makes, polyhedrin, lodges in huge quantities as crystals in the cells of the insects it infects. The insect whose cells Smith recruited as his recombinant host is the fall army worm, Spodopteria frugiperda, whose immortalized ovarian cells are available in culture. By inserting his hybrid gene into these cells, he got them to excrete glycosylated, free-standing beta interferon, unattached to any precursor or other protein, and to export it across the cell membrane.

In vivo, Smith explains, the polyhedrin gene - of which he harnessed the promoter to the beta-interferon coding sequence - is not needed by the virus to protect itself, as the protein crystals do in a living insect. Hence, it is readily fooled into making the alien, genetically engineered product instead.

The technique may provide a safe, inexpensive way to mass-produce genetically engineered products such as insulin and human growth hormones. The major obstacle in making interferon and other recombinant DNA substances is the presence of impurities that can contaminate products. (Extracted from McGraw-Hill's Biotechnology Newswatch, 2 January 1984)

Animal interferons

Biogenics International has produced commercial quantities of bovine, equine, feline and canine interferon, and has reversed the clinical symptoms of feline leukemia by orally administering feline interferon. Oral administration of species-specific interferon may stimulate natural defence mechanisms against viral infections such as equine encephalitis, bovine diarrhoea, canine parvovirus infection and feline leukemia virus. (Source: Chemical Week, 21 December 1983)

Active and inactive genes in mouse cells

Genes active in cancerous mouse cells and present but inactive in normal mouse cells have been discovered by researchers at the Imperial College of Science and Technology and the Institute of Cancer Research. The gene ordinarily produces one of the main histo-compatibility complex antigens, which help the mouse to differentiate between its own cells and foreign material. Activating the gene seems to be part of the mechanism of cancer initiation in the case of cancer caused by infection with the SV-40 virus. Chemical and viral carcinogens and other types of cancer inducers all activate this gene. The research links carcinogens with the immune system. (Source: Chemical and Engineering News, 2 January 1984)

Increasing animal growth rate

A method to immunize animals to increase growth has been developed in the United Kingdom. The technique involves injecting synthetic somatostatin and a human blood protein into sheep, which then develop antibodies to natural somatostatin, which normally acts as a brake on the release of growth hormones. When somatostatin is neutralized, sheep gain weight at nearly twice the normal rate. Some chemical firms have tried to duplicate the results of the University of Bristol team, with partial success. The proportion of lean meat to fat is also improved. (Source: New Scientist, 8 December 1983)

Research on plant genes

Controlling genes at the flick of a switch

Scientists have introduced into plant cells artificial genes that are turned on in the presence of light but not in darkness, according to a report released last October (the New York Times News Service reports). The feat was considered an important step toward

regulating the function of genetically engineered traits in plants. Such control will be necessary for many potential agricultural applications of gene splicing.

The research involved experiments in which tobacco plants were grown with hybrid genes in their cells that work only in light. Under illumination, the plants manufacture a substance that inactivates an antibiotic. In darkness, that substance is not produced. Experts throughout the world hope to use genetic engineering to endow plants with resistance to disease or harmful chemicals, to add useful new substances to those already manufactured by plants, and to improve plant growth characteristics. So far, such genetic manipulations for agriculture are not so advanced as in other fields. One of the key objectives of the new research is to modify plants so that artificially introduced genes are turned on only when needed or only in certain specific tissues, as is the case with natural genes. The research team that transplanted the light-sensitive gene is also working on techniques of introducing genes that would act only in roots or in other specific parts of growing plants.

The report of the work was made by Dr. Jeff Schell, of the State University of Ghent, Belgium, to an international symposium at the Massachusetts Institute of Technology by the Whitehead Institute.

The light-sensitive genes were artifically constructed hybrids. A genetic signalling sequence called a promoter was taken from a natural gene for part of a substance called ribylose diphosphate carboxylase, which is necessary for the process of photosynthesis. That promoter sequence was spliced to a bacterial gene which carries the instruction for an enzyme that inactivates the antibiotic chloramphenicol. The hybrid gene was then spliced into a circular piece of genetic material, called a TI plasmid, which can be used as a delivery vehicle to introduce foreign genes into plant cells. Incorporated into the plasmid, the artificially fabricated gene was put into tobacco seedlings. That new and artifical gene would now be switched on in light conditions and switched off in dark. Dr. Schell and his colleagues were pioneers in adapting the TI plasmid for use as a delivery vehicle to introduce foreign genes into plants. The plasmid exists naturally in Agrobacterium tumefaciens. When that bacterium infects a plant, the plasmid produces crown gall tumours. Dr. Schell modified the plasmid so that it would no longer cause crown gall tumours, but could still be used to insert genetic material into plant cells.

In potato plants the European research team have found genes that act in the tuber itself, but not in other parts of the potato plant. The scientists are trying to develop means of using such genes by coupling their promoters with other genes that would be useful if transplanted into potato plants. (Source: The Times, 6 October 1983)

Mutant corn elements could transfer DNA

Australian researchers have isolated two dissociator (DS) elements in mutant corn that could be used as vectors to carry foreign DNA into corn cells so that the gene for a desired new trait is passed from one generation of plants to the next. Scientists in West Germany have, in separate studies, discovered DS elements in other corn mutants. Natural infectious agents such as the tumour-inducing (Ti) plasmid of Agrobacterium tumefaciens are useful in carrying foreign DNA into the cells of broad-leaved plants. Once inside the nucleus, a precisely defined part of the plasmid, which can be manipulated to carry foreign DNA, is inserted into the cells's chromosomes. A similar system does not exist for monocotyledenous plants such as wheat, corn or barley. Genetic engineers have had problems carrying the genes past the corn cell wall and into the nucleus and chromosomes. DS and Activation (Ac) elements can move around the corn DNA and effect the expression of genes when they are close enough. DS elements, without the ability to transpose on their own, are induced to do so when Ac elements are anywhere in the nuclear DNA. If these elements can be linked to foreign genes for desirable new characteristics, they could then insert the foreign gene into corn chromosomes. The new gene would be stable and inheritable in the absence of an Ac element. A major problem is that the elements must survive until they enter the nucleus, without being degraded by enzymes in the cytoplasm. A possible solution is to present the DNA to plant cells as chromatin, the complex of DNA with specfic binding proteins in which the nuclear DNA of higher organisms exists in nature.
(Source: New Scientist, 8 September 1983)

Guayule can be cloned to produce new plants

The high-yield guayule rubber plant can be cloned to produce multiple new plants, according to NASA. Tissue culture can allow preservation of a desired genotype so that all clones will produce as prolifically as their parent if planted in the same environment. Shoot tips from lateral buds are placed on sterilized tissue culture medium containing water, agar, minerals, sucrose, thiamin hydrochloride and the cytokinin benzylaminopurine. Varying the concentration of the cytokinin determines how many new plants can be produced. The cultures can be placed in a rooting medium without cytokinin, which inhibits root growth. (Source: Life Science, December 1983)

High-protein rice tissue cultured

A high-protein, disease-resistant rice variety has been developed for the first time using the tissue culture method by Mr. G. W. Schaffer of the US Agriculture Department. This variety, when transferred to field conditions, promises good proteinated rice that has so far not accrued in conventional modes of rice cultivation. The plant was developed by adding a lysine analog (an essential amino acid for the plant) to mutants generated from pollen grains of rice in a test tube; the variety could be of tremendous help to countries with rice as a staple food. (Source: The Hindu, 24 December 1983)

Female fish may be mass produced

An unfertilized fish egg can be cultivated to produce a cloned adult fish, according to the Ministry of Agriculture, Forestry and Fisheries. Japanese loach and roach could be cloned in large quantities. The egg must be stimulated with sperm, whose chromosomes are destroyed using ultraviolet light. The stimulation prompts cell division. The egg is then rapidly cooled, doubling the number of chromosomes. Female fish with the same genetic characters can thus be mass produced. A programme is now under way to clone rainbow trout. (Source: Japan Chemicals, 29 December 1983)

Japanese fuse protoplasts for disease-resistant tomatoes

Tomato plants regenerated from the fused protoplasts of normally non-crossbreeding species have been planted and are growing in the greenhouses of the General Research Institute of Kagome Co. Ltd. at Nagoya, Japan. It is reported that these double-diploid hybrids are being used tc develop breeding stock with multiple disease resistances. The researchers achieved the cross by fusing mesophyll protoplasts from two wild-type tomato (Lycopersicum) species. Traditionally, cultivated and wild tomatoes are crossed and new hybrids selected for use in a breeding programme. This is time-consuming, and strong disease resistance cannot be achieved by crossing alone. Moreover, until now certain wild crosses were not possible. The firm expects a new variety of wilt-resistant tomato in two to three years using this method. (Extracted from McGraw Hill's Biotechnology Newswatch, 6 February 1984)

Research on yeast and fungus genes

Yeast learns two-step

A team of researchers at the National Research Council of Canada (NRC) in Ottawa has come up with a process in which a yeast produces alcohol directly from starch.

In the current technology of alcohol production, the starch must first be digested into simple sugars by the addition of enzymes called amylases, which come from other organisms, before fermentation of the sugars by brewer's yeast into alcohol can occur. This pre-treatment step with amylases is costly and time-consuming.

The novel NRC process uses only one yeast, isolated from soil some 20 years ago by a team of researchers and very similar to brewer's yeast, to accomplish both steps. The new yeast, called Schwanniomyces alluvius, produces sufficient amounts of amylase enzymes to break down the starch into simple sugars, which it then ferments into alcohol.

The NRC team, under the direction of Dr. Charles V. Lusena, has studied the conditions under which the yeast is best able to produce the extracellular amylases and to ferment the broken-down starch to alcohol. The starch raw material can be obtained from a number of sources: grains, potato, cassava, and various other root crops. In Canada, the 10 per cent of these crops that spoil annually can now be used profitably rather than lost.

Besides starch as the starting material, the versatile yeast can convert other carbohydrates, such as inulin, a large sugar from the Jerusalem artichoke, a plant easily grown in Canada and yielding more than one crop a year. Certain small sugars from wood wastes can also provide useful fodder.

Further studies are under way to make the conversion of starch to alcohol with this yeast commercially feasible. The researchers also look to other uses for S. alluvius, such as the conversion of waste starch material to single-cell protein, and the commercial production of amylases. (Source: Canada Weekly, vol. II, No. 37, 19 October 1983)

New chromosomes created

New chromosomes have been created out of copies of DNA segments found in yeast by the Dana-Farber Cancer Institute. Artificial chromosomes in yeast are copied and distributed to two daughter cells in most instances of cell division, but the artificial chromosomes have less control over the number of copies made. They are more often lost during cell division than are natural yeast chromosomes. The chromosomes include regions where chromosome replication originates, centromeres, telomeres and some yeast genes. The artificial chromosomes are 33 per cent as long as the smallest natural yeast chromosomes. The differences in behaviour may be due to the shorter length of the artificial chromosome, spacing of its elements or impaired function of one of the elements. It is also possible that some currently unknown element required for proper chromosome behaviour is missing. (Source: Science News, 15 October 1983)

Ethanol production

A new method for producing ethanol was patented for the US Department of Energy. The process uses a new strain of the micro-organism, Zymomonas mobilis. A stream containing water, sugar and yeast extract, as well as the bacteria, is passed through a reactor at a flow rate that permits conversion of the sugar to ethanol. No commercial use has yet been made of the invention. (Source: New York Times, 5 November 1983)

Research on bacterial genes

Continuous fermentation converts wood sugars into monomer feedstocks

By putting bacteria on a starvation diet, scientists at Rensselear Polytechnic Institute (RPI) are developing an economical way of converting wood sugars into a new chemical intermediate. Their project, begun last spring, produces a speciality monomer, L-2,3 butanediol, which might in future replace 1,4 butanediol as a feedstock for polyurethane and polyester resins. The new wood-based molecule is a stereospecific form of butanediol, an industrial monomer currently produced petrochemically.

The company cultures the process micro-organism, Bacillus polymyxa, in a protein-rich medium to build up cell mass, adding small amounts of glucose as the organisms multiply. At a certain point, all protein is cut off and replaced by a 5 per cent glucose-xylose solution, representing the derivatives of wood. This sugar-and-water diet deprives the B. polymyxa of nitrogen, potassium, phosphorus and other nutrients they need to turn their carbon source into new cells.

At this point, the colony's growth is suddenly suspended in the interval between cell divisions. Instead, the microbes are maintained in a stationary phase, eating wood sugars and excreting carbon dioxide, ethanol, and butanediol. In the present bench-scale stage, this reaction goes on in a three-litre continuous-stir reactor tank. Once the reaction begins, the solution is pumped out into a hollow-fibre crossflow filter with polymeric or ceramic membranes. The microbes, retained in the filter, are pumped back into the reactor. The solution removed from the system contains 2 per cent ethanol and 3 per cent 2,3 butanediol, which is recovered by standard distillation. (Extracted from McGraw Hill's Biotechnology Newswatch, 5 December 1983)

Natural ice-minus bacteria field tested

Microlife Tecnics, Inc. (MT), of Sarasota (Fla.) has been spraying chemically mutated strains of "ice-minus" Erwinia herbicola on sites in California, Florida, Georgia, North Carolina, Ohio, Michigan, Oregon and Washington. The company is testing the bacteria

under contract to the University of Wisconsin Alumni Research Foundation (WARF) in Madison. WARF holds a broad patent (US patent No. 4,161,084) on micro-organisms, including Pseudomonas and Erwinia, that affect the freezing point of water. Field results have been mixed so far because of unfavourable weather conditions, but in some tests, sour-cherry yields doubled when frost-retarding bacteria were sprayed on orchards in early spring. The firm works exclusively with Erwinia, because Pseudomonas is a more tenacious colonizer but can be pathogenic to some plants. Erwinia will colonize important frost-sensitive crops, including almonds, cherries, tomatoes and grapes. Colonization failure can usually be traced to toxic copper-based pesticides, which is widely used on some crops in California.

Genetically engineered and non-engineered ice-minus bacteria alike lack a functional cell-surface protein that in wild-type ice-plus strains acts to catalyze ice-crystal formation. Both ice-minus organisms work the same way - by out-colonizing frost-forming bacteria. (Extracted from McGraw Hill's Biotechnology Newswatch, 19 December 1983)

Research instrumentation

Automatic gene cutter

The Japanese company Daini Seikosha has developed an automatic system to cut DNA selectively. The system will be the core of an automatic analysis system for a DNA sequencer. To determine the DNA base sequence, the DNA is cut on a specific spot marked with a radioactive isotope. DNA fragments are then separated using electrophoresis and are exposed to X-ray film, which records the movement of DNA fragments. Results of the electrophoresis are then analysed to determine the DNA base sequence. Selective DNA cutting requires many steps, including adding reagents to DNA, mixing the resultant product, drying and separating. (Source: Japan Chemical, 29 September 1983)

Hand-operated DNA synthesizer

Nippon Zeon has developed Japan's first DNA synthesizer. Genetic researchers and minor research institutions have previously had to buy high-priced, computerized US imports. The Zeon Genet is a hand-operated model that can synthesize two DNA units with different genetic arrangements simultaneously in 40-60 minutes. The remaining volume of reagent chemicals is visible to the naked eye from outside the unit. The unit will be introduced in Japan and abroad. Nippon Zeon anticipates sales of 100 units in Japan alone in the first year. (Source: Japan Chemical, 6 October 1983)

DNA sample analyser

A device to automatically analyze large numbers of DNA samples is being developed by the Japanese Government in conjunction with private industry. The biorobot will be capable of performing 200 complex chemical processes. Seiko Instruments and Electronics will commercialize a version that processes 10 kinds of DNA specimens simultaneously. Genetic information in DNA is contained in various arrangements of four chemical bases. Identifying the arrangements is a time-consuming process requiring an electron microscope and complex chemical steps. The new device automates the part of the process that involves cutting out specific kinds of chemical bases with long chains of DNA. It can mark DNA chains with radioactive isotopes and add minute amounts of test chemicals. The complete system will be developed by end-1983. (Source: The Japan Economic Journal)

Gene-machines

A technique that could make DNA synthesizers obsolete has been submitted to Nucleic Acids Research by a group of scientists at the governmental biotechnology institute at Braunschweig, FRG. The paper, whose first author is Ronald Frank at the Gesellschaft für Biotechnologische Forschung (GBF), describes a new way of stringing together oligonucleotides, using phosphotriester chemistry.

Its novelty lies in taking advantage of the repetition of nucleotide bases in the structure of DNA to build a large number of fragments at one time, before finally linking them together.

Gene machines work on the principle of adding nucleotide bases one after the other to a starter chain fixed to a solid support. So one chemical cycle must be performed for each base. GBF's new method exploits the fact that with only four nucleotide bases - adenine,

cytosine, guanine, and thymine - from which to choose DNA building blocks, a number of the fragments will bear identical sequences for short stretches, and these bases can be added to a group of fragments in the same reaction vessel.

The GBF procedure also starts with short fragments fixed - in their case - to cellulose paper discs. But then the fragments are separated into groups according to which nucleotide base must be added next. The adenine group will then be treated in the adenine vessel, and so on. After each cycle, the discs are again regrouped according to their predefined sequences, and placed in the appropriate vessel. In this way, the GBF teams built up octamers, but they claim their method can be used to construct a complete gene of, say, 60 fragments, each 15 nucleotide bases long. This would require only 56 reaction cycles by the GBF method, compared to 840 cycles following the traditional DNA synthesis route.

Unfortunately, the amount of starting material that can be fixed on to the cellulose discs is only about 20μM per gramme of support, which is small compared to the 200μM used commonly to start reactions in gene machines. This means that the overall yield will be much lower.

The paper says that future developments will include alternative solid supports to improve the loading factor and testing the phosphite method, another common chemistry used in DNA building. (Extracted from McGraw Hill's Biotechnology Newswatch, 7 November 1983)

The following is a selection of commercial DNA synthesizers, extracted from McGraw Hill's Biotechnology Newswatch of 17 October and 7 November 1983. (See pp. 31-32).

Microspheres - made in space

Twenty-five grammes of latex beads are being turned over to the US National Bureau of Standards (NBS) by Professor John W. Vanderhoff of Lehigh University. The high-precision microspheres, manufactured aboard NASA's space shuttle, are described as representing the first chemistry done in zero gravity, and the first commercial product made in space. Latex particles of strictly uniform diameter have several uses in biolaboratories, notably as standards to calibrate electron microscopes. The most accurately sized microspheres in use today are Lycopodium pollen grains, but these differ in diameter by as much as 15 per cent. A scientist who sets his scope for 20,000X magnification may in fact be getting 22,300X. Beads made in orbit can be made to a tolerance of 1 per cent, and in huge quantities.

In the experiment, latex suspended in water is heated along with chemical reagents to 70° C, at which point minute spheres begin to grow in the suspension. Their diameter can be closely determined by controlling the reaction.

After the NBS puts the microspheres on sale soon, at $10,000 a gramme, scientists at various institutions will know they are calibrating to the same magnification.

On Earth, microspheres up to 10 microns in diameter can be made quite easily, but anything larger is extremely difficult. Aboard the shuttle, beads up to 100 microns can be produced readily and in abundance.

Besides calibrating microscopes, the standardized spheres have other applications of interest to bioscientists:

- They can accurately gauge the porosity of a membrane;

- In Coulter counters for more accurate counts of white and red blood cells;

- In column chromatography;

- As possible carriers of drugs and radioisotopes for diagnosis and therapy.

(Extracted from McGraw Hill's Biotechnology Newswatch, 19 December 1983)

NEWSWATCH Monday, October 17, 1983

COMMERCIAL DNA SYNTHESIZERS: Listed, Characterized, Compared

"GENE MACHINE" NAME MANUFACTURER	MACHINE SPECIFICATIONS	DEVELOPERS	USER EVALUATIONS
380A DNA SYNTHESIZER Applied Biosystems 850 Lincoln Centre Dr. Foster City, CA 94404 Tel: (415) 570-6667 Telex: 470052 Europe: [illegible] Biosystems GmbH [illegible] Pfungstadt, West Germany Tel: [illegible]	COST: [illegible] CHEMISTRY EMPLOYED: Phosphoramidite SYNTHESIS LENGTHS: Bases say 40 bases; 83 reported COUPLING EFFICIENCY: 99% COUPLING TIME: 17 minutes per cycle in adding bases	OF THE MACHINE: Valve block design by Dr. Leroy Hood and senior research fellow Michael Hunkapiller at CalTech, with Dr. William E. Efcavitch, who "married" chemistry to manual synthesizer in present automated design. OF THE CHEMISTRY: Dr. Marvin Caruthers, University of Colorado, Boulder (see Newswatch, Oct. 19, '81, p. 3).	One user reports "99% reliability" in getting desired DNA up to 40 bases. Service is good, machine down only three or four days in half year he's had it. Says machine is "very sophisticated, so needs careful operator to carry out functions meticulously."
MANUAL DNA SYNTHESIZER [illegible], Inc. 3132 [illegible] St. Torrance, CA [illegible] Tel: (213) 530-4171 Telex: 910 3477320	COST: $1,[illegible] CHEMISTRY EMPLOYED: Phosphor triester with dimers SYNTHESIS LENGTHS: up to 40 bases claimed COUPLING EFFICIENCY: 92%-93% COUPLING TIME: 17 minutes per cycle, 35 overall	OF THE MACHINE: Dr. Bruce Kaplan, City of Hope National Medical Center, Duarte, Calif. OF THE CHEMISTRY: Adapted from literature at City of Hope.	One who bought machine 18 months ago had initial leakage problems, fixed by new bottles with better seals. "It is reasonably okay," another tells Newswatch. "It does what it is supposed to." For low load at research center, it is "adequate, making one nucleotide from scratch." Another user says he routinely gets oligomers 16 to 19 bases long. He modified machine to use lower resins and chemicals.
SYSTEM 1 DNA SYNTHESIZER Beckman [illegible], Inc. Box 10200 Palo Alto, CA 94304 Tel: (415) 857-1150 Telex: [illegible] 78413 (Fullerton, CA) Europe: Beckman-RIIC Ltd. Turnpike Rd., Cressex Ind. Est. High Wycombe, Bucks. HP12 3NR, U.K. Tel: 0494 41181 Telex: 837611 International S.A. European Analytical Sales P.O. Box 308, CH-1211 Geneva 6, Switzerland Tel: 22-36-64-80	COST: $[illegible] CHEMISTRY EMPLOYED: Beaucage phosphoramidite (adapted) SYNTHESIS LENGTHS: up to 40 base additions guaranteed COUPLING EFFICIENCY: 95% or better COUPLING TIME: 27 minutes or less per addition	OF THE MACHINE: Engineering team at the firm. OF THE CHEMISTRY: Drs. Serge Beaucage and Marvin Caruthers at University of Colorado, Boulder.	First prototype unit to be placed next month.
SAM ONE Biosearch, Inc. [illegible] Kerner Blvd. San Rafael, CA 94901 Tel: (800) [illegible] (415) [illegible] Telex: 172680 Biosearch Europe: [illegible] [illegible] 6 NL-[illegible], Netherlands Tel: (31) [illegible] Telex: [illegible] NL Japan: [illegible] Ltd. 14-27 Akasaka 2-Chome Minato-ku, Tokyo 107 Tel: [illegible] Telex: J[illegible]	COST: $[illegible] CHEMISTRY EMPLOYED: Phosphite triester or phosphate triester SYNTHESIS LENGTHS: 30 residues, automatically COUPLING EFFICIENCY: 95% claimed COUPLING TIME: depends on chemistry used	OF THE MACHINE: Dr. Ronald Cook, Chairman of the Board. OF THE CHEMISTRY: Adapted by Cook from published literature.	One uses it 24 hours a day with no problems—if a strict maintenance schedule is followed. "Parts such as valves and pump don't last forever, so it's a good idea to replace before they wear out." Solvents must be prefiltered; otherwise, valves will be ruined. Corrosive agents used in DNA manufacture can ruin pump, valves, shortening their lives. Happy with overall performance after initial set-up troubles overcome. "We've consistently made oligomers with no problems." Frequent praise because user can modify program.
CRUACHEM MANUAL SYNTHESIS MODULE Cruachem, Inc. Box [illegible] Bend, OR 97708 Tel: (503) 382-[illegible] Europe: Cruachem Chemicals, Ltd. 11 Napier Square Livingston EH54 5DG Scotland Tel: 0506 32146 Telex: 72165 CRUACHEM	COST: $[illegible] CHEMISTRY EMPLOYED: phosphotriester, solid-phase synthesis SYNTHESIS LENGTHS: up to 30 bases COUPLING EFFICIENCY: 95% with company reagents COUPLING TIME: 65-minute cycles for beginners, 25 with experience	OF THE MACHINE: Dr. Brendan [illegible], firm's managing director. OF THE CHEMISTRY: Dr. M. G. Gait, Cambridge University, Cambridge, England.	Launched in U.S. at April meeting of Federation of American Societies for Experimental Biology in Chicago. Trials now going on at two U.S. institutions, including M.I.T. Introduced in Europe at "Biotech '83" conference in London last March. A semi-automated synthesizer is now undergoing final tests at the company.
MODEL 25A SOLID BASE SYNTHESIZER Genetic Design, Inc. 111 School St. Watertown, MA 02172 Tel: (617) 923-1175 Telex: [illegible]	COST: $[illegible] CHEMISTRY EMPLOYED: Phosphite-triester or phosphate-triester SYNTHESIS LENGTHS: up to 50 bases COUPLING EFFICIENCY: 97% COUPLING TIME: about 30 minutes	OF THE MACHINE: Drs. Alex Bonner and Marcus Horn of the company. OF THE CHEMISTRY: Adapted from published chemistries.	One in private industry says this is "a high-quality machine"; he likes its use of sliding valves instead of diaphragm. Makes one oligonucleotide a day. Another user has been getting "extremely good yields for two years," despite some problems in the electronic components. A university user reports routinely getting 90% efficiency "when the air isn't too humid"; he has had some trouble with moisture.

"GENE MACHINE" NAME MANUFACTURER	MACHINE SPECIFICATIONS		DEVELOPERS	USER EVALUATIONS
SYNTHESIS KIT New England Biolabs, Inc. 32 Tozer Road Beverly, MA 01915 Tel: (617) 927-0526 Telex: 95-0157 Europe: New England Biolabs GmbH Postfach 2750, D-6231 Schwalbach bei Frankfurt German Fed. Rep. Japan: Wako Pure Chemical Industries 3-10 Doshomachi Higashi-ku, Osaka Tel: (06) 203 3741 Telex: 522-6114 WAKI OSJ	COST: CHEMISTRY EMPLOYED: SYNTHESIS LENGTHS: COUPLING EFFICIENCY: COUPLING TIME:	$700 Modified phosphoramidite 16-18 bases, 30 at most 99 % if ingredients not stumped 45 minutes for layman	OF THE MACHINE: Developed in-house by team of chemists. Note: This is a kit, not a machine. Reactor vessel included. Product can be purified later with HPLC or gel method. OF THE CHEMISTRY: Dr. Marvin Caruthers, University of Colorado, Boulder.	Researchers with a small work load for synthesized materials, and who don't want to take time to order all chemicals individually, may prefer a kit to a machine, say users. One reports the kit "works well enough" but that efficiency and end-product depend entirely on purity of chemicals used. He notes that better amidites are probably available, predicts that scientists will soon generate their own as they work.
"ZEON GENET" MANUAL SYNTHESIZER Nippon Zeon Company 6-1 Marunouchi 2-1 chome Chiyoda-ku Tokyo 100, Japan Tel: (03) 216-1771	COST: CHEMISTRY EMPLOYED: SYNTHESIS LENGTHS: COUPLING EFFICIENCY: COUPLING TIME:	$8,887 solid-phase condensing method 20 to 30 bases — 40-60 minutes	OF THE MACHINE: Team under Kazuburo Ida, director of Nippon Zeon's Institute of Molecular Biology in Kawasaki City.	Sales of machine in Japan will start this month; exports perhaps by April, 1984. Manual desk-top machine is first Japanese-made DNA synthesizer, according to Zeon. The firm, which does not supply reagents or solvents, aims to sell two kits: one set composed of all 16 protected nucleoside dimers; the other of polystyrene-supported nucleoside resins and triethylammonium monomer salt.
"MICRO-1450" Systec, Inc. 3816 Chandler Drive Minneapolis, Minn. 55421 Tel: (612) 788-9781	COST: CHEMISTRY EMPLOYED: SYNTHESIS LENGTHS: COUPLING EFFICIENCY: COUPLING TIME:	$33,000 Phosphoramidite, phosphate-triester, phosphite-triester up to 42 bases reported 95 % -97 %, depending on chemistry 8 to 45 minutes	OF THE MACHINE: Koichi Itakura and Bruce Kaplan at City of Hope National Medical Center, Duarte, Calif., with Carl Sims of Systec. OF THE CHEMISTRY: Phosphoramidite, Marvin Caruthers, University of Colorado, Boulder, who holds future exclusive rights; phosphate-triester: Itakura; phosphite triester: from published materials.	One says, "Final DNA product is satisfactory, and company provides good service," but he chides Systec on its jargon-filled manual, hard for non-specialists to follow. "It eats up solvents," another notes, citing the system's price as a major advantage. Another, who makes custom oligonucleotides on an as-ordered basis, cites 30 % -40 % success with products 16 to 21 bases long.
MODEL 280 POLYNUCLEOTIDE SYNTHESIZER Vega Biotechnologies, Inc. P.O. Box 11648 Tucson, AZ 85732 Tel: (602) 746-1481 (800) 528-4882 Telex: 165572 (Vegatec) Europe: Biotronik Wissenschaftliche Dr. Gerate GmbH Postfach 630265 Beregstr. 22 D-8000 Frankfurt/M. 60 German Fed. Rep. Tel: (0611) 4112 16 Telex: 417239 BIO D Japan: Amco, Inc. 8-7 4-Chome Igusadai Chiyoda-ku Tokyo 32 Tel: (03) 265-4261 Telex: 322774 MEDCHEM	COST: CHEMISTRY EMPLOYED: SYNTHESIS LENGTHS: COUPLING EFFICIENCY: COUPLING TIME:	$22,500 to $39,500, depending on computer phosphotriester, phosphite or phosphodiester 20 to 40 bases 95 % 20 to 75 minutes	OF THE MACHINE: Dr. Leon Barstow, company's chairman of the board. OF THE CHEMISTRY: Arrangement, initially, with Itakura; thereafter, by adapting published chemistries.	One researcher reports 60 % -65 % efficiency using modification of phosphotriester chemistry by M. J. Gait of Cambridge University, U.K. Another, who uses the machine heavily for large and small oligonucleotide syntheses, is "very pleased with it," and "gets excellent results." He says the machine is very simple to use if operated correctly.

Lasers

A laser can be used to insert DNA from one organism into another, according to researchers at the Japan Institute of Physical and Chemical Research. The technique could make it easier to identify cancer-causing genes, to mass produce proteins and develop improved agricultural crops. A cell is put in a culture fluid containing DNA and then with a yittrium-aluminium-garnet laser (YAG; 35 nm) linked to a light pen and television camera, is subjected to a 10-nanosecond burst of light. A technician can perforate some 2,000 cells with holes one micrometer or smaller in diameter in a few minutes. It takes about a second for the aperture to close, during which time DNA, contained in the medium, has a chance to slip into the cell.

Last October, IPCR, which is under the supervision of the Science and Technology Agency, filed Japanese patents covering both the process and laser hardware.

For cells without efficient vectors, the researchers see the laser technique as preferable to microinjection, which involves a high degree of skill, or osmotic shock, risks damaging the cells.

Currently available manual and chemical methods of gene insertion both have drawbacks. The manual method can produce only about 1,000 engineered cells/hr, of which under 1 per cent continue to function normally. The success rate of the chemical method is far lower. The laser technique can modify about 1,000 cells/min, with a success rate of about 1 per cent. (Extracted from Technology Update, 24 December 1983 and McGraw Hill's Biotechnology Newswatch, 16 January 1984)

Advantage in high-polymer membranes

Synthetic membranes, which separate fermentation liquids or gases that distillation cannot easily purify, brought a nine-member Japanese mission to the United States and Western Europe last December to investigate up-to-date technology of high-polymer membranes that will cut energy cost and improve specificity of bioproduct recovery. The member companies of Research Association of Polymer Basic Technology (RAPBT) expect marketable membranes by the 1990s. Unlike present-day semi-permeable barriers that act like sieves, ultra-thin polymer membranes are being designed to separate substances with similar boiling points, those which distillation cannot separate. They are also working on affinity membranes that will allow desirable biomaterials to pass through at high energy savings. Typical applications: ethanol recovery and removal of toxins in wastewater treatment. The research was initially financed by the Ministry of International Trade and Industry (MITI) with a $1 million equipment grant in October 1981 to companies in the membrane-research consortium, and double that sum last year. Association members have already filed 33 patents at home, but none abroad, according to a patent manager from one of the nine companies. MITI, which is sponsoring the entire thin-membrane project, will most likely take title to all patents, with inventor companies manufacturing products under license. The participating firms are said to have invested $5 million in the national project and assigned to it about 50 researchers.

RAPBT members interested in liquid separation include: Daicell Chemical Industries Ltd. of Sakai-shi; Kuraray Co. Ltd., Sumitomo Electric Industries Ltd.; and Toyobo Co. Ltd., all of Osaka. In the gas separation group are: Asahi Glass Co. Ltd.; Mitsubishi Chemical Industries Ltd.; and Toyobo Co. Ltd., all of Tokyo; Asahi Chemical Industry Co. Ltd.; and Teijin Ltd., both of Osaka. Three government organizations collaborating with RAPBT are: National Chemical Laboratory for Industry, Research Industry for Polymers and Textiles, and Industrial Products Research Institute. (Extracted from McGraw Hill's Biotechnology Newswatch, 2 January 1984)

General

Trends in enzymes

Industrial enzyme sales total $350-400 million/year, with 80 per cent used by food processors. The only major new market to develop in the past 10 years has been HFCS, which has created a $40 million/year market for immobilized glucose isomerase. An immobilized lactase enzyme will be used in a new process to use whey to make bakers' yeast. Detergent use of alkaline protease enzymes is increasing, following a temporary reduction due to fears of product safety. Enzymes are also being developed to break down fats and

cellulose. The enzyme industry worldwide has 25-30 producers, but Novo Industri (Denmark) holds about 33 per cent of the market. Gist Brocades (the Netherlands) and Miles Laboratories (US) are also market leaders. Excess capacity and a large number of small producers will probably continue to depress the market for several years. Most enzymes are water-soluble, and thus are difficult to recover and reuse, despite the development of immobilization techniques that bind the enzyme to a solid. Enzyme stability must also be improved. A major disadvantage of enzymes is their specificity, which requires R&D costing $3-10 million. Enzymes must generally cost 1 per cent of the cost of the finished product, and production volume must be sufficient to make enzyme use economical. Enzyme detergents hold about 15 per cent of the US market and 67 per cent in Europe. Production of aspartame depends partly on an enzymatic process, and a second part of the process may also be adapted to enzyme use. Development of new applications for enzymes will create new growth opportunities. (Source: Chemical Week, 30 November 1983)

Possible cause of Alzheimer's disease

An infectious prion may be responsible for Alzheimer's disease, according to some members of a research team at the University of California (San Francisco). Prions are too small to be studied with an electron microscope, but gather into clumps that resemble and have properties similar to those of amyloid, a brain substance thought to be a waste product of Alzheimer's disease. The team's findings suggest an infectious cause for Alzheimer's disease, although there is no evidence that it is contagious. (Source: Chemical and Engineering News, 12 December 1983)

X-ray crystallography aids enzyme redesign

Scientists at the Agouron Institute at La Jolla, California are using highly-detailed three-dimensional enzyme structures by using the knowlege acquired from X-ray crystallography to decide how and where genes coding for proteins should be altered, and modified to work at high or low temperature and pH - conditions that normally make them unusable.

The first progress they report is customizing the enzyme dihydrofolate reductase (DHFR). This ubiquitous enzyme plays a catalytic role in the metabolism of one-carbon compounds used in the biosynthesis of thymidylate, purines and some amino acids. It is also the target of a class of widely used cancer drugs, including methotrexate. The team, led by molecular biologist J. E. Villafranca, directed specific amino acid changes in three chosen areas through site-specific mutagenesis, and thereby planned precise alteration of the nucleotide sequence coding for the protein. One change involved the enzymes's active site; by changing an aspartate residue to asparagine, they reduced the enzyme's catalytic activity by 99.9 per cent. The institute does not expect any direct commercial applications for the DHFR enzyme, but sees it rather as a model system. However, several other enzymes are being investigated. (Extracted from McGraw Hill's Biotechnology Newswatch, 2 January 1984)

Computer simulation of enzymes

The University of Southern California's computer simulation study of enzymes may aid genetic engineers in attempts to design artificial enzymes for medicine, agriculture and industry. A. Warshel of the University of Southern California is building and manipulating computerized models of enzymes to determine how the chemicals function. Enzymes participate in cellular production of new protein by reading genetic instructions for the process. Unlike previous studies, Warshel's research makes use of the discovery that enzymes are constantly in a state of agitated movement due to thermal energy. Although the movement appears random, the enzymes move in a manner specific to their tasks. USC scientists have charted the enzymes' specificity of movement within the random motion by simulating their motion on a computer, using similar techniques to those employed by space scientists. (Source: Chemical Marketing Report, 2 January 1984)

D. APPLICATIONS

Pharmaceutical and medical applications

New chicken pox vaccine

The World Health Organization (WHO) is drawing up guidelines for the preparation and method of inoculation of a new chicken pox vaccine developed at the Osaka University Microorganism and Disease Research Center. The chicken pox virus Oka strain isolated will be

attenuated and distributed worldwide as a live vaccine. This strain has been recommended by WHO for the preparation of chicken pox vaccine because of its excellent immunogenisity and favourable clinical results. A standard for its preparation and examination in Japan is being drawn up, and its developers are trying to incorporate and legalize the seed lot system as part of the standard.

This seed lot system manages the homogeneous seed virus so that safe vaccine with constant quality can be prepared from it. In the case of live vaccine, the attenuated virus may recover the pathogenicity during subculture or the virus may undergo a variation and lose its effectiveness. In order to create a seed virus pool, this virus must be grown in the same culture system used in an actual production process and a large quantity of virus material must be prepared. The virus material thus prepared is then subdivided, freeze-dried, and kept at a temperature below -80°C. Moreover, the number of subcultures must be limited to no more than five. Using this method, examination of vaccine need not be carried out after each lot is created, as is current practice. As a result, 20-30 million yen per batch can be saved in examination fees, labour and time, thus contributing significantly to the reduction of the cost of vaccine.

Chicken pox virus, being related to herpes virus, indicates a danger of carcino-genesis, therefore, children who suffer from reduced immune capacity as a result of basic diseases such as leukemia or collagen disease may die if further affected by the chicken pox virus. These children, medical staff and pregnant women who have never had chicken pox will be the subjects who will receive this chicken pox vaccine.

The research team is analysing the protein of the chicken pox virus using monoclonal antibodies. There are at least 50 kinds of proteins codified on a DNA having a molecular weight of 8.5×10^6, and several kinds of glycoproteins among these proteins are said to determine the immunogenicity. They have collected three kinds of monoclonal antibodies, and investigation of the commonness of these antigens is under way. However, they do not appear to be interested in making a component vaccine utilizing the antigenic determinant protein as revealed by the study of monoclonal antibodies, because the live vaccine itself is so effective that the antibody titer can be raised significantly by a small quantity of the live vaccine. (Extracted from Tokyo Nikkei Biotechnology, 4 July 1983)

Sanofi begins large-scale production of somatocrinine

As the culmination of research conducted by the Montpellier Research Center (formerly Clin-Midy) in collaboration with Professor Roger Guillemin of the Salk Institute, Sanofi is going to begin large-scale production of the cerebral hormone somatocrinine, the first therapeutic indication of which is the treatment of certain types of dwarfism. At the end of 1984 production capacity at Marnes-La-Coquette should reach 10 grammes per month, while the French demand for this use is about 8 grammes per year. This will make it possible to develop clinical tests of what will perhaps be a pharmaceutical speciality before long. (Extracted from Chimie Actualites, 26 September 1983)

Human clinical trials begun on gamma interferon

Biogen (Sweden) has begun human clinical trials on gamma interferon to test its effectiveness as an anticancer agent. The gamma form of interferon has proved more effective than the alpha form in laboratory experiments and is part of the body's natural immune system. Biogen's alpha interferon is currently undergoing clinical trials and is expected to receive FDA approval in late 1984. The drug has been useful in treating rare cancers in humans, but has not been as effective in treating breast and lung cancer. Biogen, the first firm to advance genetically engineered gamma interferon into human clinical trials, plans to produce and market the drug commercially, rather than license it to another firm for developmental work and marketing, as it has previously done. Trials could cost $50 million during the three-year test period. The clinical trials could be completed in three to four years and the regulatory approval procedure may take one year. (Source: Chemical Marketing Report, 26 September 1983)

World monoclonal antibody markets ($ million)

	1986	1990
In vitro diagnostics	-	10-20
In vivo diagnostic imaging	10	60
In vivo therapeutics	10	100
Agric. & veterinary	10	30
Purification	10	70

(Source: European Chemical News, 25 July 1983)

Diabetes and enzymes

Patients with maturity onset diabetes may have enough insulin, but underactive liver enzymes, according to E. Sotaniemi of the University of Oulu, Finland. The limiting factor in the glucose metabolism of these patients is the speed with which glucose-6-phosphatase and glycogen synthetase do their work. The enzyme inducer phenobarbital and medroxyprogesterone acetate lowered blood glucose levels from 12.7 mmol/l to 9.0 mmol/l. (Source: New Scientist, 6 October 1983)

Toxic shock syndrome

A bacterial gene that specifies the toxin linked to toxic shock syndrome has been isolated from strains of Staphylococcus aureus taken from toxic shock victims by a research group led by R. Novick, Director of the Public Health Research Institute (New York City). The toxic shock syndrome exotoxin (TSSE) was isolated by researchers at the University of Minnesota and University of Wisconsin. The findings will enable researchers to prepare large amounts of the toxin for future study, using recombinant DNA techniques. Increased availability of the toxin could hasten the development of a TSS vaccine or a test to determine susceptibility to the disease. The role of the toxin in causing the disease is not yet clear. (Source: Chemical and Engineering News, 24 October 1983)

Blood substitute

The Japanese company Ajinomoto plans to commercialize stabilized haemoglobin within five years after running clinical tests. The blood substitute is not only superior to regular blood in terms of preservation, but there is no danger of it being infected by a hepatitis virus. The stabilized haemoglobin which Ajinimoto succeeded in developing combines polyethylene glycol with haemoglobin, the main ingredient of red blood corpuscles in blood. In addition to staying longer in blood vessels than regular haemoglobin, it is completely equal to regular blood in its ability to carry oxygen. Moreover, because it removes the cell membrane in red corpuscles, it can be used in blood transfusions for people of any blood type. At present preserved blood (donor blood) kept at 4°C can be used only within 21 days. For this reason, 20-30 per cent of donated blood (depending upon the season) is disposed of when the period of effective preservation has expired. The company expects to use this abandoned blood as the raw material for its stabilized haemoglobin when it begins production.

Professor Hajime Horibara, of Tsukuba University has said that "by just simply clearing away the red corpuscle membrane, haemoglobin clogs the ureter and causes a kidney problem. Ajinomoto's research solves this problem, and therefore has considerable promise from the standpoint of surgeons. Because haemoglobin and polyethylene glycol are both substances whose characteristics are well-known, questions of safety and whether or not it is carcinogenic may be able to be successfully answered." (Extracted from Nihon Keizai Shimbun, 5 November 1983)

Cancer treatment experiments

Damon Biotech will conduct cancer treatment experiments using its cell-growth technology with the US National Cancer Institute. The Institute will use the company's Encapcel microencapsulation technology to produce large amounts of monoclonal antibodies in testing a new treatment for B-cell lymphoma and will jointly seek FDA approval for human testing. The process permits production of the required number of antibodies in 8-10 weeks versus the usual 6-9 months. The Encapcel system encloses animal cells in small porous capsules that produce antibodies. Some 15,000 people/year develop B-cell lymphoma and

10,000 people/year die from it in the United States alone. Conventional treatment consists of hospitalization, radiation and chemotherapy, which costs $50,000-100,000/year, versus $30,000-50,000/year for Damon's treatment.

Clinical trials of endogenous opiate metenkephalin as an antitumour agent for lymphoma will be conducted at Oral Roberts University. The phase I toxicity trial will involve healthy volunteers, but phase II trials will test metenkephalin's ability to stimulate the immune system against tumours in lymphoma patients. Recent discoveries have linked stress, the endogenous opiates and the immune system. At least three laboratory studies have shown that metenkephalin and beta-endorphin can increase cell-mediated immunologic activity in vitro. Beta-endorphins have been shown to increase natural killer lymphocyte activity in tests at the Minneapolis VA Medical Center and the University of New Mexico. Metenkephalin can also increase T-cell activity in serum from cancer patients. Levels of enkephalins can vary greatly between persons who exercise regularly and those who do not. Short-term stress may stimulate the immune system by triggering release of enkaphalins stored in the adrenals, but chronic stress could deplete enkephalin stores.

Summa Medical is developing a vaccine designed to stimulate antibodies against human chorionic gonadotropin. hCG surrounds new tissues or foreign matter in the body to prevent them from being attacked by antibodies. The substance also protects some malignant tumours. About 86 per cent of lung cancers and 50-60 per cent of breast cancers produce hCG. Human trials could begin in 1984. (Source: Chemical Marketing Report, 24 October 1983 and Medicine World, 10 October 1983)

Kit detects cancer and predicts spina bifida

Celltech, Ltd., Britain's government-sponsored genetic engineering company, has launched a dual-purpose monoclonal kit for testing neural-tube defects in fetuses and liver cancer in adults. The kit measures alpha-fetoprotein, a fetal protein present in large quantities in infants born with spina bifida, a condition in which the spinal cord is exposed. Alpha-fetoprotein is also a diagnostic marker of liver cancer in adults. Celltech's immunoradiometric assay (IRMA) works on a different principle than conventional radioimmunoassays (RIA) for measuring alpha-fetoprotein. It involves adding two monoclonal antibodies to the sample, both specific to alpha-fetoprotein, but one radioactively labelled, the other bound to latex particles. To this is added a 10 per cent sucrose solution. After ten minutes the latex particles drop through the sucrose solution and are read after pouring off the supernatant. (Extracted from McGraw-Hill's Biotechnology Newswatch, 7 November 1983)

Monoclonal antibody pregnancy test

Organon Diagnostics' (W Orange, NJ) new monoclonal antibody pregnancy test provides definitive data in emergency situations, such as before surgery or X-rays. The DUOCLON slide test uses one drop of urine combined with one drop of the latex reagent to detect human chorionic gonadotropin, the hormone indicative of pregnancy. The test uses two monoclonal antibodies, one reacting with HCG and one reacting with an HCG subunit to reduce interference in test results from drugs, blood or proteins that may be present in the urine.

A similar monoclonal antibody pregnancy test, TANDEM, developed by Hybritech (San Diego, CA) uses a monoclonal-coated bead plus another monoclonal that form a 'sandwich' around the HCG module in a test tube. This test provides results in about 30-45 minutes. (Source: Modern Health, October 1983)

Interferon dosage

Research at the company of Upjohn suggests that lower interferon doses increase efficacy against certain cancers and viral infections. Pyrimidinone interferon inducers stimulate the body to produce more of its own interferon. A low, constant dose may be more effective than increasingly higher doses. In experiments on mice, multiple intraperitoneal injections of 60-125 mg/kg of pyrimidinone for 3 days induced interferon production, increasing responses of the mice to subsequent injections and enhancing their resistance to later intraperitoneal injections of herpes simplex virus 1. However, the opposite happened with pyrimidinone doses of 250-500 mg/kg; the mice became hyporeactive, producing less interferon and becoming more susceptible to the injected virus. Some 50 per cent of the mice in the control group survived 35 times the dose of virus that proved fatal to 50 per cent of the mice in the high-interferon dose, hyporeactive group. Some 50 per cent of the

low-dose group could withstand 30 times the amount of the virus that proved lethal to the mice in the control group. Upjohn researchers hypothesize that high levels of interferon may activate a control factor that turns off immune system activity and localized interferon production. While high serum interferon levels appear to be important for combatting some viral infections, high local tissue interferon levels may be more important to the body's ability to fight certain other viruses, including herpes simplex 1. (Source: Chemical Marketing Report, 7 November 1983)

Vaccine against bacterial meningitis

Lederle Laboratories have developed a vaccine against bacterial meningitis, a disease which kills 2-10 per cent of child victims and causes permanent brain damage in another 25 per cent. Haemophilus influenzae meningitis is a leading cause of acquired mental retardation in the US, and is a frequent cause of septic arthritis, epiglottitis, pneumonitis and osteomyelitis. Lederle isolated the bacterial capsular polysaccharide, polyribosylribitol phosphate (PRP). Purified PRP vaccine does not stimulate an immunological response in children under 18 months, when the infections are most common. The new vaccine shows PRP antibody increases sufficient to provide protection in 90 per cent or more of vaccinated children. The combined DPT-PRP vaccine produced high levels of antibody in 97 per cent of children receiving it during infancy. Children were reinoculated at 18 months, and some were inoculated for the first time at 18 months. In the latter group, 89 per cent developed protective levels of antibody. Reimmunization at 18 months may be necessary to induce prolonged protection against H. influenzae meningitis. (Source: Lederle Laboratories News Release, October 1983)

Cancer therapy

Some Japanese researchers are of the opinion that interferon is not effective in treating solid cancers, but is effective in treating multiple myeloma, malignant lymphoma, melanoma and kidney cancer. Interferons may also be effective in treatment of hepatitis B. They are investigating treatment of diseas s with interferon in combination with radio-therapy or chemotherapy. (Source: Japan Chemicals, 3 November 1983)

PKU - prenatal and carrier detection

Dr. Savio L. C. Woo and others at the Howard Hughes Medical Institute in Houston, Texas, report another genetic step - the prenatal diagnosis and detection of phenylketonuria (PKU) carriers.

In PKU, the liver enzyme phenylalanine hydroxylase is absent, a condition that can result in severe mental retardation due to the buildup of phenylalanine and other substances in the blood. It is estimated that one in every 200 Caucasians is a carrier of the disease. PKU is transmitted as an autosomal recessive trait, meaning that when both parents are carriers each of their children has a 25 per cent chance of having the disease and a 50 per cent chance of carrying it. Until now prenatal diagnosis of PKU was not possible, nor was carrier detection, but infants could be tested for blood levels of phenylalanine and successfully treated nutritionally. Woo and co-workers report they are now able to detect carriers and affected fetuses of families with PKU history.

The technique used by the Baylor team is called restriction fragment length polymorphism where complementary DNA - one strand of the double helix - is used as a probe to detect individual discrepancies - polymorphisms - among parents and children in PKU families. Using restriction enzymes, which specialize in cleaving DNA between specific nucleotides, the researchers compared resulting fragments and found three that exhibited polymorphisms. Classical Mendelian analysis then made it possible for the researchers to sort out the fragment mixtures that showed up in affected children.

This test presently can detect prenatal defects for 75 per cent of those parents who have had other PKU children and are concerned about future ones. The other 25 per cent of existing PKU families are undetectable with the existing DNA probes, but more are being developed and Woo predicts that percentage will decrease rapidly in the future. The test may also benefit siblings of PKU children who wish to know if they are carriers themselves and people who are found to be carriers and wish to know if a developing fetus has the disease. As for the general population, the exact genetic mutations that cause PKU are not yet known and general screening procedures will not be available until they are. (Source: Science News, Vol. 124, 26 November 1983)

The nature of malignancy

The tumour marker carcinoembryonic antigen (CEA) is a more complex molecule than originally thought, according to the University of Stockholm. The molecule may shed new light on cell differentiation, gene expression and the nature of malignancy. New CEA tests using monoclonal antibodies may produce fewer false positives. CEA doubling time reflects the doubling time of the tumour, and can be used to calculate expected survival in cancer patients. Presence of the compound can allow surgery for metastases too small to appear on scans. A test using two monoclonal antibodies, each binding exclusively to a different antigenic site on the CEA molecule, will give significantly fewer false positives than any of the assays now available. Different types of CEA may be produced by different organs, although much more research is needed. This may allow determination of specific cancer sites before the tumours can otherwise be detected. (Source: Medical World, 14 November 1983)

Space shuttle experiments may lead to permanent orbiting plant

McDonnell Douglas will research biological purification techniques on space shuttle flights, which could lead to new diabetes treatments. The joint research with Washington University's School of Medicine will focus on separating insulin-producing beta cells from pancreatic tissue. The Electrophoresis Operations in Space project resulted in an electrophoresis device that separates materials in a solution by subjecting them to an electric field. Experiments in space will determine how well continuous flow electrophoresis can separate beta cells from other pancreatic cells. In the zero gravity of space, it is possible to separate 700 times more materials and to achieve purity levels four times those of similar operations at normal gravity. The EOS has successfully tested three times and three more tests are planned by the end of 1984, with a larger production prototype. If commercial operation in space proves practical, McDonnell Douglas hopes to begin operating an orbiting plant by the late 1980s. (Source: Machine Design, 8 September 1983)

Monoclonals to treat asthma

DuPont's new clinical test may be the first major commerical use of monoclonal antibodies in health care. The test is used with DuPont's Aca discrete clinical analyser to monitor the level of theophylline (used to relax bronchi muscles), in blood serum of patients being treated for acute or chronic asthma, since dosage adjustment is critical in such treatment. As theophylline is similar in chemical structure to caffeine, a polyclonal antibody test of a patient's blood serum would register theophylline and some caffeine from coffee, tea or soft drinks. DuPont has also introduced test packs to monitor antithrombin III, plasminogen and fibrinogen, which are all important in blood clotting, and the most widely used aminoglycoside antibiotic. (Source: Du Pont News Release, November 1983)

Hepatitis A vaccine tested

Merck is clinically testing its new hepatitis A vaccine. The new vaccine is conventionally made from 'live' but weakened hepatitis A viruses. Merck also has begun human trials of a genetically engineered hepatitis B vaccine and has tested a new chicken-pox vaccine on almost 1,000 children with good results. (Source: Wall Street Journal, 31 October 1983)

Cancer detecting kits

Centocor will seek approval for kits to detect cancer using monoclonal antibodies. The kits detect ovarian cancer and tumours of the stomach and intestine earlier than ever before. Tumours often develop to a large size without causing noticeable pain, and metastases are especially difficult to detect. Researchers at Dana Farber Cancer Institute and Brigham Women's Hospital have discovered that ovarian cancers shed the protein CA 125 into the blood. Antibodies lock onto antigens on foreign cell surfaces and send chemical distress signals to trigger other cells to attack the invader.

The monoclonal assay test developed by Centocor consists of polystyrene beads coated with monoclonal antibodies against CA 125. A second, radioactively labelled monoclonal antibody is then added to bind to the antigen. The beads are then placed in a gamma counter. If the antibody on the bead has picked up CA 125, the radioactive antibody will also bind to the antigen bound to the bead, resulting in a high radiation count. The kit

has a low rate of false positives, but can detect only 80 per cent of those women who actually have ovarian cancer. The kits are available in Italy, Federal Republic of Germany and Spain, and Centocor hopes to have US and Japanese approval in 1984. (Source: New Scientist, 10 November 1983)

Biogen and Japanese group join in research for anti-inflammatory agent

The international biotechnology company Biogen and the Japanese group Yamanouchi Pharmaceutical announced an agreement for development of a new anti-inflammatory agent which could improve treatment of arthritis, asthma, and dermatitis, among other disorders. Under this agreement Biogen will be in charge of purification and large-scale production of the product, while Yamanouchi will perform the preclinical and clinical tests and obtain the exclusive marketing rights in Japan, Taiwan, and South Korea under a Biogen license. Biogen will receive research funds from Yamanouchi and eventually participate in the sales profits.

This new anti-inflammatory agent, intended for an estimated market of $3 billion per year, is a protein that would be the mediator (or the next element in the biochemical sequence) of the anti-inflammatory action of steroids. (Extracted from Chimie Actualites, 5 December 1983)

Leprosy vaccine

Wellcome (UK) has begun clinical trials in Norway on a leprosy vaccine developed by the National Institute of Medical Research (UK). Trials in the UK and US will begin shortly and field trials, possibly in South India and Malawi, could start in 1985. The three countries chosen for early trials have differing incidence of BCG vaccination: Norway almost 100 per cent; UK 50 per cent; and non-routinely in the US. There may be some interaction between BCG vaccination and the leprosy vaccine, which is produced from inactivated M. leprae harvested from 9-banded armadillos. Identification of the M. leprae- specific antigens would allow production by genetic engineering. Early studies in Venezuela found concurrent administration of the leprosy vaccine and BCG vaccine cause regression in patients with advanced stages of lepromatous leprosy. This effect did not occur when either vaccine was used alone. (Source: SCRIP, 19 October 1983)

New serum assay

A new serum assay may assess the response of epithelial cancer of the ovary to treatment, according to R. C. Bast Jr. of Harvard University, and scientists at Centocor (Malvern, PA). Test results could indicate drug therapy failure. Serum levels of the targeted tumour antigen correlated with disease progression or regression, when using a monoclonal antibody. The assay could also enable earlier diagnosis of ovarian cancer, which in early stages is asymptomatic. The assay has high false-negative and false-positive rates, which may limit its usefulness. The assay detected antigen levels above 35 U/mL in 82.2 per cent of serum samples from 101 ovarian cancer patients. Elevated antigen levels were also found in 29 per cent of patients with nongynecologic cancers, including carcinomas of the pancreas, stomach, colon and breast. Serum from 6 per cent of patients with nonmalignant disorders and from 1 per cent of normal donors also contained high levels. Some tumours as large as 1 cm were missed by the assay, although rising levels and subsequent tests always indicated progressive cancer. The assay could also be used for scanning for occult metastases. (Source: Medical World, 28 November 1983)

Therapeutic monoclonals

The company of Hoffmann LaRoche, Inc. will carry out late-stage clinical testing and marketing of monoclonal antibodies developed by Centocor, Inc., of Malvern, Pa., to treat gram-negative septicemia and colorectal cancer. The firm produces radioisotope-tagged monoclonals to diagnose cancer, and has licensed US rights to Roche, for human trials only. Centocor is now developing therapeutic applications of the high-specificity antibodies hitched to radioactive iodine, indium and technetium aimed at colorectal cancer. Centocor, Inc. is studying the use of monoclonals against an antigen common to six types of bacteria that cause septicemia. Such acute systemic infections frequently follow burn injury, cancer surgery, and other trauma, accounting for the deaths of some 59,000 hospitalized patients each year in the US alone. The antibody was administered against an antigenic fragment in the bacterial coat to mice which delayed their death from burn-triggered septicemia "significantly".

Centocor is also clinically evaluating a new monoclonal diagnostic to monitor heart attacks. At the Massachusetts General Hospital in Boston, 30 patients were tested with the antibody which assesses the extent of permanent myocardial damage shortly after a heart attack. By picking up the presence of myosin - contractile muscle fibres - in the victim's blood, the test distinguishes whether the heart muscle is dead or merely wounded. This enables doctors to decide whether a patient is still at risk from infarction, and to prescribe appropriate treatment much earlier.

Centocor already sells two cancer diagnostic kits based on monoclonal antibodies in Europe through agreements with France's Atomic Energy Commission in Paris and Sorin Biomedia, a subsidiary of the Italian automobile maker, Fiat. One kit detects ovarian cancer, the other, gastrointestinal. The tests are approved for sale in the US and Japan for clinical research only. The two new kits detect ovarian cancers and tumours of the stomach and intestine at an earlier stage than ever before which should help doctors to follow a patient's progress after surgery and drug therapy. (Extracted from McGraw Hill's Biotechnology Newswatch, 7 November 1983, 19 December 1983 and New Scientist, 10 November 1983)

US company invests in Israeli growth hormones

American Cyanamid Co. has entered into contract with BioTechnology General Corp. (BTG) of New York, and Rehovot, Israel, for R&D on bovine, chicken and porcine growth hormones, including exclusive worldwide rights, under royalty, to manufacture and market BTG's animal growth hormones.

Using a proprietary vector system, BTG has developed an Escherichia coli host that expresses up to 25 per cent of its protein as bovine growth hormone (BGH). Cyanamid will start with this, for research and animal testing, using a recombinant-DNA hormone produced at BTG's pilot plant in Kyriat Weizmann, Israel. (Extracted from McGraw Hill's Biotechnology Newswatch, 19 December 1983)

Firms test herpes products

Two companies will conduct clinical tests on products that may have promise in treating genital herpes. Alcide (Westport, Conn.) began testing its Alcide-based gel for treating the viral disease. Alcide is now testing the product, which also has potential uses in health care, agriculture and industry, in the Federal Republic of Germany and has applied for testing approval in the United Kingdom.

Meanwhile, United Guardian (Smithtown, NY) says that within a few months it will ask the Food and Drug Administration to allow it to test its Clorpactin WCS-90, which the company has sold as a topical antimicrobial for several years. Tests on that drug's use against herpes are now being conducted in Japan by Maruishi. (Source: Chemical Week, 21 December 1983)

New method for purifying blood products from virus infections

A new method for purifying blood products from virus infections has been developed in Sweden by KabiVitrum. Based on binding virus particles to a special gel during drug manufacture, it is claimed to substantially reduce the risk of transmitting the hepatitis virus in the treatment of haemophiliacs, for example.

The method has already been applied in connection with the production of Preconativ, KabiVitrum's factor IX drug which is used to alleviate the effects of haemophilia. Clinical studies in Malmö and Milan indicate that Preconativ purified in this manner does not transmit virus infections. Large amounts of hepatitis virus were removed and it is probable that the method can even be used for purifying other virus types. In the studies, none of the patients showed any sign of virus illness after being treated with purified Preconativ. (Source: SIP, January 1984)

Trials for TPA and gamma interferon

Boehringer Ingelheim International, GmbH, of Ingelheim, Federal Republic of Germany, will buy bulk human tissue plasminogen activator (TPA), a blood-clot-dissolving agent from Genentech, Inc. of USA. Boehringer will handle regulatory approval and marketing of TPA in

Europe, Australasia, the Middle East, Africa, and South America. In the US, Genentech is preparing clinical protocols for Food and Drug Administration permission to conduct the first human trials of recombinant-DNA-produced TPA.

The company is also supplying interferon for the first US clinical trials of r-DNA-produced gamma interferon. These began on 19 December with one patient at M.D. Anderson Hospital and Tumor Institute of the University of Texas, Houston, and will soon start at the National Cancer Institute, Frederick, Md. Following regulatory approval, Genentech plans to market the interferon in the US under its own label.

Meanwhile, Biogen NV, Geneva, Switzerland, together with Shionogi Pharmaceuticals Co. Ltd., Osaka, Japan, began European and Japanese r-DNA gamma interferon clinical trials last September and is now treating about 40 patients. (Extracted from McGraw-Hill's Biotechnology Newswatch, 2 January 1984)

Theophylline monoclonal assay kits

Another monoclonal-antibody-based serum theophylline drug monitoring assay entered the market last November. Theophylline - an alkaloid found in tea - is widely used in treatment of asthma. Because of its toxicity, serum levels of the drug must be continuously monitored. Existing polyclonal-antibody assays cannot distinguish between theophylline and caffeine or their metabolites.

DuPont de Nemours is making use of a ready-made customer base - the 4,000 users of the company's automatic clinical analyzer (ACA), a computer-controlled system that can perform some 50 colorimetric and turbidometric clinical assays. In this assay, serum theophylline competes for monoclonal antibody with a particle-bound theophylline analog, thus reducing antibody-particle cross-linking. The rate of particle formation, as measured by forward light-scattering, is inversely proportional to serum-drug concentration. Each test costs about $3.00 and takes seven minutes to run.

Beckman Instruments Inc. takes only 80 seconds and costs $1.00 to $2.50 per assay. Their assay, like DuPont's, is tied to its proprietary detection equipment, the semi-automated ICS III or the automated Auto-ICS system. The Beckman test is also an indirect inhibition immunoassay, using a particle-based detection system, but the company's equipment meaures backscatter rather than forward scatter.

Meanwhile, the Ames/Miles Laboratories use a different detection system - a substrate-labelled fluorescent immunoassay - in its monoclonal-antibody theophylline kit, which takes 25 seconds to run and costs $1.50 to $1.20 per test. In addition to tailoring the kit for use in its own automated devices, Ames is marketing kits that can be adapted for use in other automated and semiautomated clinical testing devices and manual assay methods. (Extracted from McGraw-Hill's Biotechnology Newswatch, 2 January 1984)

First human trials of cloned cholera vaccine

Recently ten healthy men and women swallowed one million virulent cholera bacteria each. The Vibrio cholerae cells they ingested were of the El Tor Inaba strain affecting people in rural areas and urban slums of Asia, Africa and Latin America. Only one of the 10 contracted cholera.

One month earlier the volunteers at the University of Maryland School of Medicine Centre for Vaccine Development ingested an oral vaccine of genetically engineered V. cholerae that had had its gene coding for cholera toxin cut out by recombinant-DNA technology. Seven out of eight control subjects who took part in the test did not receive this experimental vaccine, and contracted fullblown cases of cholera. If the human trials still in progress go well, it is hoped later this year to start full-scale field tests in one of the many Third World countries where cholera has flared up again since the 1960s as a pandemic scourge.

The Swiss Serum and Vaccine Institute, a private company in Berne, Switzerland, is standing by to manufacture the genetically-altered oral vaccine on a large scale and at moderate cost.

There are still some bugs in the new recombinant vaccine; even if it immunizes a person against cholera, it can still cause varying degrees of mild diarrhea - depending on how big a dose of the organisms a volunteer drinks. There are other unknown factors in the vibrios that provoke diarrhea, even after the cholera-toxin gene has been deleted from the genome.

Dr. James W. Kaper, chief of bacterial genetics at the Center, prepared the vaccine as follows:

- First he cloned in Escherichia coli the 1200-base-pair gene sequence coding for the cholera toxin in the infectious vibrio. This protein consists of six subunits: a single enzymatically active "A", which stimulates cells in the mucosa lining the small intestine to excrete water from the body, and five benign identical "B" subunits that merely bind the toxin molecule to receptors on the cell membrane.

- Then Kaper and his team mapped the gene sequences coding for the A and B subunits, and by DNA-sequencing, determined that the former contains 250 amino acids, and each of the latter subunits, 103.

- Using restriction enzymes, in vitro, they snipped out both toxin-subunit structural gene sequences from the vibrio chromosomal DNA and replaced them with a gene for bacterial resistance to mercury, flanked on both sides by about seven kilobases of vibrio DNA.

- Finally, by plasmid conjugation, they transferred this recombinant-DNA construction into a culture of toxin-positive El Tor Inaba V. cholerae. As these replicated, and their DNA unwound, a single strand containing the native toxin gene occasionally crossed over and combined with the plasmid DNA carrying the homologous flanking sequences on either side of the mercury-resistance gene. This one-in-a-million event produced a toxin-negative mutant that Kaper was able to pinpoint and recover by marker rescue - introducing a second incompatible plasmid.

The mutant strain of V. cholerae, lacking a gene to synthesize cholera toxin, serves as their non-infectious but still immunogenic vaccine. This precise recombinant-DNA method of attenuation avoids compromising any other useful antigens in the cell that may be involved in immunity.

Meanwhile, he is trying to eliminate the diarrheal side-effects by scaling down the dosage. Some 40 volunteers are now swallowing 1,000 to 10,000 mutant vibrios rather than a million, to see what minimum will still colonize the gut and generate an immune response without causing dehydration. (Extracted from McGraw-Hill's Biotechnology Newswatch, 16 January 1984)

Osteoporosis treatment

A synthetic form of the kidney hormone, calcitriol, may be effective in treatment of osteoporosis, according to J. Gallagher of Creighton University, L. Riggs of the Mayo Clinic and H. DeLuca of the University of Wisconsin (Madison). Calcitriol can reduce the number of spinal bone fractures in osteoporosis patients which affects 15 million persons, mostly older females. Patients receiving calcitriol had a 50-75 per cent reduction in spinal fractures after one year. Hoffmann-LaRoche will ask for FDA approval for the use of calcitriol in treatment of osteoporosis. (Source: Science News, 10 December 1983)

Interleukin-2 planned for clinical trials

Cellular Products Inc. will file with the US Food and Drug Administration a "Drug Master File" for the production of Interleukin-2 (T-Cell Growth Factor). This will allow clinical investigators to file Investigational New Drug Applications (INDs) for the use of Cellular Products Inc.'s Interleukin-2 in various human clinical trials that involve human immune deficiency disorders and certain types of cancer.

According to Dr. Richard Montagna, President, "Because Cellular Products can produce much larger quantities of natural Interleukin-2 from human blood than its competitors, clinical investigations of Interleukin-2 are possible on a far greater scale. At present, the company supplies approximately 75 per cent of all Interleukin-2 used by the scientific

research community, and through advanced technology the company will now supply large amounts for human clinical trials." (Source: Cellular Products Inc. News Release, January 1984)

Test procedure to assist in AIDS diagnosis and other immunodeficiencies

Cellular Products Inc. has reached a license agreement with the Research Foundation of the State University of New York whereby the company will utilize a test procedure which detects the presence of serum antibodies against membrane anitgens of Human T-Cell Leukemia Virus (HTLV)-transformed cells.

"We believe that this test procedure is the most specific test available for the detection of antibodies against HTLV-induced membrane antigens," said Dr. Montagna of Cellular Products. "High concentrations of these antibodies have been detected in the sera of approximately 60 per cent of tested Acquired Immune Deficiency Syndrome (AIDS) patients," he explained. "and it is expected that this test procedure will assist physicians in the study and diagnosis of AIDS."

The licensed test procedure is based upon information developed by Doctors Bernard Poiesz and Russel Tomar of the Upstate Medical Center, Syracuse, New York. (Source: Cellular Products Inc. News Release, January 1984)

Commerical clinical applications studied

In a joint collaboration between Howard Ozer, M.D., Ph. D., and Northern Clinical Diagnostics (the clinical testing division of Cellular Products), the adaptation of research methodology for commerical clinical applications will be explored. This project has been funded by the New York State Science and Technology Foundation, a private non-profit organization that funds projects which demonstrate potential for near-term industrial application by New York State companies.

This project specifically targets the commercial application of monoclonal antibodies for diagnosis and therapy in leukemia, lymphoma and AIDS, and will take place over one year. Northern Clinical Diagnostics will use a flow cytometer, an automated high technology piece of equipment essential for accurate objective interpretations of these tests. Source: Cellular Products Inc. News Release, January 1984)

Diagnostic method to detect AIDS

The Swedish biotechnology company Pharmacia has developed a method for detecting AIDS. The test, which was originally designed as a diagnostic for kidney diseases, measures levels of beta-2-microglobulin in the blood and it has also been used as a cancer diagnostic.

The method was tested on AIDS victims in the US and it is hoped it will prove useful in determining at what stage the disease becomes contagious. It could also be used to screen samples of donated blood before transfusion.

The diagnostic detects elevated levels of beta-2-microglobulin in the blood - a condition which accompanies AIDS. The test must be repeated over a period of time to differentiate between AIDS and other diseases. AIDS causes a constant increase in levels of the substance in the blood.

The UK company Boots-Celltech Diagnostics is also currently developing its alpha-interferon assay as an AIDS diagnostic. The test, which is being evaluated in both the US and the UK, works by measuring serum alpha-interferon levels. It was found last year that AIDS patients have increased amounts of the protein in their blood.

The Swedish firm, KabiVitrum, has come up with a new method for the removal of virus particles from human blood and claims that the method could substantially cut down the risk of infectious viral diseases, such as hepatitis B, being transmitted by blood products such as clotting factors for haemophiliacs and blood transfusion.

The purification process, which uses a special gel to bind viral particles, has already been used by KabiVitrum in the production of its factor IX blood clotting factor, Preconativ, which is used to treat haemophilia. The company says that the method can also

be used to remove other types of harmful viruses from blood. (Extracted from European Chemical News, 6 February 1984)

Genetic engineering for nerve-gas antidote

A senior officer at the US Army's chemical defence establishment in Ford Derrick, Maryland, has revealed details of how biotechnology is being harnessed to devise better antidotes to nerve gas. $1.3 million has been spent on five contracts to clone the gene for the enzyme acetylcholinesterase (ACH) in bacteria, in order to make vast quantities of the protein. ACH is one of the most important enzymes in the brain. It is involved in the transmission of nerve impulses, whose action is blocked by nerve gas. The idea of the research is to insert the ACH gene into a simple bacterium such as E. coli which would then manufacture the protein along with its own. Such bacteria could then easily be grown to make vast quantities of the protein. The army's scientists could, by chemical analysis, X-ray crystallography or computer modelling determine precisely how the nerve gas interacts with the active parts of the enzyme to prevent its action - and so design better drugs to counteract the hazard to troops. Eventually it may be possible to construct a vaccine against nerve gas.

Of the five contracts for the work, three were placed within the United States, one with Invarest in Scotland, and a fifth in Israel. Altogether the US Army spends $90 million a year on vaccines and chemical antidotes, including basic research on pharmacology. About 70 per cent of that budget is directed towards nerve-gas research. (Source: New Scientist, 1 March 1984)

Vitamin B12 production

Nippon Oil of Japan has developed a process for the production of vitamin B12. Deficiencies of the vitamin often occur amongst vegetarians and can cause pernicious anaemia. The Nippon Oil process is based on the fermentation of a ray fungus on a fructose feedstock, followed by chromatographic purification. The company now intends to look into the economic feasibility of scaling-up the process. Japan is estimated to import about one ton of the vitamin each year. (Source: European Chemical News, 6.2.84)

Diagnostic

Japan's Sekisui Chemical is planning to seek approval from the Japanese Ministry of Health and Welfare for the production and marketing of an antibody-based diagnostic, which could prove useful in detecting certain forms of cancer, collagen diseases and rheumatism. The test, based on rabbit antibody, detects the protein, fibronectin, levels of which are often depressed in patients suffering from these diseases. (Source: European Chemical News, 6 February 1984)

Livestock applications

Search for sheep that shears itself

Australian scientists believe that within five years, using genetic engineering techniques, it might be possible to insert new genes into sheep that could result in an animal which would "shear itself" when fed a chemical. Researchers at the federal Government's Commonwealth Scientific and Industrial Research Organization (CSIRO) also think that it might be possible to use genes to make sheep produce more or finer wool.

Dr. Merilyn Sleigh, of the CSIRO's molecular and cellular biology unit, said that the genes could enable scientists to breed sheep growing more wool for every blade of grass consumed. The genes could come from Angora goats or even camels. Scientists are considering sheep breeds which periodically shed their coats as a source of genetic material. They would introduce the genes responsible for the shedding into Merino sheep and then develop a system for harvesting the fallen fleeces. The drawback with the plan at the moment is that the breeds which do shed their fleece do so rather patchily and not all at once. To synchronize the sheep in a flock so that they all drop their fleeces at the same time would probably require the administering of a chemical to trigger the de-fleecing genes. The sheep would probably have to be put through a combing or vacuum process to remove the wool. (Source: The Times, 7 September 1983)

Salmon-cloning

Japanese scientists have turned an abandoned British technique for cloning salmon into what could be a commercial money-spinner. Current methods of stocking salmon are wasteful. Males and females are produced in equal numbers yet for breeding one male is sufficient to fertilize the eggs of 30 to 40 females. Moreover, the flesh of the male salmon becomes unpalatable during the mating season so when caught such fish can only be used as animal feed. Salmon are ideal for cloning. They produce vast quantities of large, easy-to-handle eggs which are fertilized outside the body. The cloning technique hinges on two processes: the destruction of the sex-determining chromosomes of either the sperm or the egg, and the inhibition of the production of the polar body. This is the mechanism that the cell nucleus uses to get rid of its unwanted extra set of chromosomes, which then becomes the sex determinant for the fertilized egg. To produce female fish, Professor Onosato of Hokkaido University's Faculty of Fisheries brought together untreated eggs and sperm that had been exposed to gamma rays, which destroy the male genes. The sperm still stimulate the eggs to complete division, and so allow fertilization to occur. The egg-culture fluid was treated with a pressure of 700 atmospheres for several minutes to prevent the production of polar bodies. British researchers who pioneered this work at the Ministry of Agriculture, Fisheries and Food's fisheries laboratory in Lowestoft used low temperatures rather than high pressure to achieve the same end. The Japanese claim their method is more efficient, producing 60 per cent hatch rate within 69 days; all fry were females, 90 per cent of them identical to the mother from whom they had received all their chromosomes.

The production of males is more difficult. The sperm is left untreated and the egg is irradiated to destroy its genes. Fertilization is allowed to take place, then high pressures and temperatures are used to prevent normal division, so that the nucleus does not divide but the number of chromosomes doubles.

Since sperms have both X- and Y-chromosomes, the resultant offspring are half "normal" XX females and half "super" YY males. The mating of normal eggs with super-male sperm results in all XY-male offspring. However the male hatching rate of super-males is very low - only about 50 to 60 per 10,000, so Onosato has tried changing the sex of female fish. Immediately after birth, female fry are immersed in a solution of male hormone. Eighty per cent become able to function as males while still being chromosomally female. Other Japanese scientists have been applying Onosato's methods to breeding mice with some success. In theory the procedure can be applied to any animal whose eggs can be fertilized externally. (Source: New Scientist, 3 November 1983)

Monoclonal antibodies in livestock disease prevention

Molecular genetics' genetically engineered monoclonal antibody for livestock disease prevention has FDA approval, and will be marketed in the US in 1984. Since its approval last year, Genecol 99 has been used successfully by dairy and beef producers in Canada to reduce calf fatalities from diarrhoea. Over one million calves per year die from all types of scours, a particular problem in cold, wet weather and wherever other adverse conditions, such as crowding, stress or contamination, exist. Genecol 99 prevents the infection before losses can occur by preventing E. coli from adhering to the intestinal wall. (Source: Chemical Marketing Report, 14 November 1983)

Agricultural applications

Joint effort to develop new canna strain

Mitsui Enterprise Research Center, has provided capital for a project on the breeding of triploid of canna in co-operation with the New York Botanical Garden. The research fund together with other funds will be invested in the New York Botanical Garden through the Japanese Overseas Agricultural Development Association.

The triploid of canna which is the subject of breeding was obtained by crossing a diploid Canna indica for appreciation with an edible tetraploid Canna coccinea which also has medicinal value. The underground tuber of the new breed is bigger and the plant is more resistant to damage by blight and insects. The starch contained in the tuber is edible and can also be used in making alcohol. The results of a field test indicated a yield of 40-60 tons per hectare. Its advantages compared with cassava, which is widely grown today in South-East Asia, include: (1) it can grow in weak light, so can be grown as

undergrowth on rubber or coconut plantations without the need for deforestation; (2) its leaves cover the ground and thus help prevent soil erosion; and (3) it can sustain continuous cropping. The origin of C. coccinea is in the South American Andes and 15 strains were discovered during the last expedition. Creation of even more superior triploids is highly probable through crossbreeding C. indica with these strains collected at their place of origin. Concrete research plans include collection of the original strains of canna in the Andes during the first year, and creation of triploids by crossbreeding during the second and third years. To be able to confirm whether a triploid has been created, a research staff capable of performing chromosome examination will be necessary. The cost of travel and living expenses of the researchers in South America will be shared by the Japanese, and the National University of Taiwan. The cultivation test of the new breed of canna thus created will be undertaken by the National University of Taiwan. (Extracted from Tokyo Nikkei Biotechnology, 4 July 1983)

Peanut shells as cattle feed

Peanut shells may be digestible enough to be used as cattle feed. The shells have potential as animal feed since they are 70 per cent cellulose. Unfortunately, the other 30 per cent is lignin, which is indigestible in itself and also prevents digestion of cellulose. The shells can be rendered digestible by a nitric acid-bacteria-yeast process. The process may convert shells to cattle feed at $60/ton. The research may also find an industrial use for lignin and the bacteria which break down the shells for feed which may also be useful to treat other sorts of biowastes. (Source: The Economist, 16 September 1933)

Biological herbicide

Plant pathologists at the Coastal Plains Experiment Station in Tifton, Ga. have found a way to fight yellow nutsedge naturally by harnessing its enemy, the rust fungus Puccinia canaliculata. When the rust normally appears in August, this nutsedge - one of the few plants that serves as its natural host - usually takes hold of an agricultural plot causing serious havoc on that season's crop. Not only does the weed smother young plants and damage roots and tubers, but it also robs crops of nutrients, water and carbon dioxide. Propagated by tubers, the weed has remained amazingly resistant to herbicides and conventional pest-control strategies.

By inducing a rust epidemic early in the season, and, if necessary, continued throughout the growing season, may make this fungus an ideal nutsedge-control agent, as it has no appetite for any commerical crop grown in the United States. Since the rust has no known winter host in the USA, it is not naturally occurring in spring therefore spores had to be collected and frozen over winter, then carefully thawed before spring field inoculation. Mixed with water and flocculants, they can be sprayed on vulnerable nutsedge sprouts in April - before they have strangled crops. Although the rust will not kill all of its host, the latter become sufficiently weakened to make herbicide treatment highly effective. The major problem is how to mass-harvest rust fungus spores. (Extracted from Science News, Vol. 124, 26 November 1983)

Venture group invests in plant tissue-culture firm

Twyford Plant Laboratories Ltd. of Glastonbury (UK) which is known for its production of ornamental plants and flowers by tissue culture, with yearly sales of over £1 million, plans to exploit genetic engineering and other advanced breeding technologies to expand into vegetables, field crops and forest products.

With a new infusion of capital from a consortium of British and American venture capitalists, Twyford's three-year expansion plan will involve doubling production capacity to make it the largest plant tissue-culture centre in the world, set up a new production facility in California at a site yet to be selected, and double the firm's research budget to exceed £500,000 annually. The funds will be mainly devoted to applying cellular biology and micropropagation with an eye to automating production. It will also provide capital for joint ventures with companies in the Middle and Far East to open new markets for date and oil palms.

The company's date-palm-cloning technique achieves somatice embryogenesis using meristem as the starting tissue. (Extracted from McGraw-Hill's Biotechnology Newswatch, 2 January 1984)

Refuse derived compost

Refuse derived compost increases vineyard yields while also reducing urban wastes. Regulations on compost from refuse require a minimum of four days at 60° C fermentation to make the compost sanitary, a nitrogen content lower than 2 per cent, and a particle size under 40 mm. According to J.P. Levasseur, OTV, the product intended for farming must be properly matured, refined and attractive enough in appearance to suit consumer demands. OTV and its English associate, pulverizer manufacturer Tollemache, have specialized in the design and construction of compost treatment plants to achieve these characteristics. A key element of the OTV system is the Siloda biological treatment unit in which a giant paddlewheel automatically turns pulverized refuse to stimulate fermentation. These horizontal silos contain troughs of the refuse material over which the paddle moves. During fermentation, the temperature of the refuse must increase from 20° C to 70° C before falling progressively as maturation proceeds. (Source: World Waste, November 1983)

Research into sea water tolerant plants

Research to identify crop plants that will tolerate irrigation by sea water is being conducted by Ben Gurion University (Beersheba, Israel) scientists at an experiment station near Ashkelon. Irrigation water has traditionally been pure in spite of the fact that arid zones exist near the sea. Cotton, melons and vegetables have been grown in the Negev, irrigated by brackish water with a salt content of 3,000-4,000 ppm. Success in finding crop plants that could tolerate sea water with a salt content of 30,000 ppm could start another worldwide "green revolution" and also be of benefit to northern hemisphere developed countries. (Source: Innovation, November 1983)

Paddy ripening compound

Sankyo has introduced Tachigaren 30 per cent Liquid to promote ripening of paddy field rice in cold weather. The chemical aids ripening of rice in the 43-50 days before maturing. The compound promotes flow of carbohydrates in the leaves to the heads, increasing the yield and thickness of the grain. (Source: Japan Chemicals, 24 November 1983)

Sungene field-tests tissue-cultured corn plants

Sungene Technologies Corp., located at Palo Alto, California, are engaged in the first large-scale field trials of a genetically improved commercial corn derived from cell culture. Sungene has a proprietary technique and culture medium for regenerating embryonic corn plants from callus tissue. Sometimes beneficial somaclonal variations arise spontaneously in the plants regenerated from the inbred lines, the parents of the hybrid lines. Preliminary observations suggest that these features - altered leaf shape, early flowering, greener, taller or more vigorous plants - appear to be controlled by a single gene, and therefore can be more readily incorporated into new varieties. These somaclonal variations are apparently sufficiently uniform to obviate the necessity of going back and self for many generations with the original inbred line. Flowering is earlier, making it possible to plant in areas with a shorter growing season.

Last summer the firm planted three acres of corn seed in California derived from somatic-embryo plantlets raised in the greenhouse. The seed from that first generation of field-grown plants is now growing in Hawaii, and the seed from that crop will be tested on some 30 acres back on the mainland this summer. (Extracted from McGraw-Hill's Biotechnology Newswatch, 16 January 1984)

Cheaper fertilizers

Israeli engineer Moshe Alamaro is seeking $400,000 from American venture capital companies to fund a study which may lead to cheaper fertilizers for developing countries. He belives that an old nitrogen-fixing process, called the Birkeland and Eyde (B&E) process, can be updated to produce more efficient yields of fertilizer. He advocates a mobile production plant powered by hydroelectricity generated in the remote rural areas of developing countries. Because the process does not have to run continuously, it can use electricity at times of low demand from villages.

In the B&E process an electric arc is passed through air to produce nitric oxide which is then oxidized and reacted with water to produce nitric acid. Raw materials, such as

phosphate rock or limestone, are needed next to react with nitric acid to form the nitrates used as fertilizers.

Many developing countries do not have phosphate stone and limestone resources of sufficiently high quality for export, but they do have low-grade reserves which could be developed for use in the B&E process.

Raw materials and cheap electricity contribute to the economic case for the B&E process, but Alamaro believes there is also a good technical case. (Source: New Scientist, 19 January 1984)

Cold region crops

To produce crops tailored to the rigorous climate of the Canadian Prairies, the University of Manitoba programme is relying on improvements from traditional plant breeding techniques and agronomic practices. Recently, there has been a good deal of publicity about the application of the new techniques of genetic engineering to crop improvement. It has been reported that scientists will soon be able to combine genes from unrelated species to produce self-fertilizing and disease-, insect-, and cold-resistant "superplants". However, scientists actually involved in this research are far less sanguine. Most experts agree that conventional agricultural research holds the best promise of achieving practical results within the foreseeable future. Selective plant breeding is certainly not new. By about 5000 years ago, our ancestors had domesticated all the major cereals, grain legumes, and root crops that remain our principal sources of food to this day. The foundations of modern scientific plant breeding, however, were laid in the 19th century. The major contributor was Gregor Mendel, the Austrian monk who died 100 years ago. Mendel's interest in plant breeding was aroused by experiences on his father's orchard and farm. His experiments on sweet pea plants led to his discovery of the laws of heredity and gave birth to the modern science of genetics. In the past few decades crop yields have increased spectacularly, due largely to the pioneering work of plant breeders in the early part of this century.

The University of Manitoba's programme to improve crop production under Canadian Prairies climate conditions continues the application of this dramatically successful science-based agricultural technology, involving a number of projects, of which the winter wheat and corn breeding aspects described here are only the tip of the iceberg. Cereals are literally the staff of life with well over 50 per cent of world food supplied by these crops. In recent years, wheat has replaced rice as the world's largest cereal crop with production exceeding 400 million tonnes (metric tons) annually. The primary goal of the University of Manitoba's cold crop wheat programme is to make the widespread production of winter wheat possible on the Canadian Prairies. Winter wheat is planted in the autumn, gaining a head start in growth before freezing temperatures set in. It matures and is harvested the following summer. Except for a small area in southern Alberta, however, conditions on the Canadian Prairies are too severe for winter wheat and the spring varieties, which are seeded and harvested in the same season, are grown instead. Winter wheats have a number of advantages over spring varieties. Spring wheat on the Prairies must be grown in a short, 100-day frost-free season and so early maturing varieties are used. Unfortunately, the earlier a wheat matures, the lower its yield. In fact, for every day of growth beyond 100 days, it is estimated that there is about a 1 per cent increase in yield.

The major advantage of winter wheat, then, is that by starting growth in the autumn it effectively extends the growing season and increases yields, averaging as much as 20 to 25 per cent more than current spring wheat yields.

The key problem in growing winter wheat on the Canadian Prairies is winter kill. Temperatures of less than -16° C for five or six consecutive days will destroy tender shoots and roots just below the surface. Such cold conditions are virtually guaranteed to occur during Prairie winters. It has been discovered, however, that snow cover of approximately 12 cm or more will provide adequate insulation to maintain sol temperatures above -16° C and permit the survival of winter wheat. To grow winter wheat on the Canadian Prairies, a sufficient continous snow cover during cold winter months must be assured. While snowfall on the Prairies is adequate overall, drifting and sudden winter thaws leave fields bare long enough for winter kill to occur. The solution to this problem, the University of Manitoba's wheat project has discovered, is the so-called "zero- tillage" system of cultivation.

Zero tillage research, headed by Dr. Elmer Stobbe, has been underway at the University of Manitoba for more than a decade. Conventional cultivation is a three-step process consisting of ploughing, discing, and harrowing. With zero tillage these steps are dispensed with and a farmer only seeds and sprays. Modified seeder equipment cuts a narrow slit for the seed, disturbing only a small portion of the surface of the land.

Zero tillage has both economic and conservation advantages. It cuts fuel consumption and costs, and decreases labour and heavy machinery requirements. Because the land is largely undisturbed and the stubble is left on, wind and water erosion of soil is sharply reduced and moisture loss through evaporation is prevented. Manitoba trials of zero tillage have shown reduced fuel consumption as high as 50 per cent and, in some cases, increased yields.

The principal interest of zero tillage for the winter wheat project, however, is the stubble which is left on the field over the winter. Under zero tillage, winter wheat is planted directly into this stubble in the fall. The project's field trials have demonstrated that upright stubble between 15 and 30 cm tall will serve as a snow trap and provide adequate insulation to ensure the survival of winter wheat during Prairie winters.

The primary goal in winter wheat breeding research is to develop hardy and rust-resistant winter wheat cultivars (cultivated varieties) for use with the zero tillage system of cultivation. Spores of the fungus Puccina graminis, which causes the devastating wheat rust disease, pass the winter in the United States and are blown northward to the eastern Prairies on prevailing spring winds. Because of the direction of these winds, few spores reach the western Prairies, where rust is less of a problem. As a result, winter wheat varieties developed for use in southern Alberta at the Lethbridge Agriculture Canada Research Station have inadequate rust resistance for eastern Prairie use.

The breeding project is concentrating on breeding rust-resistance into hardy winter wheat varieties. The hardiest winter wheats, such as Norstar, developed at the Lethbridge Alberta lab, have been crossed with rust-resistant spring varieties like Glenlea, currently grown on the Prairies. The offspring, or progeny, of these matings are then backcrossed with the original winter wheat parent over a number of generations in an attempt to restore the parental hardiness while maintaining rust-resistance. Each successive generation is tested for these two essential characteristics.

The third backcross has already been completed and it is hoped to have material ready for comparative field trials by 1985. If all goes well, new varieties of winter wheat suitable for growing on the Canadian Prairies will be in the hands of farmers by 1990. However, breeding research is only part of the "complete production package" the project is developing for winter wheat. The zero tillage system of cultivation and crop management guidelines are equally important.

Given the potential economic advantages of this production package to farmers, the successful completion of the wheat project could radically alter agricultural practices on the Prairies. However, the winter of 1982-1983 provided a sobering lesson. Lack of snowfall left fields bare and much of the experimental winter wheat crop was damaged.

Another project, under Dr. E. Larter, concerns the breeding of cold tolerant, high-yielding varieties of maize suitable for widespread production on the Canadian Prairies. Larter has found that the crucial factor limiting maize production on the Prairies is cold soil temperatures during the early spring. Differences of only 1° C can be highly significant. Most maize varieties will germinate and grow well in soil of 12° C or above. Below 11° C, however, most varieties either fail to germinate or only grow very slowly. With a maximum crop growing season of 120 days under Prairie conditions, this slow early growth results in sharply reduced yields.

Larter's breeding project, then, is aimed at developing varieties which will grow vigorously in cold Prairie spring soils and then mature relatively quickly.

The chief problem facing maize breeders is that unlike wheat, which is a self-pollinating species, maize is a cross-pollinating species. Like most animals, plants are defined by two sets of genetic information, one from each parent; under normal circumstances, these two sets differ widely in their information content - which provides a species with essential variety. Such a configuration is termed "heterozygous" (hetero meaning different). In self-pollinating species, however, the information in these two

"parental" sets eventually converges (they become highly "inbred"), leading to what is called a "homozygous" condition (homo meaning alike). As a result, offspring closely resemble parents, and producing and selecting the best homozygous genotypes is a relatively simple matter. Later, crosses between these homozygous genotypes can be made to combine desirable genes in a single cultivar. This is essentially the procedure Dr. Evans is following in the winter wheat project.

Breeding with cross-pollinating species, however, is far more complicated. Genes are constantly reshuffled from generation to generation leading to a highly heterozygous plant community. Offspring genotypes will not resemble parental ones, and therefore the breeder cannot predict offspring characteristics. To produce homozygous or inbred lines, artificial self-fertilization is required. In maize, the pistillate flowers (female) in the ears must be covered to exclude pollination from other plants. Pollen is collected from the plant's staminate tassel (male) and artificially applied to the pistillate flowers. Repeated application of this process over a number of generations eventually produces inbred or homozygous lines where offspring do resemble parents. This makes it possible to identify and breed varieties with desirable characteristics.

Unfortunately, inbreeding in cross-pollinating species also leads to "inbreeding depression" or reduced vigour in the offspring. However, when plants from two such inbred lines are crossed, the resulting hybrid is likely to exceed in vigour even the progenitors of the original lines - a phenomenon known as "heterosis" or hybrid vigour. Both inbreeding depression and heterosis have long been known and were in fact very clearly described by Charles Darwin in The Origin of the Species.

This knowledge, however, did not receive widespread application to agriculture until the 1940s when hybrid maize produced by crosses between inbred lines was introduced in the United States. The extremely vigorous hybrids have since come to dominate maize production in the developed world where yields have almost tripled in the past 40 years. Given these modern maize breeding methods, Dr. Larter's first step in breeding cold tolerant, high-yielding maize has been to develop a number of cold tolerant inbred lines. Maize was originally domesticated from its wild ancestors in Central America and numerous types of maize are still grown in this area. Larter has acquired maize from Central American highland areas which, his tests confirm, is able to grow under cold climate conditions. The Central American variety is highly heterozygous so Larter inbred it to produce cold tolerant homozygous lines. Currently he has about 250 inbreds to work with and he continues to develop more.

Tests for cold tolerance are carried out in growth chambers where circulating cold water baths keep soil temperatures of the immersed potted plants at a constant 10° C. Plants which perform well at such temperatures, comparable to early spring, are then subjected to field tests.

Since Larter's cold tolerant inbreds are relatively low-yielding, the second step in his breeding programme is to cross these cold tolerant lines with more high-yielding hybrids currently used in commercial maize production. As in the wheat project, Larter is back-crossing progeny of these crosses to the high-yielding varieties to maintain cold tolerance while improving yields. The procedure is now at the first backcross stage and Larter predicts that five backcrosses will be needed to obtain a high-yielding hybrid with cold tolerance. By using growth chambers during the winters, the breeding programme can be compressed to about three years. He expects that the improved varieties could be available for commercial production by 1990, about the same time as the new winter wheats. (Extracted from Science Dimension 1983/5)

Food production and processing applications

Corn process to make artificial sweetener

Waste from French farms is about to make a useful contribution to the food industry in a novel process for making artificial sweeteners. The process depends on corn grits - an agricultural byproduct normally sold as an abrasive for the car industry. But researchers at the National Institute of Applied Sciences in Toulouse have found that grits make a good support for an enzyme system that converts solid sugar into a liquid sweetener as it passes through a column.

The process starts with a slurry of crystalline sucrose extracted by conventional processes from cane or sugar beets. The final product is a highly soluble, concentrated mixture of sucrose and its "invert" sugars, glucose and fructose, with the consistency of honey. This splitting-up of sucrose molecules occurs during the manufacture of sugar and can lead to losses of sugar, but an enzyme called an invertase can control the reaction in the final product as the slurry runs through a column.

Enzyme processes for making liquid sweeteners are legion, but the institute's process is special in several ways. Corn grits are cheap and 30 times more efficient than other column supports such as porous silica. Monsan points out that the equipment can be easily fitted into a sugar factory's process, and it saves energy. It simply takes a slurry of processed sugar one step further; there is no need to dilute it before it passes through the column, or to concentrate it afterwards.

The process also overcomes one other problem. The most common technique for converting sucrose into liquid sugars - treatment with a dilute acid - leaves a coloured product which has to be treated in an ion-exchange column. The enzyme does not discolour the product. Monsan believes that Belgian and West German sugar manufacturers, who still rely on ion-exchange and acid hydrolysis, could be especially attracted to the process for their liquid sweeteners.

Beghinsay, one of France's largest sugar firms is considering building a pilot plant large enough to supply all of the French markets, estimated at several thousand tonnes a year. This depends on how promising the final results from the small pilot plant in Toulouse are. The company also awaits the consumer ministry's official approval of the syrup's use in human food before it will make a final decision. (Source: New Scientist, 27 May 1983)

Improving the flavour of processed cheese

Extracts of microorganisms used in cheese production can be encapsulated in butterfat shells, allowing flavours to diffuse into the cheese, according to N.F. Olson of the University of Wisconsin. The enzymes responsible for gourmet flavours could thus be included in processed cheese. Each capsule could contain the microbial enzymes and raw materials for flavour-producing reactions. The capsules are added to milk and then trapped in the curd when the milk is clotted. So far, four encapsulated extracts have produced a variety of dairy-related flavours. The flavours can be produced at controlled rates to specified, stable levels in foods. If the enzymes were added directly to the foods, uncontrollable side reactions and flavour imbalances can result. Microencapsulation could be used for any food in which intact capsules can be entrapped and dispersed. (Source: Science News, 24 September 1983)

Safety clearance for sweetener

The controversial new artificial sweetener aspartame was given fresh safety clearance by a government advisory committee on food safety. The UK Committee on Toxicity had reviewed data from the United States suggesting that the sweetener might pose a risk to symptomless carriers of the metabolic disorder PKU, which can lead to severe mental retardation. The committee said it was completely satisfied that the use of aspartame is safe for such people, and in particular that the consumption of aspartame by pregnant women who are symptomless carriers of phenylketonuria (PKU) cannot cause any harm to the developing foetus. The sweetener was launched by Searle in tablet and sachet form and is expected to be used as a sweetener in food and soft drinks, particularly diet foods. (Source: The Times, 6 October 1983)

Ethanol from rice process

An ethanol-from-rice straw process has been developed by the Biochemical Engineering Research Centre. The process also yields fodder protein and lignin. The process is the result of 10 years of research. (Source: European Chemical News, 24 October 1983)

Single cell protein

Throughout the world, makers of single-cell protein (SCP) - a business based on the use of such microbial sources as bacteria, yeast or fungi to produce the nutrient from low-grade hydrocarbon feeds - are trying new survival strategies. Two basic approaches predominate: the sale of SCP technology to countries that are either rich in low-cost hydrocarbon feeds, or deficient in hard currency for purchasing natural protein; and the sale of SCP in markets in which soy protein is not a competitor - e.g. food additives for human consumption.

Such tactics, if successful, could possibly reverse SCP's ill-starred fortunes. The business got a bad start in the late 1960s when the chemical process industries (CPI), thinking that by 1980 a world food shortage would force up natural-protein prices, invested millions in some 100 SCP plants and projects. When it became obvious that this would not happen, plans were dropped and many facilities shut down.

A number of projects also faded in the mid-1970s with the increase in petroleum prices. Others, based on carbohydrates from pulpmill effluent, failed either because the product lacked visual appeal or was unappetizing. Still others succumbed because health authorities, on the basis of presumed toxicity, refused to give approval to SCP for animal or human consumption.

However firms still in the SCP business are optimistic. Optimism reigns at Britain's ICI, for example, based in part on a meeting held late last year between the company's officials and Soviet Deputy Prime Minister Leonid Kostandov. Industry sources believe that the talks could lead to the construction of a 100,000-metric-ton/year SCP plant in the Soviet Union. One possible location for the facility is Skytyvkar, about 200 km northeast of Kotlas, where the USSR is planning a large methanol operation. Another is Tomsk, where there already is a large methanol plant. The proposed SCP unit would require 200,000 m.t/year of methanol feed.

The ICI process is based on the continuous culture of Methylophilus methylotrophus bacterium in methanol. The firm uses a bubble-column loop reactor, also called an airlift fermenter. This was chosen because it can be scaled up to large sizes in a single stream and contains no moving parts. Moreover, the length/diameter ratio and the internal configuration of the vessel can be varied to select an appropriate combination of gasresidence time in the riser, gas holdup and bubble-size population, liquid-circulation velocity, and pressure drop through the heat exchanger.

Hoechst AG of the Federal Republic of Germany also has plans for SCP because the firm believes that this product will not be cost-competitive with soy protein until a pound of methanol feed costs 50 per cent less than an equivalent amount of soybean meal. It has upgraded its animal-feed SCP (70 per cent protein) to a product fit for human consumption (90 per cent protein). The improvement involves a purification process that breaks up bacterial cells in a nonaqueous solution. The lipids are dissolved, and nuclein acids are extracted. The company and its chemical engineering subsidiary Uhde GmbH have a continuous process for making SCP from Methylomonas clara bacteria in methanol enriched with ammonia and phosphorus salts.

Another company, Pure Culture, (USA) had considered making the product for animal feed in the mid-1960s, but a market study it did in 1967 concluded that the protein could not compete with the natural variety, so it has been selling SCP since 1975 to food producers as a flavouring for processed meats. Pure Culture grows Candida utilis yeast continuously in ethanol made from corn or wheat starch that meets US Pharmacopeia standards. Added to ethanol are such yeast nutrients as phosphoric acid, potassium hydroxide and magnesium sulfate. The process is started in a batch mode at a temperature of 90-100° F, then switched to a continuous 1-m.t/hour flowrate when the yeast concentration reaches 3 to 5 per cent. The product is subsequently centrifuged, pasteurized and spray-dried.

Lake States, a division of Rhinelander Paper Co. (Rhinelander, Wis.), made an even earlier progression from animal feed to food additive. Grown in sulfite liquor drawn from its parent company's nearby pulpmill, Lake States' Candida utilis yeast is sold to about 100 food companies as a flavouring for snack foods and soups. The firm claims to be the only one in the US that is successfully producing and selling an approved food-grade product made from pulpmill effluent.

The application of environmental standards to pulpmill effluent has provided the impetus for other firms to enter the SCP business. Among these is Envirocon Ltd. (Vancouver, BC), which sterilizes pulpmill sludge for 1 hour at 121° C. The sludge is cooled to 37° C and fed into an aerated reactor that contains the fungus Chaetomium cellulolyticum, plus nitrogen, phosphorus and potassium nutrients. Present as a suspended solid, the fungus attaches itself to fibres present in the substrate and secretes an enzyme that converts the cellulose to glucose. Consuming the glucose, the fungus reproduces itself and releases carbon dioxide. For every ton of carbon in the substrate, half a ton of fungus is produced. The final product - containing 40 per cent protein and 60 per cent fat, fibre and carbohydrate - is dewatered and dried to 5 per cent moisture.

The Swiss firm Cellulose Attisholz which brought a commercial process on line in 1967 and expanded it a decade later, saw SCP as a way to comply with Switzerland's strict clean-water law, while obtaining usable byproducts. The firm makes 7,000 m.t./year of Candida utilis yeast from sulfite liquor. About 40 per cent is sold as a food additive; 60 per cent is marketed as animal feed. Pollution-control rules, however, are not always a boon to SCP production, as Cellulose Attisholz itself can attest. The firm engineered and supervised the construction of a 10,000-m.t./year SCP plant based on its technology for the Finnish Ananekoski pulpmill, located some 400 km north-west of Helsinki. The plant, which produces SCP for cattle feed, may be shut down in the near future because a tightening of pollution laws could limit sulfite-pulp production at the mill. Another SCP plant at the United Paper Mills' Jamsankoski site was closed in 1981 for similar reasons.

One SCP plant that is not in danger of closing is the 7,000-m.t./year unit run by the Finnish pulp-and-paper company G.A. Serlachius Oy at its Mantta Mills. The plant, which licensed its "Pekilo" technology from Tampella Corp. and went onstream in 1982, grows the microfungus Paecilomyces in spent sulfite liquor. Prior to fermentation, most of the sulfur dioxide must be removed by steam stripping. Nutrients phosphoric acid, potassium chloride and gaseous ammonia are pumped into the fermenter, where air is used to ensure thorough mixing. After fermentation, the fungal biomass is separated from the liquor and washed in filter presses. The product is mechanically dewatered to a solids content of 35 per cent dried, by hot air, mechanically pressed, and granulated. Finland officially recognized Pekilo protein as an animal-feed ingredient in 1971.

Phillips Petroleum Co., which has a 75-ton/year pilot plant in Bartlesvilla, Oklahoma has no immediate plans to make food additives from SCP, but the firm is actively trying to market an animal-feed-grade product in the Middle East. In the Phillips process, methanol (sugar, glucose and molasses also can be used) is pumped into a continuous 1,500-litre fermenter with ammonia, oxygen and a proprietary yeast, and heated to about 30° C. The resulting liquid is drawn off and spray-dried. The final product contains about 60 per cent protein.

Ranking in size with ICI's Billingham facility is the 60,000-m.t./year plant at Curtea de Arges, Romania, which uses SCP technology licensed from Japan's Dainippon Ink and Chemicals, Inc. (Tokyo). The Dainippon process, which grows Candida parafinica yeast in paraffins, uses four 1,260-m^3 bubbling towers as fermenters. These were chosen, according to DIC, to provide the yeast with sufficient oxygen, and to disperse the paraffins. Compressed and filtered air provides the sole power for mixing in the towers. Crude protein is separated by centrifuge, heated, dewatered and dried. It costs the Romanians about $1,000/m.t. to produce SCP - $300/m.t. more than it would cost them to import fishmeal. However, Romania does have ready sources of low-cost hydro- carbons, and is short on the hard currency it would need to import protein. (Extracted from Chemical Engineering, 6 February 1984)

Chemical applications

Plastic flowers bloom in desert

A desert wildflower called popweed could provide an alternative source for plastics, according to two polymer researchers from Lehigh University in Bethlehem, Pennsylvania. The two scientists claim to have produced a tough polymer by mixing popweed oil with polystyrene. By combining the oil with sebacic acid, the material becomes a polyester, they say. Since popweed grows in areas unsuitable for most crops, it does not compete for land. It is thought possible that popweed could be grown in arid and semi-arid areas with only a minimum of irrigation and soil improvement. Popweed oil is chemically similar to castor oil, but castor can only be produced economically in tropical regions. The two

researchers think that when oil becomes scarce, natural, renewable resources such as popweed will be needed to avoid an economic crisis. (Source: European Chemical News, 19 September 1983)

Shirley Institute plans to "grow" a fabric

The possibility of "growing" fabrics in the laboratory is being investigated by the Shirley Institute in Manchester, where a two-year research project under Dr. Brian Sagar is looking into textile applications of biotechnology. At the half-way stage of the project, the team has already succeeded in producing wet-laid nonwoven fabric samples from microfungal hyphae. Nonwovens are conventionally produced from dry-laid random webs of fibres which are made cohesive by some form of fibre entanglement such as needle-punching or by application of an adhesive binder. The Institute, the leading British research organization on the artificial fibres and cotton side of the textile industry, hopes that nonwovens with novel and improved performance might be produced by this new route. The researchers are using the typically branched growth of the filamentous microfungi which usually have a diameter less than a fifth of those textile fibres such as viscose rayon that are commonly used for nonwovens. Dr. Sagar believes further work is needed but that prototypes will be ready for commercial development within a year. These are expected to have a variety of textile applications including the production of simulated leather, filter fabrics, medical and sanitary textiles and "wet-wipes". The industry has always been interested in biotechnological processes but the recent resurgence is due to the potential they offer for new industrial methods that require less energy input and are based on renewable raw materials.

As well as the work on microfungal hyphae, the Institute is also attempting to elaborate useful biopolymers from microorganisms. Other work is concerned with improving the wet-strength of viscose fabrics using dextransucrase. The aim is to find suitable enzymes to catalyse the sided-glucosylation and chain-extension of the cellulose in the presence of sucrose. If successful, these treatments could improve the flexural rigidity, abrasion resistance and tensile and tear strengths of viscose rayon fabrics.

The biotechnology work forms part of a £100,000 project sponsored equally by the Government and a consortim of UK textile and chemical concerns. (Source: Financial Times, 20 October 1983)

Indigo gene created

When scientists at Amgen cloned a Pseudomonas putida plasmid into an Escherichia coli host, their cultures turned deep blue. They had unexpectedly engineered two multigene enzyme pathways that together broke down tryptophan and naphthalene to yield indigo. The estimated market for indigo blue dye is $100 million, and preliminary estimates indicate that the firm's new proprietary method of producing indigo could significantly cut the dye's cost. Further development work is needed - and is in progress - to define the specific cost-effectiveness of the bacterial process over chemical synthesis. Chemical engineers point out that even for high-value-added specialty products, single-gene recombinant-DNA technology cannot compete with traditional chemical processes. Many industrial chemicals need only a simple one-step conversion to go from starting material to end product. However, r-DNA methods could gain a competitive edge if multigene systems can be engineered to make products that require complex chemical synthesis pathways. The genetically augmented E. coli produced out indigo because its cloned production pathway comprised the genes for enzymes synthesized for both types of host organism - P. putida and E. coli. The latter have a tryptophanase - lacking in the former - that converts the amino acid tryptophan to indole. The Pseudomonas's naphthalene dioxygenase then turns this into indigo. (Extracted from McGraw-Hill's Biotechnology Newswatch, 5 December 1983)

Plant tissue culture for chemical synthesis

Plant tissue culture techniques for chemical synthesis have been in the forefront of research interest for nearly ten years. Plant cells can be grown as if they were bacteria to produce the desired compounds in fermenters. The method may be suitable for high-markup items such as dyes, fragrances, flavours, pesticides and some drugs. The compounds most suitable for plant tissue culture methods are not needed for the plants' biochemical functions; they are produced and secreted to fight off attack from insects, herbivorous animals, microorganisms or other predators, or to attract animals that disperse plant pollen or seeds in the environment.

Mitsui Petrochemical Industries is marketing shikonin, a red dye for cosmetics and food, and an astringent derived from the roots of Lithospermum erythrorhizon. The Institute for Pharmaceutical Biology (Tubingen, West Germany) is scaling up production of digitalis, a cardiac drug isolated from foxglove leaves. (Source: Chemical Week, 4 January 1984)

Ethanol solvent pulping process

Biological Energy is developing an ethanol solvent pulping process with advantages over the kraft process. Normally wood is chemically treated to get the pulp, the by-products being burned. Earlier processes had serious problems in the amount of lignin removed, pulp quality and solvent recovery. Biological Energy has given Foster Wheeler Energy an equity position in the firm in exchange for engineering, design and construction services for the process. Battelle's Geneva laboratories is using phenol as solvent, and is collaborating on the process with Rintekno (Finland).

Biological Energy's "tree refining" process is based on US patent 4,100,016, which was bought from CP Assoc. Wood chips are refined to produce pulp, a native-like lignin and a sugar solution that contains mostly pentoses and hexoses, which could be fermented to ethanol or concentrated into a product for animal feed. Battelle's process converts wood, bagasse or straw into a cellulosic fibre for paper, a C_5 sugar stream and a pure lignin stream. A low-temperature aqueous phenol solution serves as the pulping liquor. The resulting single-phase solution contains lignin and sugars. Cellulose, which does not dissolve, is washed and collected. After cooling to room temperature, the single-phase solution separates into one layer containing lignin dissolved in phenol and one with sugars dissolved in water. (Source: Chemical Week, 4 January 1984)

New amylase plant

Bacillus stearothermophilus is the organism of choice for producing alpha-amylase at a new plant going up at Beloit, Wis. The amylase production facility is being built for an undisclosed amount by John Brown Engineers & Constructors, Inc., Stamford, Conn., and London, England.

The Beloit plant of Enzyme Bio-Systems, Ltd., a subsidiary of CPC International, Inc., both of Englewood Cliffs, NJ, will produce high-temperature alpha-amylase useful for applications in which starch must be completely converted to dextrose sugar, such as corn wet-milling and brewing. (Extracted from McGraw-Hill's Biotechnology Newswatch, 16 January 1984)

Energy and environmental applications

Canada developing biotechnology tools for pollution control

Two Canadian biologists have discovered molecules capable of recognizing and attracting dangerous metals and thus able to serve as "microscopic vacuum cleaners" in nuclear power plants and the metallurgical industry. According to "Hebdo Canada," published by the Canadian Development of Foreign Affairs, these molecules, discovered by Irvin Devoe and Bruce Holbein of McGill University, can capture the tiniest metal particles such as mercury, cobalt, uranium, cesium, and strontium with surprising efficiency. They "swallow" 99.999 per cent of the radioactivity of cobalt 60, one of the hottest waste products of nuclear reactors, so that the cooling water can be decontaminated and the concentrated waste can be fused with glass. These molecules, says "Hebdo Canada," are easy to make, inexpensive, stable, nontoxic, and withstand industrial temperatures. Fixed to glass or teflon, they are reusable indefinitely: an increase in acidity content or electrical discharge causes them to release their metal harvest. In addition to pollution control, they can be used for seawater extraction, control of industrial effluents, and preservation of pharmaceutical products by extracting the iron they contain. In brief, they can be used wherever it is desirable to extract dissolved metals, according to the two biologists who plan to market their discovery in two years time in Canada and abroad. (Source: AFP Sciences, 10 November 1983)

Effluent treatment

The unsightly colours of wastewaters that spew from pulp and paper mills may become a sight of the past if a fungus successfully adopts an effluent life-style. Coloured wastewaters pass through conventional biological treatments relatively unchanged because the bacteria in these systems fail to degrade the coloured compounds present in the effluent quickly enough. These coloured compounds consist largely of lignin, which is a cellulose-like material that acts like a cement to bind together cellulose fibres in cells, and its degradation products. The only micro-organisms capable of degrading lignin in a sufficiently short time and hence removing the colour are the fungi that cause the white-rot type of wood decay.

Researchers at North Carolina State University in Raleigh and the Forest Products Laboratory in Madison, Wis., are studying the conditions under which the white-rot fungus Phanerochaete chrysosporium best removes wastewater colour. Their recent laboratory-scale test took place in a biological reactor running at 40° C under an oxygen atmosphere and supplied with glucose and other basic nutrients. The researchers reported progress in significantly increasing the lifetime of the process, overcoming a major problem that delayed earlier commercial applications of the process. They found that if nitrogen in the form of ammonium chlori was added to coloured wastewater that came from a mills' bleaching plant and if l effluents were biologically treated first, the fungus survived for a longer time than fore. (Source: Science News, 12 November 1983)

Municipal waste processing

Peabody Holmes composting equipment economizes municipal refuse processing and recycling. Several aerobic composting plants have come onstream to rapidly convert wastes without unpleasant odour. The Peabody system lends itself to a high degree of process control and monitoring of the metamorphosis of the compost via computerized programming. End products are bagged or bulked compost, ferrous scrap and energy for use in running the recovery facility. A typical Peabody system of accelerated digestion towers has six separate chambers for each working day so batches of refuse can be isolated to prevent batch contamination. Plants have been installed in Libya, Sweden, Norway, Italy, and Japan. (Source: World Waste, November 1983)

Ice-plus strains make snow for ski resorts

By exploiting the same ice-forming microbes that cause frost damage to crops, ski-resort operators may be able to cut their snow-making costs by two-thirds. Advanced Genetic Sciences, Inc. has obtained commercialization rights to produce and test natural and mutagenized variants of Pseudomonas that enhance artificial snow-making. The method inoculates water in the snow machines with freeze-dried bacteria. The bacterially catalyzed snow crystals are shaped like natural snowflakes and last longer than conventional artificial snow. This permits good skiing at temperatures six to ten degrees Fahrenheit higher than normal, and snow quality can be "fine-tuned" to produce anything from slush to a hard powder by varying the ratio of bacteria to water.

The "snow-bug" has been field-tested at undisclosed ski slopes for the past two winters, and the firm expects it to be on the market before next winter. (Extracted from McGraw-Hill's Biotechnology Newswatch, 19 December 1983)

Anaerobic digestion and "alga filters" new biological methods for waste-water treatment

Two biological methods for the purification of waste water and the treatment of sludge have been developed in Sweden by K-Konsult, a consultancy company owned by Swedish regional and local authorities.

One method is a process for treating sewage sludge from waste-water treatment plants in which sludge is anaerobically digested to form biogas (a mixture of methane gas and carbon dioxide) that can be used for heating purposes. Aimed at producing as much combustible gas as possible, it digests sludge anaerobically in two steps, first in the mesophilic temperature range (35° C) and then in the thermophilic range (52° C), pathogens being destroyed in the second stage. The method is said to exhibit superior sludge dewatering characteristics. Raw sludge from the waste-water treatment plant is pumped to a biogas installation. After pre-heating in the first of two sludge/sludge counterflow heat exchangers of an entirely new design, it is digested in the mesophilic digester and, after

seven to ten days, it transferred via the second heat exchanger to the thermophilic digester, where it remains for a similar period. Sludge is mixed in the digesters by slowly-revolving propeller-stirrers which agitate the entire sludge content. Each digester has a volume of 3,500 m^3. The digesters, constructed of post-tensioned concrete, are cylindrical with a slightly-inclined bottom and flat top. Digester gas is removed through the top of the digesters via a pipe connected to a membrane gasometer. The digesters are designed for a maximum of 550 m^3 raw sludge/day.

None of the digester gas formed is used for heating the digesters, while about 90 per cent of the heat required for the biogas installation is recovered. More than 70 per cent of the energy needed for heating the sludge is supplied by the interchange of heat between the hot digested sludge and the cold raw sludge in the counterflow heat exchangers.

The process is now in operation at a waste-water treatment plant in southern Sweden. With the present load of raw sludge, biogas formation amounts to 1.2 million m^3 per annum. One million m^3 per year is used for heating a housing area, reducing oil consumption by 600 m^3 annually. The digested sludge, which has a low level of bacteria thanks to the high temperature of the thermophilic digester, can be used for agricultural fertilization.

The second method involves the use of algae and other water plants to purify municipal waste water and revitalize threatened lakes, in addition to providing heat and supplying raw material to the food and pharmaceutical industries. Trials at Ringsjön in southern Sweden indicate that so-called algae filters could replace chemical precipitation, the conventional third step in waste-water purification processes, thereby saving large sums of money.

Algae and other water plants consume nutritive salts, phosphorus, nitrogen and even other substances and thus effectively clean waste water, it is said. At Ringsjön, suitable varieties - the green alga chladophora, for example, and plants such as duckweed and rushes - have been set out to constitute water filters. They consume so much phosphorus and nitrogen that they increase their weight by 10-30 per cent daily.

The algae and plants remain in the water for 8-10 days, after which they are harvested and replaced by new stock. Experiments are now being carried out to determine the rate of growth for various algae and plants during different parts of the year, the goal being to develop a suitable annual alga/plant cycle.

The alga filter could also help to save lakes threatened by excessive fertilization, since it siphons off a large part of the nutritive salts, phosphorus and hydrogen in the water. In places where water is very clean, the filter could consist of alga varieties which can later be used in the production of food and pharmaceuticals. Normally, however, algae harvested after 8-10 days would be used for the creation of biogas. (Source: SIP, January 1984)

Dutch elm disease

Source Technology Biologicals developed Phyton-27, a new EPA registered treatment for Dutch elm disease prevention and control. It is the only product label-recommended for use in trees with more than 5 per cent disease. Phyton-27 is easy to use with most standard tree injection equipment and can be used effectively from mid-spring when the leaves are fully developed through early fall. Phyton-27 is being sold for use by trained arborists and those knowledgeable in tree care. (Source: News Report, 1 February 1984)

Bacteria to detect toxic material in wastes

Nitrifying bacteria can be used as bioassay organisms to detect the presence of toxic material in wastes, according to US Environmental Protection Agency. The nitrifying bacteria Nitrobacter and Nitrosomonas were used to study a toxic industrial waste and flue-gas scrubber solid waste. EPA conducts bioassay tests on three levels. One involves general bioassay analysis procedures to identify toxicity in a given waste stream. The second attempts to identify and quantify the compounds associated with the toxicity, and the third attempts to determine chronic health and ecological effects of the stream. The current first level tests attempt to determine the presence of acute toxicity, mutagenicity, cytotoxicity and soil microbiological inhibition, and were designed to determine the toxic concentrations of a range of toxicants to Nitrobacter and Nitrosomonas. The

tests also demonstrate the use of nitrifying bacteria to estimate toxicity and the type of toxicant present in wastewaters. The nitrifying bacteria are less sensitive to metal toxicants than Daphnia, trout, fathead minnow and algae. The bacteria demonstrate slightly greater sensitivity to lead and silver. (Source: Life Sciences, December 1983)

Extraction industry applications

Biological extraction processes

Biological extraction processes will recover $90 billion of strategic and precious metals in 1990-2000, according to Gorham International (Gorham, MA). With significant amounts of copper and uranium already obtained by bioextraction methods on a routine commercial basis, the potential for this process may be particularly applicable for geographically remote ore bodies, as in undeveloped nations. Laboratory tests have demonstrated the viability of microbial extraction to recover gold, silver, platinum, chronium, cobalt, manganese, nickel, titanium, tungsten, and vanadium. In addition to opportunities in the metals recovery industry, sales potential also exists for the microorganisms, nutrients, chemicals and process equipment used in biological metal-winning methods. (Source: Gorham International News Release, October 1983)

Immobilized bacteria clean up mine drainage

Cleaning up acid mine drainage by bacterial iron oxidation is the low-cost, high-capacity method favoured by the Metal Mining Agency of Japan (MMAJ). Even at low temperature and pH, Thiobacillus ferrooxidans converts at least 95 per cent of the ferrous ions in the effluent to ferric iron, according to a recent report on the government-sponsored bio-treatment plant at the Matsuo sulphur-pyrite mine in Iwate Prefecture. Once the drainage is in the ferric form, it can be treated with calcium carbonate, rather than the more costly calcium hydroxide needed to precipitate the ferrous salts and neutralize the acidity. Ten years ago the Yanahara mine in the Okayama Prefecture switched from nitrous-gas treatment ot bacterial oxidation, bringing the cost of drainage clean-up down to some $13,000 per 5,000 m^3 - a 60 per cent saving.

The key to the Matsuo mine's new 20 m^3-per-minute bio-treatment plant is the use of diatomaceous earth as a high-surface-area cell carrier. this immobilization permits dense concentrations of T. ferrooxidans to complete the ferrous-to-ferric conversion in only one hour per batch. After adding calcium carbonate, it is claimed that most of the iron and arsenic present in the drainage can be removed in the form of precipitates. The favourable settling and separation of the cell carrier permit the bacteria to be recycled at low cost. (Source: McGraw-Hill's Biotechnology Newswatch, 5 December 1983)

Copper enzyme

The enzyme copper, zinc superoxide dismutase greatly accelerates the conversion of the superoxide radical O_2^- to oxygen and hydrogen peroxide, according to studies at Duk University's medical centre. The copper ion at the active site of the enzyme has an unusually high oxidation-reduction potential because it is tetrahedrally distorted. A nearby zinc ion helps bring the enzyme-substrate complex into the first intermediate state on the catalytic pathway, and helps bring a histidine residue into position to store a hydrogen atom temporarily during the intermediate steps of the reaction. The enzyme is found in all respiring cells. (Source: Chemical and Engineering News, 28 November 1983)

Oil from seaweed

Oil can now be obtained from garbage, sewage sludge and even from seaweed. To do this Professor Ernst Bayer from the Institute for Organic Chemistry at Tübingen University has developed a thermic-catalytical process in which the biomass is converted into oil and oil-like products at temperatures of about 300° Celsius using certain catalysts. At present 50 to 200 kilograms of oil an hour are being produced in the pilot plant of an Austrian firm. By the end of next year the quantity will have risen to as much as one tonne an hour. (Source: Scala, No. 12, 1983)

Industrial microbiology

Enzyme developed to destroy cement

A venture business, Polymer Chemistry Research Center, located in Osaka is developing a decomposing agent for cement or limestone using enzyme reaction. This company is aiming, through use of this technology, at ultramicro granulation of limestone and development of absorbing agent for the treatment of Red Stream and a high performance concrete comparable in performance with epoxy resins.

The decomposing agent is commercially available in part through Yokohama Inoue Industry in Yokohama. Its composition includes a chelating agent such as calcium, with the addition of a small quantity of an enzyme derived from a marine creature. When approximately 1,000 tons of cement on board a cement transport ship solidified as a result of flooding, the Yokohama Inoue Industry was able to treat it successfully within a week by using approximately two tons of this decomposing agent. The greater part of the cement was mechanically crushed, but the thin layer of cement that clung tenaciously to the wall surfaces came off in the form of a dry powder when the decomposing agent was applied to it.

A chelating agent, Donox, for the removal of cement adhering to moulding frames used in construction work has already been developed by the Polymer Chemistry Research Center. Treatment using Donox is carried out overnight. However, 1.5 tons of the chelate solution is required to decompose 1 ton of cement. In contrast, only several per cent by weight of the new decomposing agent is required for the treatment of cement, according to estimates. Its most important feature is that it decomposes cement into powder. Research is under way at the Center to utilize this feature in the development of microgranulation of limestone, which has not been feasible technically or economically by using the conventional physical method of crushing and grinding. The first application of the microgranules of limestone is for the preparation of an agent for the treatment of Red Stream which will float and have adsorbing capacity. The second application is for the preparation of high performance concrete. When concrete is made of cement with micrograins having particle diameter measures in microns, formation of minute cracks inside the concrete can be prevented. Theoretically speaking, a dense and elastic new concrete could be manufactured. To develop these technologies, the Polymer Chemistry Research Center is negotiating technical co-operation with several cement companies. (Extracted from Tokyo Nikkei Biotechnology, 4 July 1983)

Engines run on vegetable oil

A diesel engine which can run of vegetable oil is to be manufactured by Mitsui in Japan who have acquired a licence from Elko Lizenz, a Federal Republic of Germany research institute which developed the engine. The new engine, which can use many types of vegetable oil including soyabean, rapeseed, sunflower seed, coconut and palm, consumes 25 per cent less fuel than a conventional diesel engine and does not require a radiator or fan. Applications include cars, agricultural and construction machinery. Probably the largest market for the engine is in Asia and South America where there is a plentiful supply of vegetable oil but petroleum is scarce. (Source: Financial Times, 14 September 1983)

Genetic engineering improves enzyme binding

The ability of the enzyme tyrosyl tRNA synthetase to bind with its substrate ATP has been improved through genetic engineering according to G. Winter and P. Carter of the Laboratory of Molecular Biology (Cambridge). The ability to tailor enzymes will open up new possibilities in the manipulation of human biology. A small portion of the gene coating for the enzyme was changed by sight-directed mutagenesis. Enzymes must first chemically bond onto a substrate before catalysing the reaction of the substrate with some other chemical. Enzymes possess up to 1,000 amino acids arranged in a complicated array. Changing the side chains can alter the properties of the enzyme. Not all of the side chains are of equal importance, however. The enzyme tyrosyl tRNA synthetase effects transport of tyrosine by tRNA, which may be required in protein synthesis. DNA governing production of the enzyme was altered at one nucleotide base, changing an amino acid in the enzyme from threonine to alanine. The technique opened up the possibility of redesigning proteins, from industrial enzymes to human hormones. (Source: New Scientist, 13 October 1983)

Cloned cutinase converts crop waste to "polyester"

A newly cloned fungal enzyme has the potential to convert agricultural wastes into "natural polyesters". By knocking out the same gene from its pathogenic parent, Dr. P.E. Kolattukudy, director of Washington State University's Institute of Biological Chemistry is also seeking to produce benign strains of Fusarium fungi. The enzyme, cutinase, breaks down cutins - the waxy cuticle on the exterior cell walls of leaves, stems and fruit skins. These abundant hydroxy-fatty-acid polymers, reduced to monomers by the enzyme, could serve as a novel feed-stock for specialty chemicals.

A major chemical company has already made a cream-coloured soluble polymer from cutin-derived monomers supplied by Kolattukudy, but so far he has only produced the building block molecules in bench-scale quantities. The virtually limitless supplies of inexpensive, cutin-rich substrates - such as peat deposits and food-processing wastes - and the resultant availability of new monomers for specialty products suggests a strong commercial potential. The researchers have transferred the cutinase gene from several Fusarium fungi into Escherichia coli using plasmid pBR322 as a vector. They determined the enzyme structure from the DNA sequence and are now putting the gene into expression vectors to get higher yields. (Extracted from McGraw-Hill's Biotechnology Newswatch, 5 December 1983)

Technique developed for mass-production of E. coli

Kikkoman (Japan) has developed a technology that allows mass production of biotechnology products. It involves a special carrier that can contribute to a 1,000-fold multiplication of the transplanted genes. Plasmids are usually used as carriers. Company researchers injected an enzyme gene with the ability to decompose glycerine into E. coli. Production was increased 30 times with the Kikkoman process. In a 2-litre fermentation tank, 40 per cent of the total protein produced by E. coli turned into an enzyme. With conventional techniques the highest rate is 5-8 per cent. (Source: The Japan Economic Journal, 20 December 1983)

E. PATENTS AND INTELLECTUAL PROPERTY ISSUES

Genes patent agreed

A formal announcement is expected soon from the US Patent Office confirming that Stanford University has been granted its "master patent" on the products of genetic engineering. The application for the patent came close to being invalidated after a complaint that the gene-splicing techniques of biotechnology, which lie at the heart of the patent, had been discussed in New Scientist on 25 February 1973 - 13 months before the patent application was filed.

A final decision on the troubled patent claim was expected during last summer but it was delayed again because the patent examiners had been made cautious by the publicity and the huge value of the patent. Most estimates say that it will eventually be worth several billion dollars to Stanford University and the co-inventors of the technique, Stanley Cohen and Herbert Boyer. (Source: New Scientist, 10 November 1983)

Patents awarded for foreign protein secretion process

Harvard University has received US and European patents for its new gene splicing process for producing and secreting a foreign protein in a bacterial cell. Ordinary recombinant DNA technology does not have a secretion step, so in order to recover the protein product the bacterial cells must be destroyed. This contaminates the protein with other cell proteins and debris. The new technique could lead to a continuous process for protein manufacture. Proteins such as insulin and human serum albumen could be produced in large volume by recombinant DNA techniques at less expense. Biogen (the Netherlands) paid the patent-related expenses and has acquired exclusive licenses for the technology. (Source: Chemical and Engineering News, 5 December 1983)

'Easy' assay patent

Genetic Systems Corp. of Seattle filed a U.S. patent application entitled "Compounds and methods for preparing synthetic polymers that integrally contain polypeptides." The invention is a non-enzymatic diagnostic assay whereby monoclonal antibodies or DNA probes, for example, are analysed in a machine rather than by conventional chemical means. The one-step procedure completes the diagnostic measurement of "specific biological pairs in less than three minutes."

By coincidence, on November 15, 1983, the U.S. Patent Office issued U.S. patent 4,415,665 to Pharmacia Fine Chemicals AB of Uppsala, Sweden. (Extracted from: McGraw Hill's Biotechnology Newswatch, 5 December 1983)

Selection of recent patents

	Application System/No.	Applicant/Inventors
Engineered hosts make snow	WO 83/03831	Regents of the University of California, Berkeley, Calif., U.S.A./Cindy S. Orser, Steven E. Lindow, Nicholas J. Panopoulos, Brian J. Staskawicz
Tissue plasminogen activator expressed	GB 2119804	Genetech, Inc., South San Francisco, Calif., U.S.A./David V. Goeddel, William J. Kohr, Dianne Pennica, Gordon A. Vahar
Production of human urokinase by gene cloning	EPO 092 182	Genentech, Inc., South San Francisco, Calif., U.S.A./Herbert L. Heyneker, William E. Holmes, Gordon A. Vehar
Novel cloning system for yeast	WO 83/04050	Gist Brocades, NV, Delft, Netherlands Cornelis Hollenberg, Albert DeLeeuw, Johannes Van Den Berg
Cloning vehicles usable in Streptomyces	GB 2 118 947 EPO 092 338	Eli Lilly and Co., Indianapolis, Ind., U.S.A./ Charles L. Hershberger,Jeffrey L. Larson
Implantation of viable tissue	GB 2119734 GB 2119737	Damon Corp., Needham Heights, Mass., U.S.A./ Franklin Lim
Gene amplification	WO 83/03259	Trustees of Columbia University, New York, N.Y., U.S.A./Richard Axel, James M. Roberts
Manufacture of large structural genes	WO 83/04053	Applied Molecular Genetics, Inc., Newbury Park, Calif., U.S.A./Normal Alton, Mary A. Peters, David L. Snitman
Protein gene expressed in yeast	WO 83/04051	Unilever, NV, Rotterdam, Netherlands
Manufactured urogastrone gene expressed	WO 83/04030	Applied Molecular Genetics, Inc., Newbury Park, Calif., U.S.A.
Calcitonin, calcium regulator, cloned	EPA 0070675 WO 83/04028	Applied Molecular Genetics, Inc., Newbury Park, Calif., U.S.A.
Antibodies against syphilis	EPO 0 095 346	The Board of Regents, University of Texas System, Austin, Texas, U.S.A.
Rabies virus antigenic protein cloned	EPO 0 094 887 WO 83/04052	Transgène, SA, Paris, France
Poliovirus coat protein cloned	WO 83/03972	Mass. Inst. of Technology, Cambridge, Mass., U.S.A.

	U.S. Patent No.	Assignee/Inventors
Monoclonals to diagnose and treat fluke infections	4,416,866	The Johns Hopkins University, Baltimore, Md./ Mette Strand
Support matrices for biocatalysts	4,416,992	UOP Inc., Des Plaines, Ill. Blaise J. Arena, Ronald P. Rohrbach

F. BIO-INFORMATICS

Computer programme

A computer programme to compare a nucleic acid or protein sequence to other known sequences has been developed by NIADDK. The programme searches specialized data banks and compares one sequence of a molecule or part of a molecule to other known sequences. It can compare the test sequence to all sequences in the Protein Data Bank of the National Biomedical Research Foundation or the Los Alamos Nucleic Acid Data Base. The programme looks for matches of successive amino acids or successive nucleotides. The number of successive amino acids needed for a match can be set at any number. It will also insert a gap area in the sequence if it will allow for more overall matches between two sequences. The programme will be useful to relate sequenced molecules to previously known sequences. (Source: Life Sciences, September 1983)

New computer database

A centralized computer library now logs all reported DNA and RNA sequences longer than 50 nucleotides. Called GenBank, the database already contains entries for more than 2,700 reported sequences, comprising over 2.1 million bases. Each new entry is checked for accuracy, catalogued, and annotated for sites of biological interest. GenBank is distributed via computer-readable magnetic tape and as an annual printed compendium. The system is interactive, and users can search the database by using commands close to "biological English". Several search routines are available: A user can determine locations or frequencies of specified DNA sequences, for example, or translate them into their corresponding amino acid sequences. Online access to the central GenBank computer is available, though only to a limited number of users at a time. Fees are $18 per hour between 10 a.m. and 9 p.m. weekdays, $9 at other times. The government-funded library is run by Bolt Beranek and Newman (Cambridge, Mass.) and the Los Alamos National Laboratory. (Source: High Technology, February 1984)

Computer graphics and protein engineering

The unpromising economic future of many biotechnology companies could be turned around by the clever use of computers. This is the opinion of a growing band of entrepreneurs in the computer industry who see important market opportunities in the fast-growing biotechnology business, and who are starting up small firms offering software and hardware to fill the gap.

For so many years now the larger chemical and pharmaceutical companies have been using computer graphics to picture the molecular configurations of their most promising chemicals or drugs with an eye to redesigning new products, but by conventional chemical methods. Now, however, an entirely new range of products worth billions of dollars, according to some estimates, awaits the marrying of computer graphics to the new genetic manufacturing technologies.

One of the keywords to this fast-growing corner of the computer industry is "artificial intelligence" which was reported on in the last issue.

Biotechnology production using genetically engineered bacteria presents special problems not yet encountered in the more traditional antibiotics industry based on more conventional microbes.

Aside from the still worrying question of safety which places an extra containment burden on the manufacturer, these bugs require a strictly controlled and delicately balanced environment, food nutrients, and the other substances it needs to grow, such as growth promoters, a touch of acid, minerals, oxygen must all be added in the correct amounts, and

in the correct order. Much of this technology is still black art, but computers offer the opportunity to make these processes more efficient, and so improve their chances of competing successfully with more conventional technologies. For example, they can store information to be used in production and research, data on proteins, the products of most of the companies and the complicated structure of DNA, the blueprint the cell follows in making proteins and which companies wish to alter. Their programmes will also have access to the enormous "gene banks" stored in research centres in Washington and in the European Molecular Biology Organisation, in Heidelberg.

However, the real profits probably lie in developing software programmes to design new biological molecules, which could then be made conventionally or by genetic engineering. There the big drug houses are already deeply involved in a race to design a new family of antihypertensive drugs based on the detailed structure of renin provided by computer graphics.

Renin is an enzyme which research has linked to high blood pressure. Finding a chemical which blocks its action could be worth billions of dollars. In the blood renin cleaves a precursor hormone, angiotesinogen, to release angiotensin, which powerfully constricts blood vessels, a vital first step to raising blood pressure.

Scientists think that by picturing the molecular "bumps" and "crevices" of first renin, the angiotensinogen, and then the two "docking" together, they may be able to design an effective renin inhibitor.

Professor Tom Blundell and his team at Birbeck College, University of London, created a considerable stir among these commercial contenders by publishing this summer the three dimensional structure of mouse renin from their own computer graphics programme and since then his department has developed the computer model for the human molecule. This achievement is considerable, for his software programme takes into account that biological molecules are not rigid, and constantly slightly altering their shape. His system, for example, incorporates 5,000 "vectors" - chemical bonds which it can display and rotate in real time. Renin is but one of the enzymic proteins whose function depends on a strict order of amino acids, programmed by genes in the cell's nucleus.

What is seen on the screen is not only a three-dimensional model of these forces, represented by a delicate tracery of lines, but also a fuller shading of the surfaces of these molecules, using millions of dots.

Blundell's work indicates the quality of computer software programmes tucked away in British universities and research organizations which may be of great commercial value. A small computer hardware company, Gresham Lion, spotted the opportunity and recently licensed a software programme for modelling anti-cancer drugs from its developer, Professor Stephen Neidle, head of the biomolecular team at King's College, a group supported by the Cancer Research campaign.

Cellulases, which break down fibrous plant material to alcohol, are another commercial target for computer graphics and genetic engineering as the search continues for alternative sources of cheap fuel. (Extracted from Financial Times, 9 November 1983)

Biotechnology in developing countries

The Delft University Press has recently issued the texts of papers presented at a symposium devoted to biotechnology in developing countries, held in Delft, The Netherlands, from 13 to 14 October 1982. The publication, edited by Professor Paul van Hamert covers biotechnology in development co-operation from the points of view of a donor country and a developing country; the biotechnology situation in India (biotechnology for villages); the situation in Africa, with special emphasis on biological nitrogen fixation; the situation in Latin America; the introduction of methods for large-scale production of vaccines in developing countries and the use of clonal oil palms in developing countries. The publication may be ordered from the Sales Department, Delft University Press, Mijnbouwplein 11, 2628 RT Delft, The Netherlands, at a cost of 24 Dutch Guilders.

The following, as a matter of interest, were the conclusions reached at the symposium:

- Biotechnology may contribute considerably to the development of the Third World, in particular in the production of food, feed, fuel, microbial insecticides, in biological nitrogen fixation, preventive health care (vaccin production), waste treatment, crop improvement and microbial metal recovery.

- Developing countries can benefit from both small-scale and large-scale biotechnological processes.

- The lack of skilled staff, able to evaluate, select, and implement projects, is an important problem. Hence education in the fundamentals of biotechnology is essential. The Netherlands - in particular the Dutch universities with a biotechnology programme - are able and prepared to assist in such education. Brain-drain (students not returning to their home country after having been trained abroad) might be kept to a minimum by applying the so-called Sandwich-system of education: A great part of the Ph.D. study is done in The Netherlands, but the education is completed in the home country.

It is hoped that these conclusions will result in an increase in the number of students from developing countries participating in biotechnological courses in The Netherlands, with support from the government and/or the European Economic Community.

Les biotechnologies

For those of our readers who find French easier than English, the following book published by UNESCO should be of interest: "Les biotechnologies - défis et promesses", by Albert Sasson. The book deals with recent developments in molecular biology, biochemistry and genetics and provides a systematic and comprehensive description of each domain affected by this scientific revolution in a language accessible to the layman. Biotechnology consists of taking micro-organisms - bacteria, yeast, plant or animal cells - which have the capacity to produce or metabolize substances useful to man, and harnessing them to modern technology: in the chemical industry, for instance, they are applied in producing textiles, and for improving tastes and smells; in the energy realm, biotechnology produces ethanol and biogas; it is used in the extraction of certain metals. After discussing biotechnology in the food industry, in fermentation processes and the production of vitamins; in pharmaceuticals in the making of antibiotics, synthetic hormones and vaccines; in protecting the environment through recycling of wastes; and in agriculture for improving productivity; the state-of-the-art and the potential for economic application on a wide scale, the author examines several related issues: the training of qualified personnel, the new bond between universities and industry, the marketing and the patenting of biotechnology; risks, ethics and international co-operation. The role of UNESCO and other international organizations in promoting co-operation, exchange of information, education, research and the application of science for development is likewise discussed. The book is illustrated and includes a chapter-by-chapter bibliography of recent publications.

French language journal

For our French speaking readers who have difficulty in grappling with scientific journals in English, there is a monthly magazine on European biotechnology available. It is called Biofutur, address: 56 rue de l'Université, 75007 Paris, France.

Papers on anaerobic digestion

The Central American Research Institute for Industry (ICAITI) has recently issued proceedings of the second Pan-American symposium of fuels and chemical products via fermentation entitled Advances in Anaerobic Digestion, held in Mexico City last October. The proceedings contain papers presented at the meeting, both in English and Spanish and deal with basic principles, digester design and agro-industrial applications. Copies may be requested from ICAITI, P.O. Box 1552, Guatemala City, Guatemala. Price is US$15 including air mail.

International Bio-Energy Directory and Handbook - 1984

The Bio-Energy Council released its International Bio-Energy Directory and Handbook - 1984 at the end of January 1984.

Bio-energy is renewable energy obtained from the sun via photosynthesis. Biofuels from this source are abundantly available and account for one-seventh of all energy consumed world wide.

Dr. Paul F. Bente, Jr., Editor and Executive Director of the Council noted: "Applications for bio-energy technology have been developed for production of mechanical energy, motive power, electricity and various forms of heat for industrial processes and for comfort and cooking. Because bio-energy is often the most economical energy to use, many of these applications are becoming established practice and often involve integrated systems which use byproducts and wastes efficiently." International communication about bio-energy activities is essential to wider and wiser use of bio-energy. The primary function of the Bio-Energy Council is to increase the flow of information between the technical com- munity, government, industry and the public. The new Directory-Handbook, the fifth such volume in a series, serves that purpose.

It provides 627 summaries of recent work in 60 countries and 47 US states and territories stressing specific quantitative findings. A new feature is inclusion of six authoritative essays on the emerging biomass-to-energy technologies. The volume has over 600 pages, and is priced at US$95.00.

Trends in world biotechnology - A review and analysis of advances in technology and industrial development during 1982-1983 with projections to the future

As we mentioned in Issue No. 7 of the Monitor, we are attaching to this issue, as a supplement, a paper on trends in world biotechnology written by Dr. B. K. Zimmermann. The following is an abstract of this paper:

The continued spectacular advancement in basic biological sciences, particularly molecular genetics and cell biology, has provided the sustained stimulation of the development of new applications in many areas of biotechnology. The progress in the most important areas of technological development is discussed and analysed. The commercial industry continues to attract the investment of substantial sums even though expenditures for research and development can be expected to greatly exceed sales of products for several years to come. Most new industrial development during 1982-1983 took place in the most advanced economically developed countries. There are increasing international and bilateral efforts to promote advanced biotechnology in developing countries, but strengthened basic sciences, more highly trained individuals, and sustained national commitments will be required to ensure the development of successful domestic industries. UNIDO is engaged in several projects to strengthen national efforts to establish biotechnology programmes, and to establish the international Centre for Genetic Engineering and Biotechnology, now to be built on sites in Italy and India. Forecasts are made concerning the development of selected areas of research and development that are likely to become major elements of industrial biotechnology in the next ten years, including the molecular engineering of proteins and strategies to prevent cancer rather than cure it.

G. MEETINGS

MEETINGS - SYMPOSIUMS - COURSES

DATES	THEME	SPONSOR
18-20 March 1984	Biotechnology in Oil Production, London, England	Prof. V. Moses School of Biological Sciences Queen Mary College London E14NS, UK Telephone: 01-980 4811 ext. 572
19-21 March 1984	Gene Manipulation in Plant Improvement, 16th Stadler Genetics Symposium, Columbia, Mo, USA	Dr. J. P. Gustafson Stadler Genetics Symposium Cutris Hall University of Missouri, Columbia MO 65211, USA

DATES	THEME	SPONSOR
19-21 March 1984	Molecular Cloning Workshop, Piscataway, N.J., USA	Director, Continuing Education Waksman Institute of Microbiology P.O. Box 759, Piscataway, NJ 08854, USA
19-21 March 1984	Freez[illegible]g and Quality Control: Cell Cultures and Hybridomas Rockville, Md., USA	Dr. David Grounds American Type Culture Collection 12301 Parklawn Drive Rockville, MD 20852, USA
9-11 April 1984	Biotechnology of Marine Polysaccharides, Cambridge. Mass., USA	Ms. Therese Z. Henderson Massachusetts Institute of Technology, Sea Grant Program 77 Massachusetts Ave., Bldg. E38-302 Cambridge, MA 02139, USA
17-19 April 1984	Analytical Methods and Problems in Biotechnology, Noordwijkerhout, The Netherlands	Mr. Tiny Nijhof Elsevier Science Publishers B.V., P.O. Box 330, 1000 AH Amsterdam, The Netherlands
14-18 May 1984	Plasmids in Bacteria Urbana-Champaign, Ill., USA	Ms. Edna Unfer The University of Illinois at Urbana-Champaign Council for Research Planning in Biological Sciences Urbana, IL 61801, USA
15-17 May 1984	Biotech Europe, London, England	Online Conferences Ltd. Pinner Green House Ash Hill Drive Pinner HA5 2AE, UK
15-18 May 1984	Biotechnology for Fuels and Chemicals, Gatlinburg, Tenn., USA	Dr. Charles D. Scott Oak Ridge National Laboratory P.O. Box X, Oak Ridge, TN 37830
15-18 May 1984	Workshop on Biotechnology in Industrial Development, Serdang, Selangor, Malaysia	Dr. Yassmin Mukhtar Ahmad Food Science Department Faculty of Food Science and Technology, Universiti Pertanian Malaysia, Serdang, Selangor, Malaysia
21-25 May 1984	Microbial Enhancement of Oil Recovery, Conroe, Tex., USA	Mrs. Josephine L. Wilke Energy Resources Institute University of Oklahoma, Norman, OK 73019

DATES	THEME	SPONSOR
24-29 May 1984	Capability Building in Biotechnology and Genetic Engineering by Developing Countries, Washington, D.C., USA	AAAS Meetings Office 1101 Vermont Avenue, N.W. Washington, D.C., 20005, USA
30 May - 1 June 1984	1st European Conferences on Advances in Antitumor Agents, Milan, Italy	Dr. Paolo Pennella Associazione Farmaceutici Industria, Via Santa Tecla 4 20122 Milan, Italy
4-7 June 1984	Controlled Release Technology: Polymeric Delivery Systems for Drugs, Pesticides and Foods, Vienna, Austria	Ms. Maria Clara Suva-Martin Industrial Liaison Programme Massachusetts Institute of Technology, Cambridge, MA 02139, USA
10-12 September 1984	Biotech 84, International Conference and Exhibition, Washington, D.C., USA	Biotech '84, London Online Inc., Suite 1190, 2 Penn Plaza, New York, NY 10121, 212-279-8890
10-14 September 1984	3rd European Congress on Biotechnology, Munich, FRG	Congress Secretary, DECHEMA, P.O. Box 970146, D-6000, Frankfurt/Main 97, FRG
30 September - 5 October 1984	4th International Biochemical Engineering Conference, Galway, Ireland	Engineering Foundation, 345 E. 47th St., New York, NY 10017, 212-705-7837

H. REPRINTED ARTICLES

The following article written by Dr. M. S. Swaminathan is reprinted from Science Age, January 1984. Dr. Swaminathan, plant geneticist and Fellow of the Royal Society, London, is director general of the International Rice Research Institute, Manila, Philippines. The article is based on his presidential address to the XV International Congress of Genetics at New Delhi in December, 1983.

Genetic conservation - microbes to man

The first human form, referred to as Hominid, is believed to have evolved in East Africa some 25 million or more years ago. Human beings may have existed as a species for about two million years. Yet it was only about 10,000 years ago that human beings started growing food, rather than merely gathering it from the wild state. Thus, if the existence of human beings as an independent species is equated to a 24-hour day, we have been farmers for only about seven minutes. Even during these seven we have practised market-oriented agriculture only for a few seconds. Within these few seconds, we have been confronted with numerous problems including changing consumer preferences. We do not know what new pests and soil and atmosphereic (including temperature changes from higher carbon dioxide content) constraints we will have to face in the future. We do not know what physiological and morphological traits will be needed for plants to perform well in a post-nuclear war era, if such a calamity does befall our planet. Future generations of scientists and farmers will not have the tools with which they can solve such problems if we do not make genetic resources conservation, evaluation and utilization a common cause and accord it the highest priority.

Genetic conservation, as we now understand and practise it, is a relatively young venture. In 1932, Vasilov pointed out that "the growing needs of civilized man and the development of industry make the introduction of new plants necessary. The vast resources of wild species, especially in the tropics, have been practically untouched by investigation". Concern was expressed by several geneticists over the loss of genetic stocks due to the modernization of agriculture. It was pointed out that without co-ordinated efforts around the world valuable genes could be lost through neglect.

The need for a clear national policy on genetic stocks and genetic diversity has been stressed at numerous symposia on genetic conservation. Following the corn blight epidemic in the early 1970s in the USA, the National Academy of Sciences set up a Committee on Genetic Vulnerability on Major Crops (1972) to review the situation relating to the diversity of the genetic material in widely cultivated major crops. The Committee found that the genetic diversity of many of the important crops in the USA was dangerously narrow. For example, 96 per cent of the garden pea crop was planted to only 2 strains, and 95 per cent of the groundnut crop to only nine varieties. Consumer preference and market forces were both held responsible for genetic uniformity and therefore to vulnerability.

Today, only about 150 plant species with about a quarter million local strains are important in meeting the calorie needs of human populations. With the spread of high yielding varieties of crops, the existing variability is under threat of extinction.

1983 marked the 30th anniversary of the discovery of the chemical structure of DNA. It also marked the 20th anniversary of the UN-FAO World Food Programme (WFP). It is now possible to identify portions of the genetic molecule responsible for specific characteristics and then splice this portion onto genetic molecules from another strain. Research in cell biology, molecular genetics, recombinant DNA, tissue culture and related fields is opening up new possibilities for progress in agriculture, medicine and industry.

But the food front is depressing. The World Food Programme is the largest multilateral food aid programme currently in operation and has provided food to over 200 million people. Still, over 500 million people may be going to bed on an empty stomach today.

As recently as 1968 Paul Ehrlich, in his book The Population Bomb remarked, "The battle to feed all of humankind has been lost. In the seventies, the world will experience famines where hundreds of millions of people will starve to death". So far, the world-wide food catastrophe has not materialized, thanks to recent progress in the genetic improvement of crops. The rapid agricultural transformation in countries like China, India, Indonesia, Pakistan and the Philippines was triggered by the development and release of crop varieties with the capacity to respond to good management. Rapid population growth has however consumed many of the benefits of agricultural progress. It has been estimated that early in the year 2015, about 8 billion people will have to be fed and provided with jobs. If population stabilization programmes are successful, the world population could be maintained at about 10 billion in another 50 years. The gains in production that appear possible from research and development in agriculture and aquaculture should meet much of the need for more food during the rest of the century.

For periods beyond, it is important that progress in fields like recombinant DNA technology, production of monoclonal antibodies, tissue culture and protoplast fusion should be fully harnessed. It is now feasible to construct new genes and to modify the old ones. The main practical results have been obtained with genetic manipulation of micro-organisms, notably Escherichia coli. However, studies to alter the genomes of other prokaryotes and several eukaryotes are in progress using an increasing array of new vectors and techniques.

Human and other animal genes have been incorporated into plasmids of E. coli. Expression of these genes has resulted in the production of human insulin and several other pharmaceutical productions that are now undergoing clinical tests. By changing the sequences of nucleotides in known genes, new proteins have been obtained. In this way, interferons with an enhanced effectiveness against viruses are being developed.

Genetic conservation hs been described as an evolutionary responsibility. Are we discharging this responsibility? We can discern three major groups of responsibilities based on the action needed, namely professional, political and public.

The scientific aspect of genetic conservation first of all involves defining the categories of material worthy of preservation and the major methods of preserving them. The following categories are usually regarded as important:

(a) Cultivated varieties (cultivars) in current use. These are varieties of recognized value and performance released for cultivation after testing and approval. Successful cultivars are widely used in plant production in a given country or in several countries having similar cropping conditions. Uniformity of characteristics is a feature of this category.

(b) Obsolete cultivars. These are varieties that were cultivated in the past, but have been replaced by the new cultivars. Uniformity is also, to a certain degree, a feature of this category.

(c) Primitive cultivars or land races. These are varieties that have been used for centuries in traditional agricultural systems. They were the products of selection by man, but have not been improved by way of plant breeding. Variability in characteristics as observed in the field is a feature of this category.

(d) Wild species and weedy species closely related to cultivated varieties. These ancestors of cultivars are species of crop plants that have not been cultivated varieties through plant breeding. This category also covers species of direct economic value, such as forest trees.

(e) Wild species of potential value to man. These are species which are not cultivated and whose importance has not yet been assessed, but may be identified through exploration.

(f) Special genetic stocks. This is material that has normally been developed by man and is or has been used in ongoing breeding programmes. It includes mutants, "breeders' lines" and lines with identified genes or gene combinations. Material of this type is particularly useful because of the identification of genes for specific characteristics.

Conservation methodologies can take three forms: The first involves the entire biomass - the total preservation of vast tracts with in situ conservation of animals and plants. This level of preservation will be extremely important in slowing the rate of species extinction.

The second involves in situ preservation as land races and wild relatives where genetic diversity exists and where wild/weedy forms are present, often hybridizing with the cultivated. These are evolutionary systems that are difficult for plant breeders to simulate and should not be knowingly destroyed. Their preservation is probably not possible but slowing down their disappearance will give us more time to better understand how these systems evolved. Considerable potential for creative institutional arrangements exists for in situ preservation, especially in the developing countries.

The third method involves ex situ preservation as seed or in vitro cell lines stored in gene banks under appropriate conditions for long-term storage. To be useful, such a system requires documentation to know what to request. Information management will be as important as the physical arrangements of the gene bank. Ex situ preservation involves exploration, collection, storage, evaluation and documentation, and, lastly, breeding for the effective use of desirable genes.

Without green plants, higher orders of life cannot exist since they are directly or indirectly the basis for nutrition for animals and man. This is why in situ conservation of the habitats where gene pools of wild plant species occur within their natural communities is so important. This aspect of conservation has received high priority in the World Conservation Strategy launched in 1980. This strategy has recommended a three-pronged approach: ex situ protection, as the chief and generally the only means of conserving cultivated material and as a back-up means of conserving wild material; and a system of sound planning, allocation and management of land and water uses to achieve a sustainable combination of development on the one hand and of maintenance of the biological resources for development on the other.

A global network of gene banks exists. But despite recent advances in long term in situ conservation, many scientists believe that gene banks - whether seed, clonal, or tissue culture - will never be adequate to ensure the availability of genetic varieties to the desired extent. For example, Hugh Iltis states, "I think germ plasm banks are tremendously important for crop improvement and scientific research, but they will not save the genetic diversity of plants for the next 2,000 years. For one thing, such banks are vulnerable to accidents, even deliberate destruction." Germplasm conserved ex situ in several developing

countries have been damaged as a result of power failures, breakdown of refrigeration equipment, strikes and civil disorders preventing personnel from entering the facilities, and drought and floods during the growing season when seed increases are made. Some experts would like to achieve some kind of freezing of the genetic landscape including hot spot locations for pests and pathogens where screening for resistance can be done in an effective manner under natural infection.

The International Board for Plant Genetic Resources (IBPGR) has recently reviewed the work on in vitro storage. In vitro work many involve many different culture systems ranging from protoplasts and disorganised cells and calluses, to organised shoots and somatic embryos (embryoids). Although plants can be propagated clonally using all types of culture, such studies as have been carried out for genetic conservation purposes have tended to concentrate upon non-adventitious shoot-tips (often erroneously referred to as "meristems", which in fact form only part of each explant or culture) and axillary buds. Whilst these may offer greater genetic stability and be entirely appropriate for some species, like the potato, their wide use may not be feasible for others which lack sufficient axillary meristems and which are propagated in the field by adventitious means. Further, many basic studies on storage by cryopreservation (freeze-preservation) have been carried out using disorganised systems which must regenerate by culture systems. Thus, only restricted use is being made of the full repertoire of available in vitro techniques, a limitation which is likely to become more apparent as in vitro work assumes greater importance in agriculture and plant breeding, particularly through the involvement of genetic engineering. A more balanced view should be taken on the relative merits of different types of culture.

Taking rice as an example, I would like to illustrate the value of a properly planned and maintained gene bank. The genus Oryza has 20 wild species and two cultigens, O. sativa and O. glaberrima. The full spectrum of genetic resources in Oryza consists of (1) wild species, natural hybrids between the cultigen and wild relatives, and primitive cultivars of the cultigens in the areas of diversity; (2) commercial types, obsolete varieties, minor varieties, and special-purpose types in the centres of cultivation; and (3) pureline selection of farmers' varieties, elite varieties of hybrid origin, F_1 hybrids, breeding materials, mutants, polyploids, aneuploids, intergeneric and interspecific hybrids, composites and cytoplasmic sources from breeding and related research programmes.

It has been estimated that slightly more than 120,000 cultivars may occur in O. sativa and O. glaberrima on different parts of the world. The International Rice Germplasm Centre at IRRI has about 67,000 Asian cultivars, 2,600 African rices, 1,100 wild rices, and 690 genetic testers. Between 1962 and 1982, the centre provided more than 91,000 seed samples of both cultigens and wild species to nearly 2,500 scientists. In addition, the centre provided IRRI scientists with nearly 350,000 seed samples.

Obviously, having a large collection by itself has no significance unless the collection is carefully studied for its genetic representativeness and for minimising genetic redundancy. The IRRI collection is carefully screened both for eliminating duplicates and for assessing the useful characters they possess. A multi-disciplinary genetic evaluation and utilisation programme (GEU) helps to get maximum benefit from such an invaluable assemblage of genotypes. Recently, in collaboration with IBPGR and national government agencies, a five-year plan (1983-87) has been drawn up to collect the remaining genetic material with the help of appropriate national organisations, so that we can preserve for posterity the fruits of thousands of years of natural evolution and human selection.

When the ecology of crop fields is changed in a direction favouring higher yield, conditions also become more favourable for pests and pathogens. Also, as a result of unscientific irrigation, an increasing amount of land is being affected by soil constraints such as salinity, alkalinity, acid sulphate conditions and waterlogging. Fortunately, in nature there is considerable variability for many of these characteristics. Let me cite two examples. Resistance to the Grassy Stunt virus came from a wild species, Oryza nivara collected from Uttar Pradesh in India. The famous hybrid rices of China, which now cover about seven million hectares in that country, could be developed because of the discovery by Chinese scientists of cytoplasmic male sterility in a wild rice plant found on Hainan Island.

At present, the world's rice crop amounts to over 400 million tons a year, feeding a population of more than 2.3 billion people. Between 1968 and 1981, the total rice production in Asia rose by 42 per cent. The average yields rose by about 30 per cent during this period when, unfortunately, the population increased by over 25 per cent. Since there is little difference between cultivable and cultivated land, further increases in production will have

to come largely from productivity advances. For this purpose, we will need a wider range of high yielding varieties which can perform well both in ecologically handicapped regions and in farms cultivated by economically handicapped farmers. This emphasises the urgency of collecting, classifying, and utilising all available genetic variability. Considering the fact that the total expenditure on rice germ plasm conservation in the world now may be about US$1.25 million every year, the returns from such an investment are obvious. The time available for saving the remaining genetic variability may hardly be a decade.

Some estimates suggest that tree formations are being lost at the rate of 11 million hectares every year. In tropical America, Africa and Asia, for nearly 10 hectares of forests lost, hardly one hectare is being reforested. Not only has this serious implications with regard to the in situ preservation of genetic variability but also affects the quality of life of millions of forest dwellers. Some estimates indicate that so far only 1 in 6 of tropical plants and animals has been given a scientific name. We may not even know what we are losing due to the destruction of forest canopies.

The International Union of Forestry Research Organisations (IUFRO) has been collecting, synthesising, and disseminating data on the genetic impoverishment of tree species. FAO also began publishing a data book on endangered forest tree species and provenances since 1981. An FAO/UNEP/IBPGR technical conference held in 1981 underlined the importance of greater attention to forest genetic resources, particularly species used in arid and semi-arid zones for fuel. Leguminous shrubs which can enrich soil fertility through biological nitrogen fixation and at the same time provide fodder, feed and fuel are particularly worthy of greater attention. Among other tree species which need greater scientific attention are neem and casuarina. Neem is a unique plant with multiple uses particularly in pesticide and fertiliser industries.

Microbiologists have long recognised the need for conservation. In the past, the greatest scientific effort was directed primarily towards microorganisms causing diseases and spoilage. Recent genetical and biochemical advances, however, have led to a surge of interest in the use of microorganisms for the production of valuable foods, fuels, and wide range of biochemicals. This has resulted in the establishment of microbiological gene banks particularly for the support of biotechnology. Some countries favour a central facility on considerations of economy and efficiency, while others prefer a decentralisation system with some arrangements for co-ordination.

From the early 70s when the cost of fossil fuels went up steeply, interest in biological nitrogen fixation has increased. It is now widely recognized that in breeding programmes relating to leguminous plants, the variability of Rhyzobium bacteria needs to be considered in conjunction with the genetic variability of the host legume. Interest in the exploration, collection, documentation, and preservation of microorganisms of major importance to crop plants is now growing.

Blue green algae (BGA) and Azolla are bio-fertilisers with great potential. The ability of a number of genera (BGA) to fix atmospheric nitrogen has implications for soil fertility under both natural and cultivated ecosystems. In particular BGA are of importance in rice fields where their growth and nitrogen fixing activity can be enhanced by inoculation and cultural practices, thus providing a cheap source of nitrogen for the crop.

The high nitrogen content of some genera, especially Spirulina, the possibility of using certain strains as food, feed, and as a source of useful biochemicals also make them valuable. Finally, there is an academic curiosity about organisms that constitute the largest, the most diverse, and the most widely distributed group of photosynthetic prokaryotes.

The induction of mutations to enhance nitrogen-fixing capacity does not seem to be a profitable approach to improve strain efficiency as most of the mutants seem to have lost their ability to fix nitrogen.

The success of Rhizobium strain selection in increasing N_2-fixation in legumes has drawn attention to the possibility of selecting superior strains of other nitrogen-fixing microorganisms. However, requirements for a symbiotic prokaryote are different from those of a free-living BGA exposed to the harsh competitive world of the rice field. There is hence need for the collection and screening of BGA strains which can fix N_2 equally well under diverse conditions of soil environment.

Azolla, an aquatic fern capable of fixing atmospheric nitrogen through a symbiotic blue-green alga living in cavities of its leaves, has long been used in China and Vietnam as green manure for rice. Its usage is now being tested and expanded in many rice growing countries of South East Asia.

The major problem for Azolla collection is that the material cannot be shipped by mail and has to be hand-carried. Fronds deposited on a paper tissue inhibited with culture medium in a plastic Petri dish remain viable for 8-10 days if aerated at regular intervals and kept in the lower part of a refrigerator as often as possible.

Despite considerable progress our present knowledge of the genetics of free-living and symbiotic BGA is far less than that of bacterial genetics. The collective properties of BGA (oxygenic photosynthesis, chromatic adaption, nitrogen fixation, cellular differentiation) make them attractive organisms for genetic research.

Although the number of animal species (excluding insects and fishes) which have been domesticated during the past several thousand years is scarcely more than a dozen, specific agro-ecological, economic, and cultural needs have resulted in each of these species numerous breeds and strains or races. Consequently, we have now an enormous wealth of animal genetic resources in the world as a whole. While for a long time local communities were wedded to their own specific breeds of animals, there has been extensive replacement of indigenous animals with exotic strains in many developing countries in recent decades. Breed substitution, planned or unplanned cross-breeding or the creation of new composite breeds are all now important components of animal improvement programmes in cattle, sheep, goat, poultry, pigs, etc. Experience has shown that this process has two possible negative consequences - first, the new breed or hybrid may lack adaption to local conditions, particularly with regard to pests and diseases and secondly, the animal genetic resources being replaced may be lost for all time.

Knowledge concerning the comparative advantages and disadvantages of indigenous and alternate breeds under different environments is lacking in many developing countries. Because of unhappy experience, there is the opposite trend among some animal geneticists of placing emphasis only on the improvement of indigenous breeds in isolation, without the use of strains which have proved their worth in other locations. More studies on the interaction between genotypes and environment particularly the management systems feasible of adoption under different socio-economic and cultural conditions are needed. Meanwhile, breeds at present having little to offer a production system but which may have hidden or identifiable production strengths such as resistance to disease, ticks, etc. should be retained in herds of optimal size or in cryogenic storage.

For developing a scientific strategy for conservation, there is need for more detailed information on breeds in danger of extinction in each country. The IUCN's (International Union for Conservation of Nature) Red Data Book does not contain information on the breeds threatened within a domestic species. The problem of genetic erosion in domesticated animals is not confined to developing countries alone. In developed nations, breeders keep only the best producers for reproduction. Thus, lines are formed whose genetic isolation becomes more and more strict. Breeders using the same lines often form a society whose chief purpose is to keep a herdbook in which only animals conforming to established standards of size, colour, conformation, and performance will be registered. After a while, there is a tendency to close the herdbook and permit no more entries. A survey conducted under an FAO-UNEP pilot project on conservation of animal genetic resources revealed that in Europe and the Mediterranean region about 115 indigenous breeds of cattle were threatened with extinction in the early 70s. The reasons vary from breed to breed but include factors such as preference of specialised breeds for milk and meat production rather than dual purpose breeds and the replacement of draught cattle with tractors. New reproduction techniques such as artificial insemination with foreign frozen semen also promote rapid gene replacement.

The IUCN has set up a Genome Conservation Specialists Group as part of its Species Survival Commission. As a first task, the Group is compiling a list of existing collections of frozen germ cells of endangered species and their close relatives. The in situ conservation of animals suited to the production of food, fibre, and work is receiving greater attention at country level. India, for example, has set up a National Bureau of Animal Genetic Resources for promoting both in situ and ex situ conservation. Animal Genetic Resources data banks are being set up in different countries and training facilities in conservation and animal genetic resources are being expanded.

During the next few years, it is likely that the techniques of embryo transfer, long term storage of embryos, and the cloning of embryos for even more rapid multiplication of desirable genotypes will be developed to commercially viable levels. These techniques will have applications both in the field of genetic conservation and in the rapid upgrading of animal productivity. It will be prudent for developing countries endowed with a large animal wealth to get a critical mass of scientists trained in the new techniques.

There are many symbiotic linkages between plant and animal genetic resources conservation. Where uncontrolled overgrazing takes place, the native flora soon takes the form of only plant species which are not eaten by animals. When plants which produce nectar, pollen, honey dew, propolis and which are visited and pollinated by bees in general are destroyed, the bee populations dwindle and disappear. When pesticides are applied indiscriminately, the natural enemies of pests are destroyed and pest incidence could in many cases pose more serious problems. Conservation in crop fields involves the adoption of management procedures which will help to build up the population of natural enemies of pests. At the IRRI, for example, it has been found that an intensive rice production system involving weekly planting and harvesting of rice with a total production of about 18 to 20 tons of rice per hectare per year will be possible provided we protect and conserve the natural enemies of pests, cultivate varieties with multiple resistance to pests and diseases, and adopt timely applications of appropriate chemical pesticides based on a careful monitoring of the build-up of pest populations.

Conservation will have to be a total approach, starting with micro-enviroments and extending up to macro-systems.

It has been estimated that about 200,000 species of plants and animals may have their homes in the oceans. This amounts to about 2-4 per cent to earth's 5 to 10 million species. However, the oceans contain nearly two thirds of all animal phyla. Because many marine species tend to be more uniformly distributed than terrestrial species, it has been assumed that the threat of extinction is less. Recent studies have indicated that many marine populations may be quite variable genetically and that this variability is particularly high in species-rich communities such as those of coral reefs.

The need for greater attention to the conservation of genetic resources of the sea arises from increasing damage to marine ecosystems from human activity. Sedimentation and siltation from land sources, pollution from inland and coastal sources and unscientific commercial exploitation are all threats to marine genetic resources. The coastal zones also support some of the densest human populations on earth. Of the 50 or more cities that are projected to have populations exceeding 5 million in the year 2000, half are located on estuaries.

In the tropics, many coral reefs and mangrove communities have been degraded or destroyed along extensive sectors of coasts of the Americas, Africa, India, Thailand, Malaysia, Vietnam, Indonesia, Philippines, and east and south Australia. In recent years, some steps to promote conservation through the establishment of Marine National Parks have been taken but more co-ordinated action to protect both living inland water and ocean resources is necessary at the country level.

Even the small proportion of marine organisms examined to date has yielded numerous extracts and compounds of importance for medicine. The marine world is a valuable source of a wide range of biomedical compounds. Recent research on the development of cloning systems for producing commercially important chemicals, pharmacologically active compounds and metamorphosis-stimulating substances present in marine organisms, is one of promise. Attempts are underway to develop useful drugs from the sea, including antineoplastic, antibiotic, analgesic, and antispasmodic agents. Genetic engineering techniques are also being applied to improve fish, molluscs, and crustaceans in natural environments and hatchery systems.

In several parts of Europe and also in North America, "acid rain" affects fresh water fishes. It has been reported that in southern Norway, there are hundreds of lakes without fish and that salmon is no longer to be found in many river systems. Both laboratory and field experiments indicate that acid water first affects fish eggs and fry. Massive kills of salmon and trout have been observed during snow melt and after heavy rain. Conservation of genetic resources in such vulnerable areas will have to receive priority attention.

The Nordic Symposium on Gene Banks held in Helsinki in 1978 recommended that Gene Banks may be established in each country based on the establishment of "Egg Banks" involving indefinite storage of eggs and milt at low temperature; the propagation in captivity of each strain; and conservation in the natural environment, with legal protection from fishing and other human interference. Similar programmes are needed in every part of the world.

Any discussion on the conservation of human genetic resources cannot be divorced from ethical, social, racial, religious, and political issues. Advances in the development of sperm and egg banks have opened up possibilities for the long term preservation of human genotypes. The clinical technology of in vitro fertilisation is now five years old. There are reports on cloning and on the establishment of sperm banks of "genuises". All that can be said in favour of such research is that in addition to helping those who suffer from infertility, safe storage of sperms and eggs of persons with valuable traits (particularly of those who promote co-operation) for further use might prove to be a step in the right direction, if the world is engulfed in a nuclear war.

There was growing apprehension among several developing countries that the introduction of plant breeders' rights and crop variety patenting may hinder the availability of useful genetic material to developing countries. Under a convention signed by several countries in Europe, the breeders of a new plant variety will be eligible for royalty for a least 18 years in the case of trees and vines, and at least 15 years for all other plants.

The major aim of legislation relating to Plant Breeders Rights (PBR) is to provide stimulus to private sector breeding and investment. Various views have been expressed on the positive and negative implication of PBR legislation. According to IBPGR, the issue of PBR in relation to genetic resources is of no great significance. What is urgently needed is greater effort in the collection and conservation of the basic sources of variation in wild and weedy species and primitive cultivars to prevent genetic erosion. However, IBPGR has also warned that "consent for the transfer of material under development may be more difficult to obtain than hitherto".

So far the UPOV (Union for Protection of New Varieties of Plants) Convention has only been concerned with patenting of genotypes. However, there are suggestions that the convention should also allow the patenting of specific genes. A fear has been expressed that when plant breeding companies are purchased and managed by pesticide companies, there may be a temptation for not including genes for resistance to those pests for which chemical pesticides are available. If this happens, the cost of production of high yielding varieties could further increase. Today, some of the most widely grown varieties like the IR36 variety of rice are preferred by farmers only because of the broad spectrum of resistance to important pests and disease which such varieties possess. The breeding of such varieties is facilitated by international co-operation in getting segregating populations subjected to severe pest pressures in hot spot locations. It is true that patent rights could stimulate private enterprise in plant and animal breeding. At the same time, they provide scope for the emergence of monopolies in genetic material for specific traits unless a sample of existing variability is also maintained at a government controlled genetic resource centre. There is hence need for examining whether adequate incentives could be provided for plant and animal breeding initiatives without in any way endangering the possibility of free exchange of genetic material among and within nations.

One immediate method of assisting developing countries in genetic conservation and utilisation is the establishment of a global grid of genetic resource centres, all committed to the cause of free exchange of material. For many developing countries, the availability of genetic variability itself will not provide any insurance against genetic vulnerability. They need help in the short term in breeding and evaluation. A global grid of genetic resource centres will have to be linked to a complementary grid of national, regional, and international selection and hybridisation centres.

A World Gene Fund was suggested by the Government of the Netherlands in a letter to the FAO Secretariat in June 1983. Such a fund will help to accelerate collections in endangered habitats, train more geneticists and breeders from developing countries, and organise international selection and hybridisation gardens to generate material of relevance to the countries needing them.

The FAO has estimated that the USA and Europe may hold about 340,000 and 750,000 accessions of seed crops respectively. The People's Republic of China has over 300,000 samples of seed crops. Some of the other major collections are the following:

		Accessions (nearest '000)
USSR	Wheat and wild relatives	70,000
USSR	Barley, oats and rye	30,000
IRRI	Rice	70,000
ICRISAT	Sorghum	20,000
ICRISAT	Millets	15,000
CIMMYT	Maize	15,000
USSR	Food legumes	26,000
USSR	Vegetables	35,000
USSR	Oil seeds	20,000

It is necessary to have these collections replicated and conserved at different places for ensuring their security. Also, there is need for an integrated computerised data bank from which anyone interested can get information.

Governments should also consider mobilising the help of defence services in work relating to the collection of genetic resources from endangered habitats. Some of the areas with considerable genetic wealth are not easily accessible due to political or defence considerations. Given the requisite training, army personnel will be easily able to collect material for remote areas which cannot readily be reached by civilians. It will be useful if a small corps of officers, especially trained in genetic resources conservation, is established within the defence services of each country. This corps could assist the concerned agencies of government both in germplasm collection and in situ conservation work.

Political considerations become particularly important while developing public policies for the establishment of human sperm and egg banks. In vitro fertilisation, for example, has now been in use for 5 years. In Australia and United Kingdom, policy governing its use is actively being formulated. The President's Commission for the Study of Ethical Problems in the USA in its 1982 report entitled "Splicing Life" has referred to a number of anticipated impacts of rapidly growing knowledge of molecular genetics, genetic screening and diagnosis, and the curing of genetic disorders.

How can the above message become part of the daily life of every citizen in every country? How can we generate widespread awareness of the economic and biological necessity of conservation measures? There is no single or simple method of involving people in conserving their own environmental assets. The message has to start from the primary school and will have to become over a period of time a way of life.

In the past, rural communities replenished soil fertility through organic recycling. Women selected the best cobs or panicles to use as seed during the next growing season. By this process, they unconsciously selected genotypes which could resist or tolerate the major pests in a particular region. Similarly, selection was practised among animals with the result that adaptation to local conditions is the major characteristic of indigenous breeds of farm animals.

Conservation agriculture gave way to exploitative farming. With specialist agencies taking over the responsibility for seed production and fertiliser and pesticide distribution, the involvement of the local people, particularly illiterate women, has diminished or vanished. Consequently, conservation is now regarded a government responsibility rather than a joint sector activity between the people and public agencies.

Television, the radio, and the press are powerful tools for education and awareness. I would like to suggest that every TV and radio station and every newspaper should carry at least one small item on genetic conservation each day. Just as reporting on weather has become an integral part of daily news reporting, reporting on genetic conservation and eco-development should also become a daily feature.

In view of the enormous quantitative and qualitative dimensions of the problem of conservation, it is obvious that efforts will have to be selective. Developing countries will have to work on reliable and low cost ex situ conservation techniques, such as storage of seeds in permafrost areas and in cold desert regions. This will help to overcome some of the difficulties like power failure to which I had made a reference earlier.

With the advent of new techniques for genetic manipulation and analysis of biological functions, it may be possible in future, as already demonstrated in some cases, to tailor-make genes for the hyper expression of functions in desired traits.

It can be visualised that casettes of DNA clone carrying useful genes in forms for their maximal expression will be constructed. However, complete reconstruction of genetic background in which they should be functioning will be almost an impossible proposition for such vast numbers of organisms for which we have use. Clearly, the strategy would be to incorporate the genes from the casette libraries backgrounds of homologous or heterologous organisms already adapted to local field conditions or to the kinds of nutritions and substrates that can be made available for the exploitation of these organisms in new ways. This approach requires that organisms with the right kind of adaptive functions be conserved even if at this time they are of little economic value.

In other cases it would appear that specific characters would be transferred to organisms of economic value for the latters improvement or for the production of novel kinds of biochemicals for human welfare. In such cases it may not be essential to have very exhaustive conservation.

A variety of standard procedures are in vogue for the long time preservation of bacteria, fungi, and their parasites. These include storage of agar slants under oil and in cold, lyophlisation, and deep freezing in glycerol. Since it has been noted that certain soil bacteria remain viable in soil samples for very long periods, such storage should also be employed. In the developing countries where microbiology is not yet very advanced, soil samples and other kinds of primary samples should be stored from both typical and atypical habitats, for isolation of the resident microorganisms in future.

Several human populations in the disease-endemic areas should provide cellular material for preservation because of the adaptive traits they possess. In such cases germ line cells, specific kinds of B-cells and perhaps cells from some other specific tissues could be preserved in either of the following ways: cryogenically after culturing or as tissue and as hybridoma cell lines. Similar strategies could be adopted for preserving the genotypes of interesting propositii for analysis in future. The sperm banks that are coming into being could complement his approach. It may perhaps be possible to store fertilised eggs or cells derived from very young embryos for long periods of time. These banks could serve a variety of purposes beside providing resource material to safeguard against extinction of races or genetic damage against vast populations of humans in the events of man-made and natural catastrophies.

The recombinant DNA procedures today allow cloning of any foreign DNA into E. coli. Current research is making this possible in other organisms also and efficiency of the technology is bound to get improved. Cloned DNA, DNA and material having DNA in its native state should all be used for genetic conservation from now on.

Finally, non-viable material representing valuable genotypes stored in Gene Banks need not be discarded. They could become sources for DNA libraries from where a relevant gene or combination of genes can be recovered. Today, an integrated genetic conservation strategy can be planned at the level of populations, individuals, tissues and organs, cells and DNA libraries.

A national conservation strategy could include an optimum mix of the above.

I. ASSISTANCE SOUGHT

Assistance required: Assistance wanted

We have received a request for assistance in the following:

> Process technology wanted for an aqueous coating carrying tiny doses of agricultural chemicals of nitrogen fixing bacteria to help the seedling. A coating used for seeds with such material in a dry form is required.
>
> Please reply to Sanwar Misra, P.O. Box 443, El Marij, Libya, with a copy to the UNIDO Technology Programme, P.O. Box 300, A-1400 Vienna, Austria.

J. MAILING LIST FORM

FOR NEW SUBSCRIBERS ONLY:

UNITED NATIONS **NATIONS UNIES**

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

UNIDO MAILING LIST QUESTIONNAIRE

Genetic Engineering and Biotechnology Monitor
(Code: 503)

UNIDO MAILING LIST, INDUSTRIAL INFORMATION SECTION,
P.O. BOX 300, A-1400 VIENNA, AUSTRIA

	Type or print clearly (one letter per box) and leave a space between each word
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TITLE OR POSITION	
ORGANIZATION	
STREET AND No. (or P.O. Box)	
CITY AND STATE OR PROVINCE	
COUNTRY	

PLEASE DO NOT WRITE IN THESE SPACES

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CITY ☐☐☐☐☐☐☐☐☐☐☐☐